LONG-ACTING CONTRACEPTION

edited by

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PREFACE

Until the present century, fertility regulation meant sexual abstinence, coitus interruptus, a variety of concoctions to be inserted into the vagina or smeared onto the penis, and abortion. Certainly, these methods were ineffective, dangerous to the point of death in many cases, generally not available to most people, and obviously not acceptable to the vast majority of the growing population of the world.

The modern era of fertility regulation began about 100 years ago, with the introduction of spermicidal formulations that were more effective and far safer than the preparations used during the past 2000 years, and with the discovery of rubber and the subsequent development of barrier contraceptives -- condoms, diaphragms and cervical caps/pessaries.

Then, only 23 years ago, the discovery of steroidal contraception and the re-emergence of intrauterine contraception revolutionized fertility regulation. For the first time it was possible to think of and develop large-scale programs that would bring contraception to the masses of people. Disappointed with the problems of oral pill use and IUDs, many women and men elected to undergo voluntary sterilization. Indeed, during the 1970s, the number of sterilization acceptors grew to the point where voluntary sterilization (male and female) is the number one method of family planning in the world and the number of acceptors continues to increase.

In the 1980s, then, people wishing to control their own fertility have a much wider choice of methods. Along with this increasing choice, however, have come problems of supply and distribution, cost, training of medical and paramedical personnel to provide the services, and many other problems related to the technology of these new methods. Despite the problems engendered by the so-called "cafeteria" approach to fertility regulation, providing couples with a choice gives users a tremendous sense of personal control over their own fertility. Most important, the variety of contraceptive methods now available encourages widespread community involvement in organized programs of family planning.

Continuing progress is being made in the development of new and improved methods of fertility regulation. These advances not only include the development of new methods, but encompass a whole range of concerns that involve social scientists, public health workers, medical personnel, pharmaceutical and instrument manufacturers, engineers, and reproductive scientists. Accordingly, it is appropriate that individuals with these diverse interests come together from time to time to discuss and update their knowledge on the recent advances in fertility regulation.

During the past 10 years in Egypt, an acute awareness of the health consequences of excessive population growth has developed. Mounting a large-scale effort that carries all aspects of a family planning program into the village community, the Egyptian government has been notably successful in meeting its goals. The program relies mainly on modern

and effective methods of fertility regulation. Despite the initial and hard-won successes in promoting the concepts and use of family planning, much more needs to be done to restore a better balance between birth and death rates. Obviously, without modern contraception, mass programs such as the one in Egypt could not have attained their present levels of success. It is hoped that newer advances in fertility regulation will continue to provide the increasing momentum that is so necessary to bring about the solution to the world's problems of excessive population growth.

The organizers of this Seminar, would like to express its appreciation to the staff of the Department of Obstetrics and Gynecology, Shatby Hospital, and the Program for Applied Research on Fertility Regulation, Northwestern University for coordinating the myriad details so necessary for a successful meeting.

Much gratitude and appreciation must also go to the United States Agency for International Development for their financial support of this Seminar.

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CONTRACEPTION IN THE ARAB WORLD

Abdel R. Omran

THE NEEDS

The Arab world represents a unique group of countries that shares common social, cultural and linguistic traits.

Demographically, the Arab countries have great similarities. Rich and poor alike, they have a very high rate of population growth, an overly young population composition, a large family size as norm, an uneven population distribution, a high rate of urban expansion and unhealthy city growth, a maldistributed and under-utilized labor force, and a low participation rate by women in the economic activities outside the home. Marriage is a universal institution in the Arab world, and young age at marriage is the norm. High parity, young age at pregnancy, continued childbearing beyond age 35, and close spacing of children are overtaxing the health and survival chances of the Arabian woman and her children.

These traits prompted me, a few years ago, to call upon all Arab countries to adopt population policies to correct their demographic stiuation according to their own national goals. Today, I am going a step further and am calling upon all Arab countries to adopt family planning. Besides the rewards of demographic adjustment, there can be little doubt that the high reproductive risks in the region can be substantially mitigated by family planning. The ability of parents to instill cultural values in their children, and to raise them as capable and well-educated

citizens, is greater for a small than for a large family. This chapter will, therefore, address briefly, these three major rationales for family planning in the Arab world:

a. the demographic rationale,
b. the health rationale, and
c. the socio-cultural rationale.

In addition to these needs, this chapter will discuss the constraints to, and prospects for, high contraception acceptance in the region.

Family planning for demographic adjustment

Not all the Arab countries are in urgent need to adjust their demographic growth rate to their land and economic resources. Some countries have enough resources and land space to accommodate population growth for a while. Several other countries, however, are already suffering from increasing population pressures on limited resources. These include Morocco, Algeria, Tunisia, Egypt, Sudan, Syria and Jordan. Soon to experience similar population pressures are the two Yemens, Mauritania, Somilia and Djibouti, countries where the population growth rate used to be partly checked by high mortality. The death rates have, in recent years, been falling in these countries and, in absence of contraception, population explosion is inevitable.

Altogether, we have at least twelve Arab countries in immediate need of demographic adjustment. Fertility in this group of twelve countries is high, with a birth rate of 38-50 per 1000, and a total fertility rate of about 6-8. These are to be compared to a birth rate of 15 per 1000 and a total fertility rate of 1.9 for the more developed countries in the world. Even with declining death rates in these Arab countries, the population growth is about 30-35 per 100 per year (Table 1) and is higher than the 18 per 1000 for the world as a whole (1983 estimate), and much higher than the 6 per 1000 in the more developed countries. The population of 145 million in these twelve countries in mid-1983 may reach 230 million in 23 years, with little or no chance for an equal growth in economic, social or land resources to accommodate such rapid increase.

High population growth has been overtaking the economy and impeding the process of development in the countries concerned. Population growth is also exerting serious pressures on the education system, health services, public services, housing, job creation and manpower development, all of which are currently substandard, to say the least. It is also distressing to find that a sizable proportion of economic resources in these countries is absorbed in what is called "demographic investment", i.e. activities to cope with the increasing population in an attempt to maintain the same standard of living and prevent it from deteriorating further. The problem of overpopulation in these countries is compounded with population maldistribution, poor population characteristics and young age composition.

All of this represents the demographic need for family planning.

Family planning for health in the Arab world

This is by far the least controversial and the more universally appealing rationale for family planning in the Arab world. It is also the one rationale most endorsed by Islam, the predominant religion in almost all Arab countries. The health rationale is, furthermore, equally relevant to countries with demographic pressures on their resources, as well as those with adequate resources.

In virtually all the Arab countries, pregnancies are poorly spaced and improperly timed. About one of every four births in Arab countries occur to mothers at maternal ages of risk, i.e. under twenty years or over thirty-five years. These ratios are to be compared with a ratio of one in twenty in Japan (Figure 1). Furthermore, high parity, particularly grandmultiparity, a condition that is rapidly disappearing in the more developed countries, is still prevalent in the Arab world. Compounded with poor prenatal and natal care and inadequate child care, unregulated fertility can result in serious health risks to the mothers and children. Family planning can, therefore, mitigate substantially these problems.

World experience has confirmed most convincingly several relationships between family formation patterns and maternal and child health. The most impressive health benefit has been the documented improvement in chances of childhood survival. The family formation patterns responsible for this improvement are adequate spacing of pregnancies, limiting the number of offspring, and appropriate timing of pregnancies to occur between ages of 20 to 34. Scientists measure the health risks to children in terms of proportion of pregnancies lost (pregnancy wastage), proportion of babies born dead (stillbirths), the population of infants who die before their first birthday (infant mortality), and the proportion of children who die between one and five years of age (childhood mortality). With unregulated fertility, all of these mortality risks to children increase. Other measures of reproductive health risks to the child include prematurity, malnutrition, poor growth and development, congenital defects, delayed sexual maturation and mongolism, or mental retardation. One of the most disquieting findings is the risk of low average intelligence quotient found by many studies to be associated with large family size.

Maternal chances of survival are also affected by family formation patterns. Poor obstetric performance, increased gynecological problems and higher rates of systemic diseases, such as diabetes, are all functions of unregulated fertility. Until recently, very little information about these relationships has been available for Arab countries. Recent epidemiologic studies of the health risks associated with unregulated fertility have, fortunately, been carried out in a number of these countries. These include studies by the World Health Organization in Lebanon in the early 1970s, and in Syria and Egypt in the late 1970s; by the Interntional Fertility Research Program in Sudan and Egypt, by the High Institute of Public Health in Alexandria, by Assiut University, by the American University in Beirut, and by the Central Bureau of Statistics in Syria. These studies have confirmed the world experience and make a good case for family planning to safeguard the health of mothers and children. We will cite a few examples.

1. In a study in six maternity centers in Egypt and Sudan, perinatal mortality was found to increase with parity of mothers, especially for grand multiparas (Figure 2).

2. Disease of children increase with family size (or the number of their sisters and brothers). This was illustrated in the World Health Organization study in the Assiut area where, for example, the prevalence of parasitic infestation increased with parity in both rural and semi-urban areas (Figure 3).

3. That high parity affects mothers' health adversely is attested to by several studies. For example, the World Health Organization study has found an increase of prolapse with parity among Syrian women in these areas (Figure 4).

4. Poor timing of pregnancies also has a negative impact on the health of mother and children. For example, stillbirths as a percent of total births, are significantly higher among children born to mothers aged 35 and over compared to children born to mothers aged 20 to 34. There is also some increased risk for children born to mothers under age 20. This is demonstrated in the above mentioned Syrian study (Figure 5).

5. Close spacing of pregnancies is certainly associated with high risks to mothers and children. This is demonstrated by the World Health Organization studies in Lebanon, Syria and Egypt. As shown in Figures 6a, 6b and 6c, the highest risks occur for birth intervals of less than one year and two years; the risks are minimal for intervals of 3 to 5 years, but increase slightly for longer periods, perhaps because of the older age of mothers.

6. Alarming reports of the negative impact of large family size on intellectual development of children have been accumulating since the 1930s from a number of countries. On the average, the IQ of first, second, and third born children is higher than that of fourth and later born children. This has been documented by studies in Scotland, France, England and in the United States (The U.S. National Center for Health Statistics, 1974). More recently, a similar impact was found in several developing countries by the World Health Organization studies, particularly in Turkey, the Philippines and Colombia. It was also demonstrated in a large study among 20,000 school children in Taiwan.

Investigation of this vital issue in the Arab countries is just beginning and is most enthusiastically encouraged. In a small study in the Assiut area, it was demonstrated that (a) the mean IQ of children decreased progressively with birth order (and parity), and (b) the mean IQ of children born to mothers aged 20 to 34 was higher than those for children born to mothers under age 20, or over age 35 (Figure 7).

I have deliberately given more emphasis to the health rationale for family planning in the Arab countries for a good reason. While controversy continues to confuse the issue of family planning legitimacy in Islam, there is no hesitation to endorse family planning for health objectives.

This was expressed most fluently and convincingly by the late Sheikh Shaltut, and is evident in his statement (Figure 8).

Family planning for socio-economic aspirations

Being the cradle for so many civilizations, the Arab world is always haunted by joining the present with the past. This is not impossible if serious and long-term master plans are formulated and sincerely put to work in successive incrementl stages. Among these plans should be a cultural revival through younger generations, including care of the mind and the body. In view of deteriorating societal values, however, it is obvious that the major cultural upbringing of children lies with the family. With so many demands on the time and resoucres of parents in modern day life, their ability to devote time and effort to their children on a one-to-one basis is limited. Certainly, the smaller the family, the greater the opportunity for family interactions. Such a task cannot be left to overcrowded schools, decaying communities, and misguided peer groups. Thus, planning one's family can result not only in physical health benefits, but also in better spiritual development of children.

Arab women can also benefit from family planning by a reduction in the physiologic burden of repeated pregnancies within short periods of time, and the physical strain of caring for large families. With better chances for her own education and potentially to participate in economic development, the Arab woman will be better able to raise her children and share with her husband, directly or indirectly, the cost of modern day living.

THE CONSTRAINTS

Despite the obvious health and socio-cultural benefits of family planning and availability of medically approved contraceptive methods, it is difficult to understand why Arab couples are not using contraception to any great extent. One may speculate as to the following constraints.

1. The inclination to equate numbers with power has prevailed since tribal times.

2. Because the family planning movement is identified with Western institutions, many Arab authorities fear that it is a plot to reduce the number of Arabs.

3. Most of the Arab governments do not view rapid population growth as a national problem. Some do even endorse increased growth for national gains. While this is understandable from the oil-rich countries, it is deplorable for countries with mounting population pressures on limited resources.

4. Awareness of high risks associated with unregulated fertility is very limited, even among the educated public. Only recently has the media given some credence to this issue.

5. Large family sizes continue to be appealing to some groups for personal reasons, as (a) desire for a son when only daughters have been

born to the couple, (b) loss of previous children, (c) the exaggerated economic rewards of larger numbers of children, and (d) insecurity of old age without children.

6. The commitment of political leadership to solve the population problem is insufficient in most countries, even those with overpopulation problems.

7. The religious leadership has shown inconsistency and hesitation in their support of family planning, an attitude that has resulted in confusion. Such an ambivalent attitude has had a negative impact on the family planning movement in the Arab world.

8. There is insufficient enthusiasm and involvement of the medical profession in the family planning programs.

9. There is the continued inclination of having as many children as possible to safeguard against child loss. This is an aftereffect of centuries of high child mortality which could be offset only by high fertility.

10. There are also programmatic constraints. Family planning services may be totally lacking in communities where it is most needed, namely the rural and remote areas, or marginal areas in cities. They may be irregular, inconveniently located or timed, or provided with insufficient information.

11. Rumors exaggerating the side effects of contraceptive methods prevail in many areas, and may discourage adoption of contraception. The media do little to antagonize these rumors.

12. The poor performance of family planning programs in some countries led people to believe that there is no hope for family planning in the region.

THE PROSPECTS

There are reasons for both pessimism and optimism in regard to the future of contraception in the Arab world. The reasons for pessimism have been generally covered herein under the discussion on constraints. There have been, in addition, some administrative constraints and experimental disappointments to family planning. It seems that the mechanism for administering a successful program dealing with sensitive issues like marital relations and family planning is very limited in many Arab countries. The success of family planning campaigns has been limited relative to the size of administrative and financial inputs. The reluctance of many Arab countries to adopt explicit population policies is also disappointing.

Nevertheless, being the eternal optimist that I am, I feel that the future for family planning in the Arab world is not dim. Family planning is not foreign to this region. It has been used by Muslims, though sparingly, since the time of the Prophet Muhammad. The Prophet knew about and sanctioned withdrawal (al-azl); if family planning were prohibited by Islam, The Qur'aan would have stated so.

Contraceptives, other than withdrawal, were also used. The Arab medical texts were the first and foremost in world history to include explicit chapters about contraception. This is particularly intriguing because most of the medical texts in Europe and the United States, up until 1950, ignored completely this major medical and social concern. It appears that when the Arab medical texts were adopted by European medical institutions, the chapters on contraception were systematically edited or deleted.

Many Arab countries have active family planning programs through official (government support) and/or through voluntary organizations. Some of these programs have been successful, such as the national program in Tunisia, and the voluntary program in Lebanon. Furthermore, the diffusion of contraceptive knowledge and practice is increasing, even in countries without official family planning policies.

In spite of constraints, the health rationale for family planning is being slowly recognized in Arab countries, especially by educated couples. Given the decline in infant and child mortality in most countries, couples will no longer be inclined to have too many children as a safeguard against potential loss. Furthermore, family planning and contraception no longer have the social stigma they had a decade or so ago. Continued discussion of the religious attitudes toward family planning are expected to eventually reinforce the positive stand of Islam on family planning.

CONCLUSION

Family planning is needed in the Arab world for three main reasons: (a) for demographic adjustment in countries with population pressures on limited resources; (b) for safeguarding the health of mothers and children, and (c) for the socio-cultural benefits of having smaller families. While several political, cultural and administrative constraints hinder the diffusion of contraceptive use, the prospects for increasing acceptance in the following decade are encouraging.

CONTRACEPTIVE DEVELOPMENT FOR THE FUTURE

Gerald I. Zatuchni

Contraceptive practice has undergone a revolution in the past 20 years following the developments of oral hormonal contraceptives, plastic IUDs and technological advances in female sterilization. Accompanying this contraceptive revolution was a significant increase in the social and economic environment of many societies. The rights of women and their social status have constantly improved, along with consequent changes in attitudes towards family size. The 1970s witnessed significant progress in the decline of unwanted fertility, and this decline was noted in both developing countries and the more economically privileged ones. It is likely, however, that in 1982 on a global basis no more than 200 million couples (approximately one-third of couples of reproductive age) used some measure of fertility control - traditional or permanent, and including legal or illegal abortion.

In 1982, an estimated 150 million women worldwide had a live birth; another 100 million women suffered a spontaneous abortion or a stillbirth; and 50 million women, legally or illegally, had induced abortions. Repeated national and international surveys indicate the likelihood that 30 to 60% of the conceptions, or 90 to 180 million pregnancies, were unplanned and mostly unwanted. This huge number of unplanned pregnancies occurred due to ignorance of contraception, the unavailability of contraceptive methods presently available. Additionally, another group of about 300 million women worldwide are "at risk" each month having an unwanted or unplanned pregnancy.

Table 1 indicates the estimated use of methods of fertility regulation in 1982. It also indicates the contraceptive use-effectiveness rates. Sterilization of the male or female has become the leading method of fertility regulation. Oral steroids, intrauterine devices, condoms and vaginal barrier methods are also commonly used. Approximately two-thirds of the methods are used by the female, and approximately one-third by the male.

TABLE 1. Methods of Fertility Regulation by Estimated World Use in 1982 and by Use-Effectiveness Rates

Method	Couples (in millions)*		Use-Effectiveness (in %)**
Sterilization	90		
Male (Vasectomy)		35	99.7
Female (Tubal sterilization)		55	99.4
Oral Steroids	48		96
Condoms	46		92
Intrauterine Devices	45		95
Vaginal Barriers/Spermicides	25		88
Withdrawal/Rhythm	?		80
Induced Abortion	50		100

* Estimates obtained from U.S. Agency for International Development and United Nations Fund for Population Activities.
** Mean estimates of various studies

Current contraceptive technology has limitations with respect to the use-effectiveness of the methods, the known health risks, the possibilities of unknown risks particularly after long-term use, consumer acceptability, and continuity of use. Women are more fortunate in the sense that they can choose from a wider range of methods for fertility regulation, but each method has certain disadvantages that limits its appeal and use. In the case of men, short of surgery (vasectomy), a male has only the choices of withdrawal or condom use - neither of which are very acceptable or effective.

In modern times, the almost universal use of contraception in industrialized nations has led to increasing interest in reproductive biology and the application of this new knowledge in turn is leading to the development of more appropriate and more acceptable methods of fertility regulation.

Table 2 presents a list of criteria that must be considered in the development of new methods of contraception. Although the medical criteria of effectiveness, safety and reversibility are highly important, the

other criteria indicated are equally as important with respect to the extent of use of a particular contraceptive. Even the most advanced technological method may not be utilized because of attitudes molded by the religious, social and cultural environment.

TABLE 2. Criteria for Contraceptive Acceptability

Criterion	Contraceptive Characteristics of Concern
Medical	
Effectiveness	Level dependent upon needs of couple.
Safety	No method 100% safe. Risks versus benefits.
Reversibility	Dependent upon life-cycle stage of couple.
Mode of Administration	Oral most useful. Injections preferred in some societies. Vaginal methods not acceptable in some societies.
Personal	Ease of use; freedom from minor side effects, independence from act, male or female application, long-lasting effect from single administration, appropriateness to life-cycle stage.
Cultural	Suitability of method to local customs concerning sex, reproduction, menstruation, etc.
Religious	Catholic attitudes toward mechanical/chemical methods; Islamic attitudes toward menstruation. Religious opposition to abortion.
Sexual	Real or perceived effects upon libido, machismo, pleasure.
Logistical	Distribution through health-care systems or over the counter, availability of supplies and trained persons.
Economic	Manufacturing and distribution costs; costs to consumer; costs to society.
Political	Degree of welcome given to "outside" products. Degree of enthusiasm by government for fertility regulation.

Adapted from Freedman, R. and Berelson, B. The Record of Family Planning Programs. Studies in Family Planning 7:1-40, 1976.

In addition to the above indicated criteria, contraceptive methods must meet certain social-biological requirement that will vary with the life-cycle stage of the couple. An unmarried 18 year-old female, for example, having relatively infrequent intercourse has contraceptive needs that

are quite different from her married 20 year-old sister who may desire to have children, but much later in her marriage. One can appreciate then that, in addition to the highly important characteristics of contraceptives, their eventual use is modified in turn by the particular needs of the individual couple at certain times during their reproductive life. Accordingly, there will never be an "ideal" contraceptive that could meet all the above criteria and at the same time be appropriate for use in stages of a couple's reproductive cycle. Further, when one considers the world with its tremendously differing societies, and the multiplicity of groups within each society, it soon becomes obvious that the greater the variety of fertility regulation methods available, then the more the widespread use will occur.

This chapter will provide descriptions of newer methods of fertility regulation that are currently under investigation and development. Some of the newer approaches are modifications of existing methods, while others represent entirely new concepts in the regulation of human fertility. Each of the research developments will be described in accordance with its intended method of interference with specific reproductive processes.

PHARMACOLOGICAL METHODS THAT INTERFERE WITH SPERM FORMATION, MATURATION MOTILITY OR FUNCTION

A large number of chemical compounds and pharmacologic agents, both steroidal and nonsteroidal, have been shown to cause direct or indirect interference with the process of spermatogenesis. The first chemical compounds tested for their potential application as contraceptives were the nitrofurans, commonly used to treat urinary tract infections. Unfortunately, clinical trials indicated severe untoward effects.

Investigators have noted that alpha-chlorohydrin and other chlorinated sugars exhibit significant decreases in fertility among all animals tested, including sub-human primates. Apparently, these compounds inhibit enzyme activity in the sperm, rendering them less motile and perhaps decrease or eliminate their fertility capability. Unfortunately, these compounds or their metabolites are found in high concentrations in cerebrospinal fluid, and they may inhibit glucose transfer mechanisms; consequently, human use is unwarranted.

Other investigators have utilized the antiandrogen cyproterone acetate in animal studies and in men. Under treatment, sperm lose their motility and fertilizing capacity, apparently due to the epididymal effects of the drug on sperm maturation. However, large doses of cyproterone acetate are required to induce this condition, and these high levels affect other androgen target tissues as well. Other antiandrogenic compounds are under study that would selectively focus activity on the epididymis, seminal vesicles or prostate. Until this can be achieved, the eventual contraceptive use of this class of compound is negated.

It has been known for many years that the administration of certain gonadal steroid hormones will produce oligospermia or even azoospermia. This action may be a result of decreased synthesis and/or release of pituitary gonadotropins, or due to local testicular effects. Varying hormonal agents have been investigated, including estrogens, progestins

and androgens. The estrogens, obviously, are not acceptable for use in the male because of their feminizing effects, and other serious side effects. Progestins, as a group, induce oligospermia, but at doses that also cause suppression of testosterone production. This undesirable effect at the doses required to reduce sperm concentration preclude progestins from being used as single contraceptive agents in the male.

Testosterone, when administered in appropriate dosage and at appropriate intervals does lead to severe oligospermia or azoospermia. This effect is reversible after discontinuation of hormone administration, and even sudden increases in sperm concentration ("rebound" effect) can occur with low levels of administered testosterone. A major research attempt was undertaken to combine testosterone with other hormonal agents, e.g. antigonadotropins (danazol), or progestins. The concept underlying these hormonal combinations was that both agents might act in a synergistic fashion, at low dose levels, sufficient to cause severe decrease in sperm concentration without the production of unwanted side effects. Certain studies have indicated the feasibility of the concept with regard to their synergistic action on spermatogenesis; however, all combinations revealed serious side effects, including libido decline, gynecomastia, and elevated serum transaminase levels.

Steinberger has presented considerable evidence that administration of testosterone, by itself, at appropriate doses and appropriate time intervals will cause azoospermia, and this condition can be maintained for long periods of time. Importantly, the doses of testosterone necessary to achieve this antispermatogenic effect do no need to result in significant elevation of blood testosterone levels. He has been able to demonstrate that the negative feedback of testosterone on LH production and release may allow spermatogenic arrest to occur even in the presence of normal levels of plasma testosterone. Additional studies are required to better define dose-response activity of testosterone administered in a chronic fashion.

According to reports of Chinese investigators, a product found in the pigment glands of cotton-seed, term Gossypol, has been administered to 10,000 men and proven to be highly effective in inducing azoospermia, with a high degree (over 90%) of reversibility when the drug is discontinued. The Chinese came upon this discovery when they noted a high level of infertility among men eating unrefined cottonseed oil. Subsequent epidemiological investigations and laboratory animal studies confirmed that gossypol does severely inhibit spermatogenesis. Unfortunately, major side effects have occurred in some men, and the question of the extent of reversibility still remains an important issue. During the next years, synthetically produced analogs of gossypol may be developed that could cause the desired antispermatogenic effect, but without the other toxic side effects demonstrated in many animal species and in men.

LHRH super analogs

LHRH is a peptide hormone produced in the hypothalamic area of the brain which participates in a major way in normal reproductive physiology, both in the male and in the female. Analogs of LHRH have been synthesized and these analogs possess potencies many more times the activity of the

naturally occurring hormone. The analogs are of two major classes depending upon their activity, agonistic effects or antagonistic effects, on the reproductive axis.

Animal studies with LHRH super agonists indicate that treatment paradoxically results in suppression of spermatogenesis. These synthetic compounds may exert this effect by one or more mechanisms at the central and local levels. Early clinical studies in the human male have determined that LHRH super agonists can suppress spermatogenesis over long periods of time by appropriately administered doses and in a reversible manner. However, the agonists also suppress the production of testosterone with consequent ill-effects. Theoretically, this could lead to decreased androgenization with its accompanying untolerable side effects - loss of hair, loss of libido or even impotence. Accordingly, it may be necessary to combine treatment (contraception) by LHRH super agonists or antagonists with appropriate doses of testosterone.

LHRH antagonistic analogs have been synthesized and tested in the rat. Studies from several laboratories indicate that the antagonistic analogs may be more appropriate compounds for suppression of spermatogenesis. Much research still needs to be accomplished with regard to the efficacy and reversibility characteristics of this approach to male contraception before it can be properly evaluated.

METHODS THAT BLOCK SPERM TRANSPORT IN THE MALE TRACT

Though vasectomy is a simple out-patient surgical technique which can be performed under local anesthesia and is almost 100% effective, acceptance of this procedure by men has been at a low level in most societies. Only in China, India and the United States has this procedure been done in large numbers. Indeed, the number of vasectomies performed in these countries alone account for over 60% of all vasectomies ever done. The acceptability of this simple procedure is greatly thwarted by the machismo attitude prevalent in many cultures; the confusion of vasectomy with castration; the confusion of vasectomy with loss of libido and even impotence; and the lack of easy and effective reversibility should the need arise. Accordingly, new approaches to vas occlusion are being studied with the intent of developing a procedure that would be more acceptable to men.

Non-surgical percutaneous vas occlusion techniques

In 1972, Coffey and Freeman, and other investigators, injected a variety of chemical sclerosing agents into the vas deferens of various animals. Later, a combination of 90% ethanol with 3.6% formaldehyde was selected and injected into ten human volunteers. The technique demonstrated simplicity and a moderate level of efficacy in closing the vas. Davis has improved this technique by injecting a smaller quantity of the ethanol-formaldehyde mixture via a series of multiple site injections percutaneously directly into the vas deferens. Preliminary results indicate that approximately 75% of the men develop vas occlusion, with consequent azoospermia. The technique is being further refined in an attempt to increase the efficiency of the method. Other than hematospermia noted in the first one or two ejaculations post-injection, there have been

relatively few side effects reported.

Several investigators have studied a percutaneous vas occlusion technique that utilizes electrocautery. A specially designed bipolar electrode is inserted directly through the skin, under local anesthesia, and a suitable electrical current is applied. In about six weeks, the cauterized vas undergoes extensive fibrosis and occlusion. Early clinical experiments have delineated the simplicity of this approach, its high efficacy in closing the vas, and a noticeable lack of complications resulting from the procedure. More extensive clinical trials have been started.

Reversible vas occlusion devices

The irreversibility of vasectomy, except in the hands of a highly trained surgeon using an operating microscope, has stimulated investigators to attempt developing various occlusive devices that would be highly effective in shutting off the flow of sperm, and that would be easily reversible, either by removing the occlusion or by the principle of a value arrangement. Scientific and engineering interest has led to the development and implantation in human volunteers of various devices; silicone or nylon threads, a sophisticated valve having the capability of an on-off arrangement, bypass tubular valves, disks of micro-dimensions, polymers, and metalic wires, especially copper ones. The presence of a foreign body in the vas deferens, depending upon its material, may be inimical to sperm motility and/or function.

Currently, no method of reversible vas occlusion has been found satisfactory. Problems have been encountered because of the extremely narrow lumen of the vas, the strong muscular wall of the vas which can cause displacement of the device, the tendency for epithelium of the vas to regenerate causing spontaneous fistulae to develop, thereby by-passing the obstruction, and other technical difficulties. One of the most promising attempts has been a double plug made of polymer connected via a nonbiodegradable polymer suture which is implanted into the vas lumen via two needle injections in the vas deferens. The loop of suture remains external to the vas for later removal should there be a desire to have sperm flow restored. Work on this development is about to reach the stage of human trials, based on promising monkey studies.

METHODS THAT BLOCK SPERM TRANSPORT IN THE FEMALE REPRODUCTIVE TRACT

Vaginal contraceptives

Present available spermicidal preparations are extremely effective *in vitro*. In the human female, however, the use-effectiveness of the spermicides, whether in the form of jellies, creams, foams, or suppositories, leave much to be desired. Much of the reported high failure rates with these types of vaginal preparations is related to their lower rates of *in vivo* spermicidal potency, technical problems with the vehicle used to suspend the spermicide, the short duration of activity (usually less than two hours), and improper use by the woman. Accordingly, several investigators are examining the possibilities of utilizing chemical compounds that interfere with the fertilizing capabilities of sperm rather than trying to obtain a spermicidal effect. A significant number of such com-

pounds - termed sperm enzyme inhibitors, have been studied and found to be more effective than commercially available spermicidal preparations in the animal model. These inhibitors may interfere with sperm motility as well as interfere with enzymes located in the acrosomal cap of the sperm that are necessary for penetration of the egg. Importantly, such compounds have been found effective in extremely small doses.

Other investigators have attempted to develop compounds that would retain their spermicidal potential for longer periods of time - up to 72 hours, when inserted into the vagina. Many problems remain to be overcome due to the absorption propensities of the vaginal mucosa, the effects of gravity when the woman is in the upright position, and the continual daily production of vaginal and cervical fluid which exerts a diluting effect on any chemical.

Vaginal barriers

Vaginal sponges for contraceptive purposes were first prescribed over 3,000 years ago, and consisted of cotton or lint impregnated with lemon oil, honey, and other substances. Natural sea sponge is still in extensive use by women living in the Mediterranean area. As there are virtually no side effects associated with barrier methods, the research questions revolve around increasing their effectiveness and increasing acceptability characteristics.

A barrier contraceptive sponge (Today) made of polyurethane containing nonoxynol-9, has been recently approved by the FDA. Results of early trials have indicated some problems with efficacy (failure rates of 10-12%) and user acceptability. Newer sponges are being developed and will soon be in clinical trials.

Diaphragms, in one form or another, have been available for about 100 years, and until recently, there has been little scientific inquiry aimed at improving the technology. The disadvantages of the diaphragm plus spermicide method are many and well-known. In an attempt to overcome these acceptability and effectiveness problems, several novel types of diaphragms are under development.

Individual investigators and pharmaceutical companies are developing diaphragms in which the spermicidal material, usually nonoxynol-9, is incorporated. When inserted into the vagina, the spermicide is slowly released over hours or even days. These spermicide-releasing diaphragms would be disposable after one-time use. Investigators in Japan are developing a spermicidal-releasing vaginal ring that fits into the vagina in a manner similar to that of the diaphragm. The ring does not act as a mechanical barrier, but merely as the vehicle for spermicide release.

An interesting concept in vaginal contraception is the development of polymer materials that include spermicide, and are then manufactured into a shape resembling a condom. The plastic film is water soluble. The film is draped over the penis, and upon intromission, the film dissolves in the vaginal fluids, thereby depositing an effective dose of spermicide in the posterior fornix and around the external os. Clinical trials with this water-soluble, spermicidal condom are soon to get underway.

Cervical cap

Unlike the diaphragm, which blocks the upper part of the vagina, the cervical cap only blocks the cervix. Cervical caps have been made of metal or rubber, and most recently of polyethylene or latex. A major advantage of the cervical cap is its potential usefulness in women with uterine prolapse, the absence of need for a spermicidal preparation, and the potential for long-term use.

Currently undergoing large scale clinical trials is a cervical cap, made of latex, that is custom-fitted to the women's own cervix. An impression is made of the cervix, similar to a dental impression, and the latex is molded to this impression. The resulting cervical cap is quite thin and has a flap valve. The cap is placed over the cervix and is held there by the suction-like effect of the thin layer of fluid between the cap and the cervix. Theoretically, the flap valve permits menstrual blood to escape, but does not permit spermatozoa to enter the cervical canal. Preliminary studies have indicated the potential for this type of barrier method, but only large-scale clinical trials will answer the important questions of acceptability and use-effectiveness of the method.

Intracervical devices (ICDs)

Though the major antifertility effect of progestational hormones (progestins) is the suppression of ovulation, many studies have demonstrated that these compounds also interfere with the production of cervical secretion, thereby exerting a local (cervical) antifertility effect. Progestins administered orally or released from implants in microdose quantities do effect the physical characteristics of cervical mucus (fernıng, viscosity, and spinnbarkheit) and chemical characteristics of the mucus with respect to its content of enzymes, electrolytes and proteins. Accordingly, several research developments are underway to investigate intracervical delivery systems that would release microgram quantities of progestins daily over long period of time. The intracervical device is merely the vehicle for release of drug, and does not serve the purpose of acting as a mechanical barrier to sperm transport through the cervix. (See Chapter 17.)

Transcervical approaches for female sterilization

Recent advances in the techniques and instrumentation of hysteroscopy, and improvements in laparoscopy, have stimulated new interest in the attempt to seek out the uterotubal junction and apply one method or another in order to cause obstruction to sperm transport from the uterus to the Fallopian tubes.

One of the first attempts to cause uterotubal occlusion was by a "blind" approach with an electrocautery instrument. More recently, the uterotubal junction has been electrocoagulated under direct vision by hysteroscopy. A large-scale clinical trial performed in over 500 women indicated, however, that the failures and complications associated with this procedure were too high for further human studies. Nevertheless, a few investigators have continued to use this method and claim a very high effectiveness rate and a very low complication rate.

Instead of electrocoagulation, another investigator has attempted to cause necrosis and subsequent scarring of the cornual areas of the uterus by using cryosurgery. Preliminary animal studies and some human investigations have indicated the remarkable regenerative powers of that portion of endometrium.

A large number of investigations have been carried out in animals and in humans in an attempt to find an appropriate chemical that would cause tubal scarring and closure when administered transcervically. Despite the large number of available compounds that can cause tubal epithelial necrosis, problems have existed with each of them regarding their potential toxicity if delivered into the systemic circulation, and/or their possible peritoneal effects if the compound leaked out the fimbrial end of the tube. Actually, only two compounds are still under investigation at this time. The first of these is an anti-malarial drug, quinacrine, which has been extensively utilized as a fallopian tube occlusive agent by Zipper.

The second chemical that offers promise is methylcyanoacrylate (MCA), a tissue adhesive. This compound causes acute inflammation when applied to epithelial structures, and the inflammation leads to necrosis and fibrosis. Recently, a uniquely engineered delivery system has been developed (FEMCEPT Device) that delivers 0.6 ml of MCA to the tubal lumen. (See Chapter 22.)

Reversible methods of obstructing the uterotubal junction

A team of investigators have developed a possibly reversible occlusion technique that utilizes silastic as a viscous liquid instilled into the Fallopian tubes under hysteroscopic control. Polymerization occurs rapidly and a tubal plug is formed. Early results indicate excellent effectiveness, although major technical problems remain to be solved. Results are yet too preliminary to comment upon the long-term effectiveness of the procedure in preventing conception on the one hand, and the possibilities for reversal when the silastic plug is removed years later.

Occlusive devices made of solid inert materials that are inserted into the uterine ostia of the Fallopian tubes, under hysteroscopic guidance, are being investigated by several researchers. One of the most promising devices is the Uterotubal Junction Device (UTJD), which is a polyethylene plug, approximately 10 mm in length, having four metallic spines attached to the base of the plug. The spines fix the plug in place in the tubal opening by penetrating the adjacent myometrium. Extensive testing in baboons and in a few women indicate that the devices do consistently block sperm transport when properly inserted. Furthermore, at least in baboons, fertility is restored upon simple removal of the device. Early clinical trials have just started, but certain technical problems need solution prior to more extensive trials.

INTRAUTERINE CONTRACEPTION

Much of the present research on intrauterine contraception centers around improvement of the method regarding effectiveness, bleeding, pain and expulsion.

Contraceptive effectiveness

The basic mechanism(s) of contraceptive action of intrauterine devices is incompletely understood and, hence, a completely effective device cannot be designed except by trial and error. Presently available copper IUDs are associated with high effectiveness rates when the device is in the proper uterine position. Accordingly, there is little room for improvement in this parameter. Affecting rates of contraceptive effectiveness is the duration of action of an IUD. Non-medicated IUDs possess long-term contraceptive effectiveness - perhaps for the entire reproductive age of the woman. On the other hand, presently available copper IUDs have a lifetime use of about three to five years. This is so because the copper wire used in these devices fragments after some years in the uterine cavity. This fragmentation is quite variable from individual to individual, and cannot be predicted. New forms of copper IUDs are in large scale clinical trials and these devices have been developed to avoid the necessity for changing the IUD every three years. Preliminary, but extensive, studies with these new IUDs indicate that the addition of a copper sleeve(s), rather than copper wire, does extend the long-term use to ten or more years.

The duration of action of a hormone-releasing IUD is dependent upon the nature of the steroid, the reservior, and the type of IUD carrier. The use of potent progestins, for example, levonorgestrel, in a suitable IUD reservoir provides much longer duration of action than the presently available progesterone-releasing IUD, which must be changed annually.

Bleeding

The major unwanted side effect of IUD contraception is bleeding, probably accounting for over half the IUD discontinuance rate. The bleeding is rarely sufficient to cause anemia, except in malnourished women where the IUD-induced blood loss can aggravate an underlying anemia. The cause of the increased menstrual bleeding and intermenstrual spotting is unknown. (See Chapter 14.)

Expulsion

The major factor influencing retention of an IUD is the geometry of the device - its size, shape and configuration, all of which must be in concordance with the geometry of the particular intrauterine cavity. The efficiency of this relationship is best summarized in the measurement of expulsion rates. Many subfactors, however, also influence this important relationship; age, parity, anatomical variations, racial differences, and characteristics of the device itself.

Hasson has developed a measuring device that can provide the exact dimensions of the endometrial cavity, including its geometric shape. Use of this device offers promise of better fitting of IUDs in the particular woman, with expected consequent improvement in expulsion rates, and perhaps improvement in discontinuance due to cramping pain and/or bleeding. (See Chapter 15.)

Research efforts are underway to utilize presently available IUDs or

develop special IUDs for special uses. For example, a loop has been redesigned to provide excellent retention characteristics when inserted into a postpartum uterus immediately following delivery of the placenta. Biodegradable devices are being considered for short-term use extending over a period of several months. Standard devices are being utilized as post-coital contraceptives in those women who have had unprotected intercourse.

Future systems may include agents or drugs that would exert fertility-inhibiting effects much beyond those of available IUDs. Certain substances, e.g. quinacrine, could be loaded onto an IUD and its subsequent release could cause tubal inflammation and eventual fibrosis at the site of entry of the Fallopian tube into the endometrial cavity. It is also possible for certain drugs known as luteolytic agents to be housed on an IUD and released in minimal daily doses, causing interference with corpus luteum function and/or decidualization. More effective intrauterine contraception may be provided by the incorporation into an IUD of various immunological or spermicidal agents that would interfere with sperm motility or capacity for fertilization. The incorporation of antifibrinolytic agents, e.g. epsilon aminocaproic acid, or trasylol, or inhibitors of prostaglandin synthetase, may prevent or considerably decrease the bleeding associated with IUD use. (See Chapter 14.)

LONG-ACTING CONTRACEPTIVE DELIVERY SYSTEMS

A major approach to improving the effectiveness, safety, and acceptability of steroidal contraceptives is to develop long-acting preparations and delivery systems that can provide continuous medication at minimal daily doses. These minimal doses must be sufficient to obtain therapeutically effective blood levels in order to suppress ovulation or spermatogenesis. Two different developments have taken place in the attempt to achieve minimal intervention fertility control - a pharmacologic approach, represented by injectable steroids having intrinsic chemical properties which provide for slow release, and the bioengineering approach which utilizes inert drug carriers to control the rate of drug release. The delivery systems have assumed a variety of forms, including injectable depot formulations, injectable or implantable biodegradable capsules and rods, nonbiodegradable subdermal and intrauterine systems, and other medicated devices to be inserted into the uterus, vagina, or cervix. (See Chapter 3.)

Injectable long-acting steroids

Approximately twenty progestins have been studied as long-acting compounds in the female. The injection regimen has varied from two months to six months, depending upon the formulation of the depot preparation and the characteristics of the steroid itself. In most series, complete inhibition of fertility does result as long as there is a sufficient blood level of the steroid present to inhibit ovulation. The injectable progestins are convenient and easy to administer. Because they contain no estrogens, the well-known side effects due to estrogen are eliminated. Although the advantages are excellent, the disadvantages are that treatment cannot be immediately reversed; there is a high incidence of abnormal bleeding, leading to amenorrhea in many women; there is some question

about how soon the woman can return to a state of fertility following the last injection. (See Chapter 4.)

Non-biodegradable implants

Silastic implants impregnanted with a variety of steroids and inserted, via a small skin incision, into the subdermis of the arm or leg have been studied from contraceptive effectiveness and consumer acceptability points of view.

The in vivo release profiles are similar for most progestins when the implant is made of silastic; namely, a rapid, but decreasing rate of release for the first two or three months, followed by a much slower decline in the rate of release. Individual variation among subjects treated with identical silastic implants may not be a solvable problem.

Silastic implants containing progestins are effective in preventing pregnancy, although the dose release is erratic and can lead to irregular menstrual cycles, amenorrhea, or irregular bleeding. The implants are retrievable, although with difficulty. The question of consumer acceptability seems to be paramount in whether this novel method of long-term contraceptive administration will become popular. (See Chapter 12.)

Biodegradable contraceptive systems

Copolymers, containing various percentages of lactide and glycoclide have been blended with levonorgestrel, a long-acting steroid. The mixture is extruded into rod shapes for implantation under the skin. In vivo, the steroid is released at constant daily rates by both diffusion of the steroid through the polymer and by bioerosion of the polymer. Prototype systems have been developed that will release steroid for long periods of time - up to eight years. The duration of activity is dependent upon the molecular weight of the polymers, the dose loading of the steroid and the characteristics of the steroid itself. The advantage of the system is the complete biodegradation of both the system and the steroid over a known period of time. The rod system can be retrieved, however, but with difficulty.

Another type of biodegradable system has been developed consisting of an injectable steroid in the form of a microsphere. The prototype 3 and 6-month system consists of microspheres made of a biodegradable polymer, polylactic acid, in which micronized crystals of norethindrone are homogenously dispersed. (See Chapter 11.)

IMMUNOLOGICAL APPROACHES FOR FERTILITY CONTROL

Anti-pregnancy immunization

Much research is being directed toward the acellular, gelatinous layer surrounding the ovum - zona pellucida. The zona is essential for sperm recognition and attachment prior to fertilization. The zona has a number of proteins (antigens) that could be utilized to induce antibody formation and consequently immunologically prevent attachment of the sperm and/or fertilization. The feasibility of this approach has been eluci-

dated by using antigens derived from pig zona and these antigens are effective cross-species. For example, dogs and marmosets have been actively immunized with antigens obtained from pig zona, with consequent interference in the process of fertilization.

The placenta is a rich source of antigens which are present within the woman for a brief period, and are in general, "non-self" components, thereby lending themselves to the potential development of an antipregnancy vaccine. There are at least three placenta-specific soluble proteins exhibiting hormonal activity, and quite a few more non-hormonal compounds that have been isolated. Of the identified placental hormones, most research in the field of vaccine development has been carried out with chronic gonadotropin.

hCG is a placenta-specific hormone that is initially elaborated by the fertilized ovum in order to provide gonadotropin support to the corpus luteum in early pregnancy. The corpus luteum in turn produces progesterone and estrogen. Following implantation, hCG is produced by the cytoplasm of the syncytiotrophoblast. Experimental studies in several animal species indicated that antibodies raised to hCG were effective in neutralizing the activity of the hormone. Because of the overlap with LH, antibodies were raised to the beta-subunit of the hCG molecule, which allowed no cross-reactivity with LH. As the beta-subunit of hCG is a weak antigen, a unique linkage with tetanus toxoid was developed. When this combination was injected into primates, the antibody response to both the beta-subunit and tetanus toxoid were of high order, at least initially. Unfortunately, later studies in female volunteers indicated that beta-hCG antibody levels were not sufficiently high to provide long-lasting immunization. Another investigator has attempted to increase the efficiency of the immunization mechanism by utilizing a small portion of the beta-subunit of hCG. These peptides, consisting of 30-45 amino acid residues, also were only weakly immunogenic.

Sperm antigens

Antibodies to sperm can be detected in serum of females and males. Following vasectomy, sperm antibodies can be found in the male in the majority of instances. Whether "naturally" occurring antibodies to sperm play a role in the development of infertility remains a topic of serious controversy. Nevertheless, as demonstrated in many animals experiments performed during the past 50 years, and in some clinical situtions, antibodies to sperm antigens that exist in the female genital tract can cause infertility by somehow interfering with sperm motility and/or function.

In the past ten years, several sperm antigens have been isolated and characterized. One in particular, known as lactic dehydrogenase (LDH-C_4), has been isolated from sperm cells of several species. Antibodies raised to this enzyme will react with intact sperm cells and such sperm have evidenced reduced fertilizing capacity. Interestingly, sperm LDH-C_4 appears to exist among several species, so that antibodies raised aginst LDH-C_4 obtained from mouse sperm can provide an antifertility effect when injected into female rabbits or baboons.

All of the above immunological approaches, and others not discussed, will

require many more years of research and clinical studies before any of these fertility control methods could be approved for general use. The research questions revolve not only around efficacy of this antifertility approach, but most importantly, revolve around the issues of unknown, long-term potentially serious side effects. The major question of reversibility of the infertile state following successful immunization also needs resolution. In addition to these concerns with safety, a host of technical problems remain to be solved in the development of appropriate and useful anti-pregnancy vaccines. Finally, our basic understanding of the entire immunological system is rudimentary at best. Accordingly, it will take years of fundamental research and new knowledge in this area in order to develop, in a systemic fashion, an effective, reversible, and safe vaccine.

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PHARMACOLOGICAL ASPECTS OF SLOW-RELEASING STEROIDAL SYSTEMS

Lee R. Beck

The discovery of synthetic materials that are both histocompatible and biodegradable opened a new vista in the search for long-acting steroidal contraceptives. Programmed delivery of contraceptive steroids had its origin in the early 1970s with the discovery that histocompatible polymers in the form of subdermal implants could be utilized to achieve slow release of steroid hormones. This led to the development of medicated contraceptive systems of various types including Silastic implants, medicated intrauterine, intracervical and intravaginal devices, and biodegradable implant and injectable formulations.

The rationale for programmed delivery is to improve the safety, effectiveness and acceptability of conventional contraceptives by more efficient utilization. The biological response to hormonal stimulation is dose-dependent. It follows, therefore, that the degree of risk cannot be considered independent of the dose and method of administration of the drug. The optimal dose and method of delivery is one that evokes effective fertility control with minimum therapeutic intervention. The concept of minimal intervention fertility control and how it might be achieved through programmed delivery is illustrated in Figure 1. The curves compare the blood levels of the hypothetical steroid following conventional and improved delivery. For this example, conventional delivery is by the oral route, and improved delivery is by the use of an injectable formulation which provides programmed release. The blood level of the drug dose necessary for contraception is represented by a

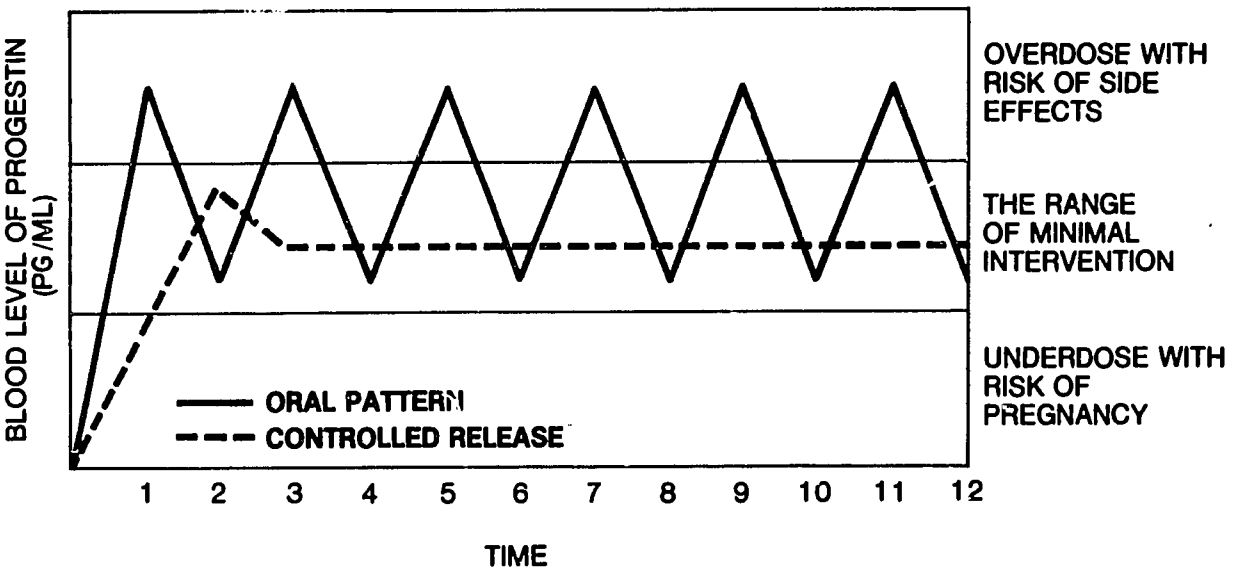

FIGURE 1. Serum levels of a hypothetical steroid following oral ingestion and programmed delivery.

narrow zone. Doses in excess of the optimal therapeutic range constitute overmedication with potential for dose-dependent side effects; whereas, doses below the effective range can result in contracpetive failures. Minimal intervention fertility control occurs when the steroid is maintained within the therapeutic effective range. Oral administration results in immediate high blood levels that decrease with time and repetitive doses must be given at frequent intervals to keep the blood levels within the effective zone. This results in blood steroid fluctuations, the peaks of which exceed what is necessary for contraception. The programmed delivery system meters the steroid into the blood at a controlled rate designed to maintain the blood level in the desired range, thereby achieving minimal intervention fertility control. Controlled release allows for reduction of the total amount of steroid administered over a prolonged period of time and reduces the chance of human error by eliminating the need for repetitive self-administration.

Two different approaches have been used in the attempt to achieve minimal intervention fertility control. The pharmacological approach represented by injectable steroidal formulations relies on the pharmacological properties of the drug to achieve slow release. The properties include solubility in the drug in the body fluid at the injection site, affinity for receptors in the body fluid and tissues, and rate of metabolism and excretion from the body. The systems engineering approach utilizes inert drug carriers to control the rate of the drug release. Although the degree of control may vary from one carrier to the next, the systems approach can be distinguished from the pharmacological approach on the basis of a controlled-release mechanism which is neither a body nor drug component.

Long-acting steroidal contraceptive systems can be further classified as those designed for systemic or local delivery. The implant and injectable systems as well as medicated intravaginal devices are designed for systemic delivery; whereas, medicated intrauterine and intracervical devices are intended for local delivery. The rationale for local delivery is to reduce the steroid load even further by direct delivery to the target organ. This completely avoids the possibility of systemic side effects.

Injectable Depot Formulations

The first contraceptive steroids were synthetic progestogens which had to be administered at frequent intervals because they had short biological half lives. The synthesis and screening of new compounds led to the discovery of structures having longer durations of action which made administration by injection an attractive alternative to oral contraception.

Two progestogens, medroxyprogesterone acetate (MPA) and norethindrone enanthate (NET-EN), emerged from this early work promising injectable formulations. Upjohn Pharmaceuticals developed MPA under the trade name Noristat. Other progestogens which have been administered by injection include hydroxyprogesterone caproate (Delalutin, Squibb), dihydroxyprogesterone acetophenide (Deladroxate, Squibb), levonorgestrel unducylate (Schering AG), and levonorgestrel nonanoate (Schering AG). Clinical experiments with these compounds are presented in other chapters of this book.

The injectable progestogens are effective, convenient, easy to administer, do not inhibit lactation, free the patient from having to remember to take medication on a daily basis, and are free from side effects of estrogen. The disadvantages are as follows: treatment cannot be immediately reversed; there is a greater incidence of irregular bleeding; there is possible delay in return to fertility; self-administration is impossible; and there is a limited choice of compounds available for use.

The most significant shortcoming of the injectable progestogens is the poor linear release profile. The initial blood levels of NET far exceed that which is necessary for effective contraception. There is a gradual decline during the first few weeks post-treatment before the deposited progestins pass through the zone of minimal therapeutic intervention. Slow release in this instance does not satisfy the concept of minimal intervention fertility control.

Although there is little doubt that the approach is extremely attractive, the role of the injectable progestogens remains uncertain. At present the choice is limited to only a few compounds, and although the search is ongoing, new compounds having more acceptable release profiles are not yet available.

Subdermal Implants

The evaluation of contraceptive implants which utilize an inert carrier to control the rate and duration of drug release began in 1964, with the

discovery that silicone rubber can be used as a carrier for prolonged drug therapy.

Subdermal Silastic implants impregnated with megestrol acetate (MA) were shown to be effective in preventing pregnancy in early clinical trials. The original aim for the implant was to administer a daily dose of progestin sufficient to inhibit fertility without interference with normal ovarian function. High pregnancy rates with single implants prompted the use of multiple devices in order to achieve higher blood levels of the progestin and longer durations of release. Four capsules provided 9 to 10 months protection; five capsules 12 to 15 months; and six capsules, 18 months.

The contraceptive effectiveness and acceptability of Silastic subdermal implants containing either levonorgestrel or norgestrienone have been compared in a multi-national clinical trial. Four hundred ninety-two women treated with levonorgestrel capsules (180 mg) had a cumulative 12-month pregnancy rate of 0.6% and a continuation rate of 74.6%. Four hundred ninety-eight women treated with norgestrienone capsules (180 mg) had a cumulative 12-month pregnancy rate of 3.5% and a continuation rate of 79.4%. The major side effect for both steroids was irregular bleeding patterns. The rates of termination due to bleeding irregularities were 12.3% for levonorgestrel and 6.3% for norgestrienone.

Norethindrone was found to be ineffective in preventing pregnancy using up to 12 implants containing 20 to 30 mg of NET each. Gestrigone (R-2323), delivered by Silastic implants, is effective in preventing pregnancy. However, it has been excluded from further use as a systemic contraceptive because it has been shown to elevate transamidinase levels in Chilean women.

The 19 norsteroid ST-1435 has a high rate of in vivo release from Silastic capsules (40 mg/cm/day) and provides effective contraception when used as a single implant. The rapid rate of release, however, limits the duration to less than one year.

Lynestrenol has in vivo release rates from Silastic capsules even greater than ST-1435 (i.e., 60 mg/cm/day), and studies have been discontinued because of rapid release.

Silastic capsules, 22 mm long containing 40 mg of norethindrone acetate which have an in vivo release rate of 128 ug/NET/day, provide protection against pregnancy for approximately 10 months. The short duration of effect represents a disadvantage compared to other longer-acting implants.

The in vivo release profiles are similar for all progestins: rapid decrease in rate of release for the first 50 to 100 days followed by a much slower rate in decline. The plasma levels of the progestins delivered from Silastic implants vary as much as threefold between individual subjects treated with identical implants.

In general, it can be concluded on the basis of the clinical studies that Silastic implants containing synthetic progestogens are effective in pre-

venting pregnancy and represent an acceptable form of contraception for some populations. The duration of effect is dependent on the rate of release of the steroid from the Silastic capsule. Accordingly, steroids having higher rates of release have corresponding short durations of action; whereas, steroids having lower rates of release, have longer durations of action but require multiple implants in order to deliver effective daily doses. If one balances the number of capsules necessary to give contraceptive protection against duration of release and side effects, levonorgestrel and norgestrienone appear to be the most attractive steroids for use in subdermal Silastic implants. Levonorgestrel is a more effective contraceptive. However, the incidence of irregular bleeding is significantly greater for levonorgestrel than for norgestrienone.

The use of Silastic rods instead of capsules to obtain higher rates of levonorgestrel release reduces the incidence of breakthrough bleeding and increases amenorrhea. The estimated in vivo release rate from rods is three to four times greater than from capsules. Bleeding irregularities can be controlled to some extent by adjusting the daily dose of the progestogen. There is also some evidence to suggest that the incidence of intermenstrual bleeding decreases with time. Successful use of subdermal implants on a wide scale will require effective management of bleeding problems that will arise unless more effective systems can be developed. One possibility for achieving better bleeding control which is currently under investigation is to include estradiol in the implants.

The Norplant, which has been developed and tested by the Population Council, is Silastic subdermal implants that contain levonorgestrel. Six implants each of which contain 36 mg of levonorgestrel are implanted in the arm using a trocar. The release rate is approximately 50 ug/day for the first year, 30 ug/day for the second year and remains constant for the next 4 years. (See Chapter 12.)

Subdermal dimethylpolysiloxane implants containing potent progestogens in the form of capsules and rods have been shown to provide effective contraceptive protection without serious side effects. The advantages of Silastic subdermal implants over oral contraceptives are as follows: (1) the improved therapeutic dose; (2) continuous constant release for periods of up to one year or longer; (3) the necessity of only one administration; (4) lack of vehicle discomfort; (5) reliability of administration; (6) rapid return to ovulation upon removal; (7) easy reversibility; (8) avoidance of liver portal circulation; and (9) avoidance of intermittent single bolus stimulation of the liver.

The main shortcomings of Silastic implants are as follows: (1) because they have limited surface area as many as six or eight devices are required to provide effective blood levels of the contraceptive drug, (2) since silicone rubber is not resorbed by the tissue, the spent devices have to be removed surgically, (3) variation in solubility of different synthetic steroids limits the choice of progestins that can be delivered by this route; and, (5) significant variation occurs in the blood levels of individual subjects treated with identical devices.

Medicated Intrauterine Systems

Medicated intrauterine systems represent a major advance toward achieving minimal intervention fertility control. The medicated IUD represents the first steroidal contraceptive system to focus on local, rather than systemic, delivery. The rationale for intrauterine steroids is based on the principle that progestogens delivered directly to the uterine lumen in low doses will act directly on the uterine mucosa inducing changes in the endometrium which prevent implantation. Supposedly, this can occur without influencing normal ovarian function and/or other systemic effects.

This concept grew out of the earlier work on subdermal implants and the related development of controlled release delivery systems. The first medicated intrauterine system were modeled after subdermal implants. Doyle and Clewe were the first to test a steroid-releasing intrauterine device in animals.

Alza Pharmaceutical Company was the first to launch a comprehensive program to develop a long-acting steroidal intrauterine contraceptive system. This led to the development of the Progestasert, a T-shaped IUD, which delivers 65 ug of progestogen per day for 365 days. The Progestasert represents a major advance toward minimal intervention fertility control. Up until this time all controlled-release devices had high initial rates of release that decreased in linear fashion with time; whereas, the Progestasert provides a constant rate of release for the life of the unit. In order to achieve this degree of control, advanced technology in polymer chemistry was focused on the problem of developing a polymeric membrane capable of providing a constant zero order rate of progesterone release with a high degree of precision and constancy. Several prototype systems having different rates and durations of release were developed and tested in animals. The system selected for human trial was a T-shaped device having a 36 mm vertical stem and a 32 mm transverse arm. The transverse arm contained 32 mg of crystalline progesterone in medical grade silicone oil and barium sulfate. The polymeric diffusional rate-limiting membrane consisted of a polymer of ethylene vinyl acetate containing titanium dioxide. The rate of progesterone release from the device was 65 ug/day for a duration of 12 to 18 months.

Many studies have evaluated contraceptive effectiveness, acceptability, side effects and mechanism of contraceptive action of Progestasert. (See Chapter 14.)

Intrauterine progesterone at dose levels insufficient to inhibit ovulation has been shown to have a wide spectrum of effects including the induction of morphological changes in the endometrium and oviduct; alteration of sperm capacitation properties of uterine fluid; alterations in prostaglandin concentrations of endometrium and menstrual blood; changes in biochemical, enzymatic, and trace elements in the endometrium; alteration of the ovarian hormone levels; reduction in menstrual blood loss; and inhibitory effects on embryo development and transport. The exact mechanism and/or combination of mechanisms which inhibit fertility is not known.

The need to change the Progestasert annually is considered a disadvant-

age, and this has motivated the use of potent synthetic progestins as the active principal. New intrauterine devices that release progesterone for three years are being tested by the World Health Organization, and plans have been made to test devices that release levonorgestrel at the rate of two mg/day. Theoretically, these devices will have effective life spans of five years or greater. (See Chapters 16 and 17.)

In spite of the initial promise, the medicated IUDs have not been widely accepted for good reason. The design of the device offers no advantage over conventional bleeding, pain, and uterine perforations. If the medication is taken away, what remains is a conventional IUD with all of its inherent problems. The original intent for the medicated intrauterine system was to rely on the medication for contraceptive effect, thereby affording greater flexibility in design of the device itself. Unfortunately, there has been little effort to design smaller, less troublesome IUDs for use as intrauterine drug-delivery systems. If intrauterine progestin alone is enough to inhibit fertility, without synergistic effects of the device, then it should be possible to design devices of novel form free of those side effects which characterize conventional IUDs.

Medicated Intravaginal Systems

The rationale for the MIVD is based on the knowledge that steroids rapidly penetrate the vaginal mucosa, and that foreign bodies of considerable size can be left in the vagina for long periods without discomfort. The possibility of intravaginal contraception became apparent with the discovery that Silastic rubber can be used to achieve controlled-release of steroids for extended periods of time. The entire area of vaginal rings is presented in another chapter of this book.

The major advantage of the MIVD over other types of controlled release steroidal contraceptive systems is that the treatment is self-administered and reversible at will. Although self-administration may be an advantage in populations where motivation and compliance is good, it may be a distinct disadvantage in populations with poor motivation. Sanitation and proper care of the device may also present problems. Better design of the system may help to improve acceptability. For example, systems designed for disposal after a single insertion would eliminate sanitation concerns. Biodegradable systems might help to improve acceptability because they can be left in place, thereby eliminating responsibility of the user to remove and care for the device.

Biodegradable Systems

The use of biodegradable polymers for the programmed delivery of steroid hormones represents a major advance in contraceptive technology, the full impact of which is yet to be realized. On the surface there is the obvious advantage that biodegradable systtems comprising drug polymer combinations eliminate the need for device removal following use. An underlying and more significant consideration is that the use of polymers that biodegrade allows for greater flexibility in systems design.

There are three basic types of biodegradable systems under current deve-

lopment that differ in structure, method of administration and mechanism of drug release (Figure 2). Capsules and rods are designed for implanting under the skin, and small particulate systems are designed for injection. The capsule or reservoir devices have an outer shell surrounding a central drug core, whereas the rods or monolithic devices are solid structures with drug homogeneously dispersed throughout the matrix of the device. In order to distinguish between the small spherical reservoir devices and small spherical monolithic devices, we use the term microsphere for the reservoir configuration and microsphere for the monolithic

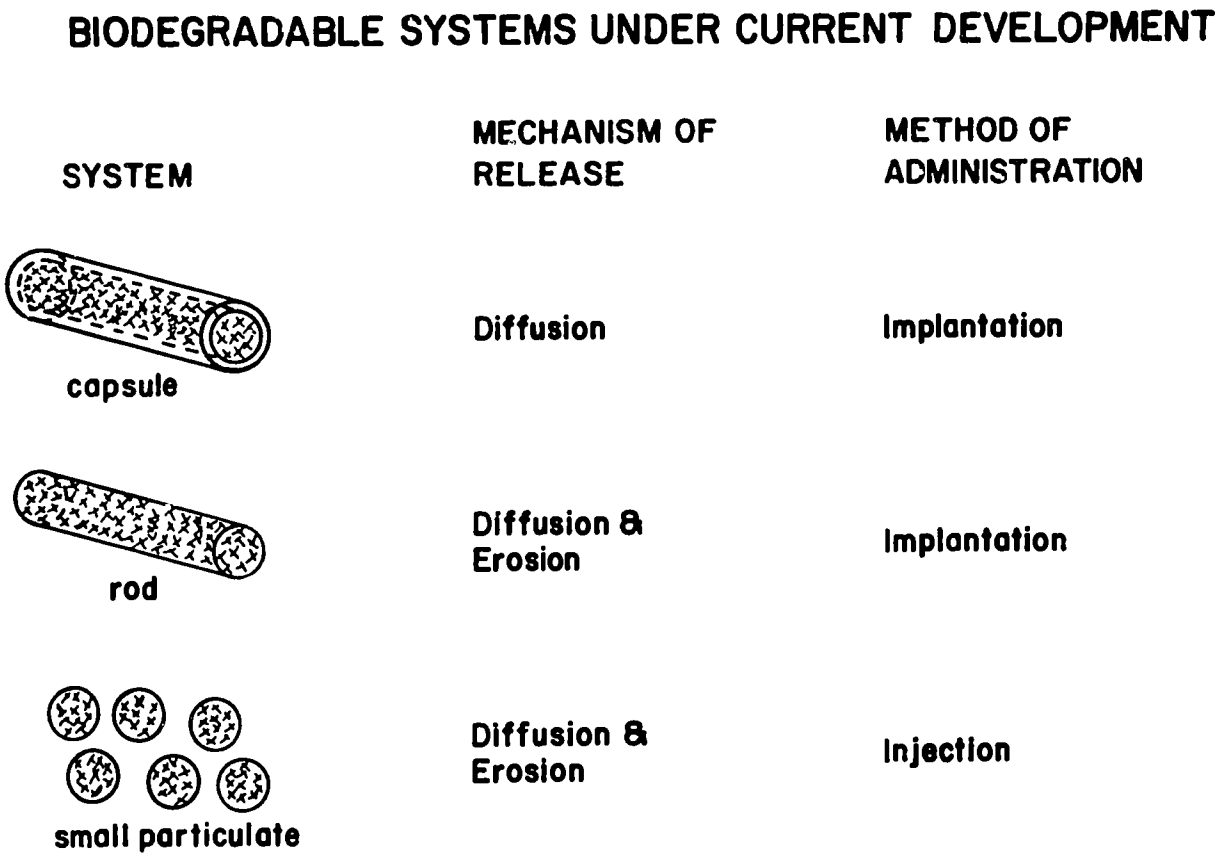

FIGURE 2. Structure and administration of biodegradable systems under current development.

form. In the past the term microsphere has been used to describe small spherical systems in general. Reservoir devices in microcapsular form are designed to release drugs from the reservoir by diffusion across the capsule wall. For this to occur, the drug must be soluble in the biodegradable material used to formulate the capsule. Controlled release cannot occur in the absence of an intact outer wall. Accordingly, the rate of biodegradation of the capsule wall must not exceed the duration of drug release. Pitt and associates are using polycaprolactone capsules implanted subcutaneously to deliver levonorgestrel and norethindrone for periods ranging from 6 to 12 months. The prototype system is designed

to release the drug at a constant rate for up to 12 months after which the empty capsules biodegrade. These are large capsules which are implanted subcutaneously.

Monolithic devices in the implant or injectable form can release drug by diffusion and/or erosin. The mechanism of release depends on the solubility of the drug in the polymer and/or the rate of biodegradation of the polymer. Alza Pharmaceutical Company has developed a synthetic polymer called Chronomer which erodes at a constant rate in vivo. Implantable monolithic devices in the form of rods made of this polymer are being used to deliver norethisterone and levonorgestrel. The prototype system has a 3-month duration of drug release in vivo. The steroids are not soluble in the polymer. Accordingly, bioerosion is the sole mechanism of drug release from Chronomer polymer. Work on this sytem was discontinued due to adverse reactions at the site of implantation.

In a program sponsored by PARFR, Dynatech Research Corporation has developed a biodegradable implant which consists of a co-polymer containing 90% lactide and 10% glycolide blended with 50% by weight levonorgestrel. The mixture is extruded into rods designed for implantation under the skin. Following implantation, levonorgestrel is released at a constant rate by diffusion and bioerosion of the polymer. The prototype system has a duration of levonorgestrel release in vivo of approximately 8 years. The low rate of release requires the use of multiple implants to achieve adequate daily doses. Work is currently under way to increase the rate of release and shorten the duration.

The Department of Obstetrics and Gynecology at the University of Alabama in Birmingham and the Biosystems Division of Southern Research Institute have been engaged in a continuous program of research to develop and perfect a biodegradable microsphere (monolithic) contraceptive delivery system.

The system consists of small particles of a biodegradable polymer (d,l-polylactic acid) in microsphere form, which contain 20% by weight crystalline norethisterone homogeneously dispersed throughout the matrix of the microspheres. Figure 3 shows a scanning electron micrograph of typical norethisterone made by a solvent evaporation process. The microspheres vary in diameter and the relative size distribution can be controlled to some extent during the manufacturing process. The size fraction of a microsphere comprising a dose is an important consideration because the rate and duration of drug release is dependent on the surface area of the microspheres. (See Chapter 11.)

The rate and duration of NET release from the prototype microsphere formulation are dependent on the drug loading and the size of the microspheres. The smaller particles have faster rates of NET release. We have shown that it takes approximately one year for DL-PLA microparticles to biodegrade. Accordingly, a build-up of DL-PLA occurs following repeated injections. Theoretically, this could be avoided, at least in part, by substituting polymeric excipients that afford microspheres having similar NET release kinetics but that biodegrade faster. This prompted us to develop second-generation microsphere formulations that biodegrade within 6 months. Reduction in biodegradation time, without compromising

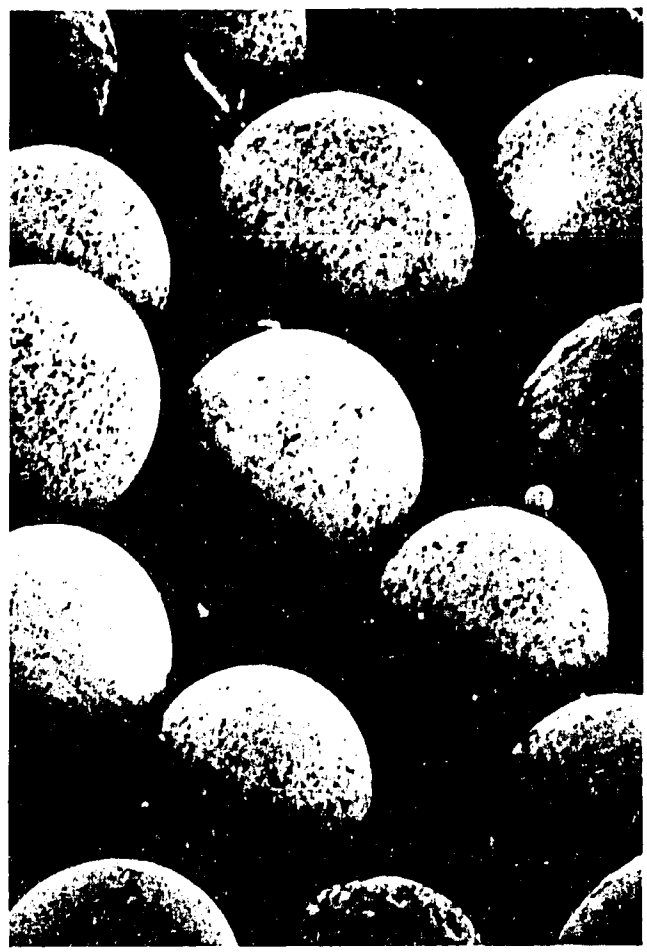

FIGURE 3. Scanning electron micrograph showing d,l-polylactic acid microspheres containing 20% by weight norethisterone.

the NET release kinetics, was achieved by using a copolymer consisting of DL-lactide and glycolide in lieu of DL-lactide alone. The result is an improved formulation that has utility as either a 3- or a 6-month injectable contraceptive.

Microspheres made from a biocompatible, biodegradable polymeric excipient, poly(DL-lactide-co-glycolide) (DL-PLGA) that contained 22 wt percentage norethisterone (NET), were prepared by a solvent-evaporation microencapsulation process. NET microsphere formulations have been identified for clinical testing which releases NET for 3 months and biodegrades completely within 6 months.

Pharmacokinetics and pharmacodynamics of the second generation long-acting injectable microsphere delivery system were tested in 10 women. Two doses of the microsphere formulation contains either 150 ro 200 mg of NET were administered by intramuscular injection on Day 5 of the menstrual cycle. Treatment suppressed ovarian function and inhibited ovulation in all subjects for three months. Norethisterone serum could be detected for 20 weeks post-treatment. Norethisterone levels in subjects that received the higher 200 mg dose were proportionately greater

than those who received the lower 150 mg dose. Following injection there was a rapid rise in the NET serum levels followed by a gradual decline until 8 to 10 weeks. Between 10 and 20 weeks post-treatment there is a secondary rise and fall in the NET serum levels. The biphasic NET release profile occurred in all 10 subjects and is pharmacokinetic, which is characteristic of this formulation. Treatment caused suppression of the endometrium for 3 months, and, with the exception of spotting and irregular menstrual cycles, there were no adverse side effects. Treatment has no significant effect on serum lipids.

CONCLUSION

One of the major problems with use of steroidal contraception in developing countries is the need to take a pill on a daily basis. Even where motivation for daily use of contraceptives is good, compliance is often poor, owing to inadequate education or understanding. Another limitation is the relatively great expense of the drugs. Hence, there is a great need to develop steroidal contraception that can be administered on a long-acting basis.

Several injectable steroidal contraceptives are presently being used in developing countries, but although these methods eliminate the need for daily motivation to take a pill, they have not been widely accepted because of problems with irregular menstrual bleeding and amenorrhea, and with related psychosexual and religious considerations.

Accordingly, it is hoped that the principles outlined in this communication that emphasize a constant low blood level of steroid will result in adequate fertility control without the present bleeding problems. If this can be accomplished, we will have come a long way toward providing adequate and acceptable fertility control for women in developing countries and in developed countries as well.

The work to develop long-acting contraceptive systems follows a trend towards the application of more sophisticated technology and wider diversity of technological expertise. The new systems being developed require input from biomaterial specialists, life scientists and clinicians. The multidisciplinary approach to research requires centralization of expertise and a broad funding base in order to be effective. The current philosophy of government funding is leading in the opposite direction. The technical expertise required to develop highly sophisticated long-acting steroidal contraceptive systems is available. The challenge which lies ahead is to focus the full spectrum of this expertise on the problem. This review is intended to describe where we have been so that we can better plan where we should be going.

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LOW LEVEL PROGESTOGENS

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B.M. Landgren

In conceptual terms the history of low level pregestogens as fertility regulating agents may be traced to the end of the last century, when Beard and Prenant observed that no ovulation takes place during pregnancy. However, to realize that the same condition can be duplicated by the administration of progesterone necessitated the continued efforts of hundreds of chemists, biologists and clinical investigators during more than half a century, until it was shown that in women ovulation can be inhibited by the oral administration of progesterone, or of synthetic progestogens, such as norethynodrel. The idea that progestogens may interfere with fertility even when administered in doses so small that they do not invariably inhibit ovulation was launched in the mid-sixties by a group of Mexican investigators.

Why did it take almost a decade after the introduction of combined oral contraceptives before progestogen-only formulations were tried? With the methods used in the mid-sixties for the large scale synthesis of the first contraceptive steroid, norethynodrel, it was difficult to completely remove a relatively important impurity, a strong estrogen, the 3-methyl

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ether of ethynylestradiol (mestranol). When the complete separation was finally achieved, it was found that the pure progestogen caused significantly more bleeding irregularities than the "impure" one. This observation led to the standardization of 1.5% mestranol "impurity" in the first marketed oral contraceptive, Enovid; it also caused some hesitation whether or not to develop progestogen-only contraceptives. Indeed, the majority of the 80 million women taking steroidal contraceptives today are using combined estrogen-progestogen formulations, rather than low-dose progestogens. The limited popularity of the latter is attributable in part to their lower efficacy and in part to the higher frequency of bleeding irregularities associated with their use.

Why bother then and try to develop improved low-dose progestogens? The answer is that the majority of adverse effects of steroidal contraceptives are estrogen dependent. Would it be possible to improve the efficacy and/or bleeding patterns achieved with low-dose progestogens, then these formulations would acquire an important place in our contraceptive arsenal, because of their established safety. It should be stressed, however, that it will hardly be possible to improve the performance of low-dose progestogens without a great deal of mission-oriented basic research on their mechanisms of action when they induce infertility and intermenstrual bleeding.

The objective of this chapter is to review the more recent information on low level progestogen contraceptives when administered by various routes. Special emphasis will be placed on human pharmacokinetic and pharmacocynamic investigations.

CHEMISTRY

These steroids have been studied either as "minipills", or following their continuous release from various delivery systems, such as vaginal devices, or subdermal implants.

Most published information is available on chlormadinone acetate, norethisterone and levonorgestrel. Following the withdrawal of most C-21 steroids, because of the (highly controversial) issue of mammary nodules in beagle dogs, the continued development in this field became largely centered on norethisterone and levonorgestrel and their closely related analogues.

PHARMACOKINETIC PROPERTIES

A simplified view of the expected profile or peripheral plasma levels of a progestogen administered by different routes is depicted in Figure 1.

What this figure intends to illustrate is that an even, near zero order rate of release is most likely to be achieved by the use of delivery systems such as vaginal rings, biodegradable or non-biodegradable subdermal implants, and perhaps transdermal systems. Depending on the rate of hydrolysis and/or dissolution (in the case of microcrystalline formulations and implants), the profile of various long-acting injectables may show considerable differences.

Minipills

In the case of minipill formulations, the peripheral plasma levels are known to exhibit marked ups and downs. Because of the risk of pill omission, the removal half-life of the progestogen used is of practical relevance for its efficacy. Since, as indicated in Table 1, the removal half-life or norethisterone is much shorter than that of levonorgestrel, "missing" a pill or two will have a more marked effect on the plasma levels of norethisterone than on those of levonorgestrel.

Vaginal delivery systems

In the WHO studies conducted in Stockholm, blood was drawn 3 times weekly (Mondays, Wednesdays and Fridays) during a pre-treatment (control) cycle and during 90 days (3 segments) with the devices in situ. The data indicate ie little, if any, initial "burst" effect and fairly constant

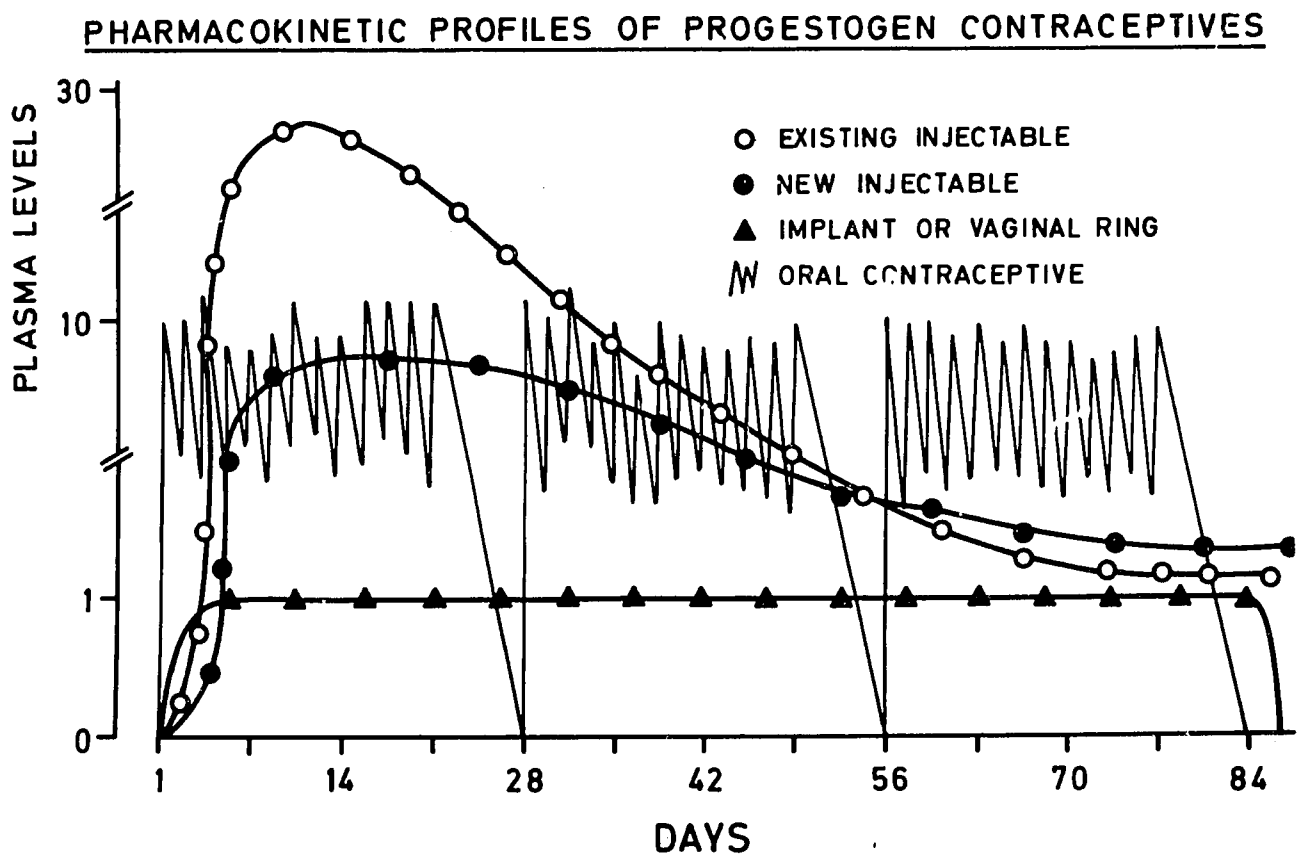

Figure 1. Schematic representation of the expected, pharmacokinetic profiles of progestogens administered by different routes and in different formulations.

release rates in association with considerable individual variation in ovarian response to the same peripheral level of norethisterone achieved by markedly different release rates (50 and 200 ug/24 h, respectively). The data indicate the high degree of reproducibility in individual levonorgestrel levels, even when rings of different origin are used by the same subjects.

The mean levels of levonorgestrel and norethisterone in the peripheral plasma of women using vaginal delivery systems with different release rates are indicated in Figure 2.

From the equations of the lines it can be calculated that the daily decline in levonorgestrel levels (at a release rate of 20 ub/24h) was 0.3%,

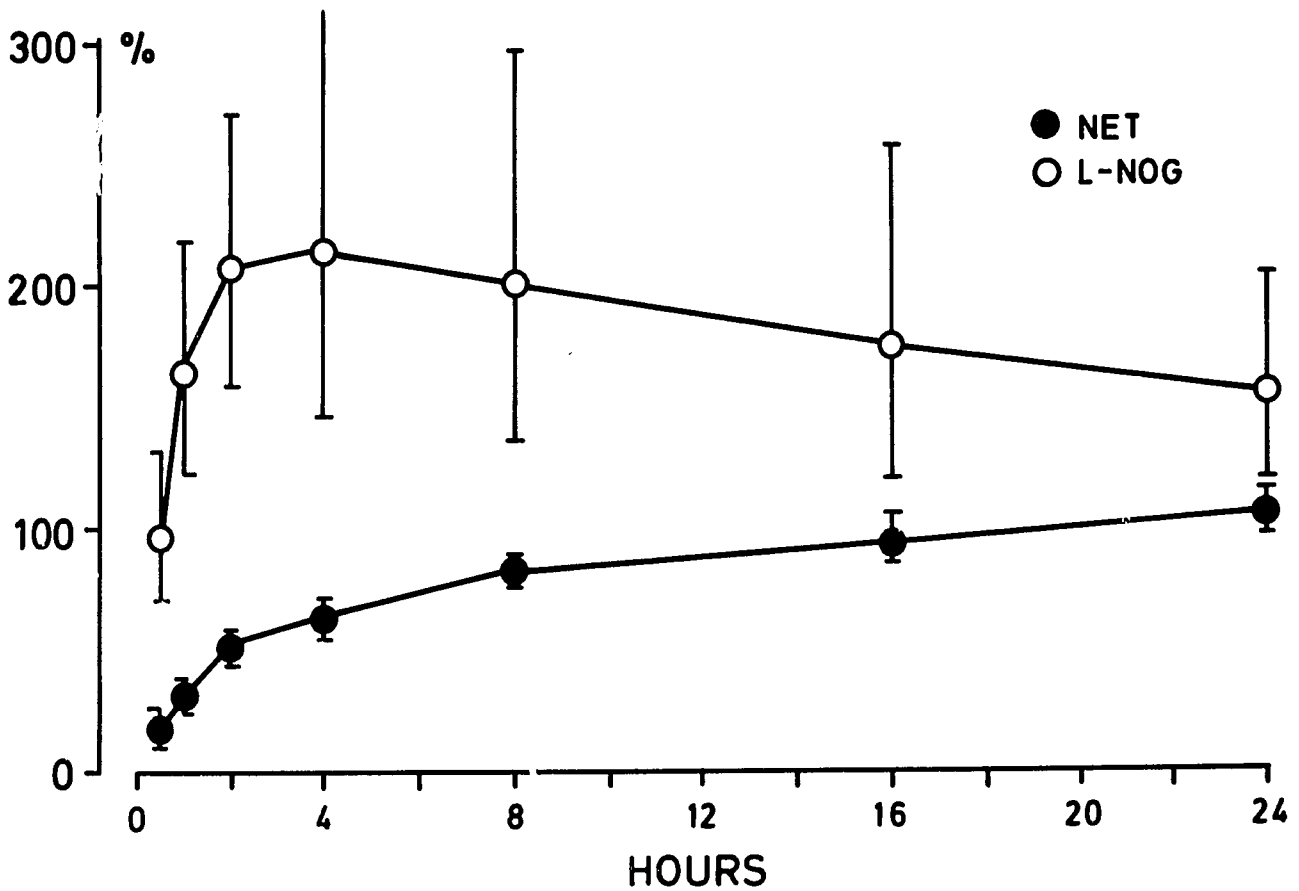

Figure 2. Geometric mean values and 95% confidence limits of the peripheral plasma levels of norethisterone (filled circles) and levonorgestrel (open circles) in 8 and 7 subjects, respectively, during the initial post-insertion period of vaginal delivery systems releasing norethisterone at a rate of 200 ug/24 h. The values are expressed as percentages of the constant levels found on the 8th post-insertion day. (Modified from the data published by Landgren et al.)

whereas in norethisterone levels it amounted ot 0.2% (at a release rate of 50 ug/24 h), respectively. These data suggest that the useful life span of these devices could be considerably prolonged. Moreover, the data also indicate that the initial absorption rate of levonorgestrel is significantly faster and its removal half-life significantly longer than the corresponding characteristics of norethisterone. Hence, ceteris paribus, the pharmacokinetic profile of levonorgestrel as a low level progestogen is more favorable than that of norethisterone.

Subdermal silastic implants

A system (Norplant) consisting of 6 silastic capsules (each 30 mm in length and 2.4 mm in diameter and with a load of approximately 35 mg of levonorgestrel) has been developed and tested by the Population Council. This system is placed under the skin of the upper arm with a 10-gauge trocar, and it provides contraceptive effectiveness for a minimum of 3 years. It is described in detail by Hefnawi in this volume. It is mentioned briefly here, since the available data suggest that some ovulatory cycles occur in the presence of levonorgestrel levels which are rather similar to those reported by Landgren et al. with vaginal devices releasing the same compound at a rate of 20 ug/24 h.

Other implants

Several other systems have been studied in clinical investigations, such as a single implant releasing norethisterone acetate and the Capronor system (Ory et al.) releasing levonorgestrel. The future of the first-mentioned one is uncertain, whereas the latter one - with a potential to be developed as a biodegradable system with several years' duration - is being actively pursued. From the preliminary evidence it would appear that ovulation inhibition is not invariably achieved. Therefore, for the time being, these systems may be classified as low-dose progestogen systems. The testing of these has not yet advanced much beyond the Phase I stage.

Biodegradable implant systems

Such systems were developed to release norethisterone at an approximate rate of 70-100 ug/24 h and levonorgestrel at a rate of 25-35 ug/24 h. Since some local irritation has been observed with these devices, their clinical testing has been discontinued.

Microencapsulation

Microsphere systems have been developed in which the duration of action of progestogens is prolonged by encapsulation into polylactic and/or polyglycolic acid microspheres, which are biodegradable and appear to provide sustained blood levels for several months. Such systems undergo Phase I to II clinical testing for the time being. (See Chapter 11.)

PHARMACODYNAMIC PROPERTIES

The most important aspects in this respect include not only pituitary, ovarian and endometrial function, but also metabolic effects and possible

adverse reactions. In the latter context, it should be emphasized that much better and more stringent information may be obtained form those studies conducted with long-acting injectable formulations in which a large number of subjects were continuously exposed to large doses of progestogens during prolonged periods of time.

Normal values

It should also be re-emphasized that a conditio sine qua non for the proper assessment of the pituitary, ovarian and endometrial effects of any fertility regulating modality in general and of low-level progestogen formulations in particular is adequate information on the hormonal and morphological indices characterizing these functions in normal ovulatory cycles. A review of the literature reveals that, with few exceptions, such normal material was not available to the majority of investigators, which resulted in considerable differences in their definitions of the indices characterizing a normal cycle.

In view of this, efforts have been made to obtain a representative normal material as to the peripheral plasma levels of LH, FSH, estradiol, progesterone, 17-hydroxyprogesterone and 20a-dihydroprogesterone and the relationship of these hormonal parameters to a variety of morphometric indices characterizing normal endometrial function.

Furthermore, an analysis of the daily hormone levels in 100 normally menstruating women revealed that 96% of them exhibited a plasma progesterone level of 16 nmol/l or more for a minimum of 5 days. Additional experience gained with daily assays in 40 women during the past 2 years confirms the previous contention that this is a minimal estimate and that it is by far the most reliable characteristic of a normal ovulatory-like cycle.

There is also an enormous amount of information on the morphological changes taking place in the human endometrium during the menstrual cycle and under various pathological conditions; a discussion of these changes is beyond the scope of this review. The relevant aspect in the present context is the objective, quantitative assessment of morphometric histochemical, cytochemical and perhaps receptor changes of the normally cyclic endometrium in order to evaluate the specific alterations induced by progestogens. This problem will be discussed shortly in connection with the bleeding irregularities associated with the use of low-level progestogens.

For more than a quarter of a century, the dating of the endometrium has been based on the classical system of Noyes et al., which proved to be most useful. However, viewed in the light of modern criteria, the system has 2 shortcomings, since it is not based on morphometric measurements and since, for historical reasons, it could not take into account the variability of the characteristic hormonal events of the cycle as reflected by the peripheral hormone levels measured daily. Indeed, a parallel dating carried out independently by Noyes & Haman on more than 1,000 biopsy specimens agreed only in 63% of the biopsies and it correlated with the basal body temperature shift and with the date of the subsequent menses within one day only in 60% of the biopsies. In the more recent

assessment of the endometrial effects of low-dose progestogens carried out in Stockholm, a morphometric analysis was always carried out in conjunction with the assay of peripheral hormone levels.

Pituitary effects of low-level progestogens

From the mid-sixties onward, many studies have been conducted to assess the pituitary effects of various progestogens. More recently, the effects were studied by the analysis of daily peripheral FSH and LH levels in conjunction with the estimation of estradiol and progesterone levels in more than 40 women taking the 300 ug norethisterone minipill. It was found that the predictive value of FSH and LH analysis is indeed limited; in women with completely suppressed luteal function, the FSH and LH levels did not differ from those exhibiting normal ovulatory-like steroid profiles. In general, the bizarre FSH an LH profiles induced by various progestogens were uncorrelated with their ovarian effects.

It appears, therefore, that the occurrence of a discernable preovulatory FSH and LH surge is not a prerequisite for normal ovulatory-like steroid levels and that the estimation of peripheral FSH and LH levels in women using low-level progestogens is of limited value in the assessment of the hormonal effects of gestagens.

Ovarian effects

Since the classical studies of Martinez-Manautou it is established thet minipill formulations containing different steroids do not invariably inhibit ovulation. However, in these studies the interpretation of the hormonal indices, especially of the progesterone levels defining a normal ovulatory-like cycle, varied considerably. Therefore, Landgren & Diczfalusy established a system for the classification of ovarian response to low-dose progestogens, which is also applicable to other forms of steroidal contraceptives. This system of classification, which is based on the normal levels indicated above (Table 1) and on the daily estradiol and progesterone levels analyzed in 43 women taking the 300 ug norethisterone minipill, is indicated in Table 2. In this system, follicular maturation is assessed on the basis of estradiol levels and luteal function on the basis of progesterone levels.

Reactions type A and B are characterized by the absence of any luteal activity; in case of C-type reaction, the luteal phase progesterone levels are significantly but inadequately elevated. Whether this reflects granulosa or theca cell luteinization, or the presence of a tru corpus luteum with suppressed steroid secretory ability, cannot be stated at present.

Moreover, from the analysis of daily 7-gydroxyprogesterone and 20 a-dihydroprogesterone levels in 42 cycles, it appears that they provide little, if any, new information in this respect beyond that provided by daily estradiol and progesterone assays.

The data indicate that some 40% of the 30-day segments (or cycles) studied with the 300 ug minipill and half of those investigated with vaginal devices releasing levonorgestrel at a rate of 20 ug/24 h were normal ovulatory-like ones. Since the efficacy of various low-level progestogens is

much higher than that, it must be concluded that ovulation inhibition is not the principal mechanism of their antifertility effect. Hence the relative importance of other mechanisms (sperm transport, implantation) requires elucidation.

The data indicate that some 40% of the 30-day segments (or cycles) studied with the 300 ug minipill and half of those investigated with vaginal devices releasing levonorgestrel at a rate of 20 ug/24 h were normal ovulatory-like ones. Since the efficacy of various low-level progestogens is much higher than that, it must be concluded that ovulation inhibition is not the principal mechanism of their antifertility effect. Hence the relative importance of other mechanisms (sperm transport, ovum transport, implantation) requires elucidation.

The data also indicate that the ovarian effect of the 50 ug/24 h norethisterone devices was too weak and that of the 200 ug/24 h devices perhaps too strong. These findings must be related to the efficacy and endometrial effects (including intermenstrual bleeding) of these formulations. Indeed, a Phase II trial indicated an unacceptably high pregnancy rate for the former and an unfavorable bleeding performance for the latter. The bleeding patterns observed with these formulations are indicated in Table 5 and will be discussed later. The data also indicate that the ovulation inhibiting potency of 200 ug norethisterone when released continuously from a vaginal delivery system is considerably stronger than that of 300 ug of the same compound administered daily in a discontinuous fashion as a minipill.

Endometrial effects

Prolonged exposure to small doses of progestogens results in a suppressed proliferation and abortive secretion, which may gradually turn into an endometrial atrophy. Some of the changes in endometrial vasculature (such as the dilatation of venules) are suspected to be instrumental in causing intermenstrual bleeding the problem is, however, that such changes were not observed invariably, and especially not when biopsy specimens were studied instead of the entire uterine lining. Another problem is that the majority of investigators did not assess the ovarian function pari passu with the endometrial changes. Since a considerable proportion of minipill users exhibit normal ovulatory-like progesterone levels, whereas others have anovulatory cycles, and since anovulatory and ovulatory-like cycles often alternate in the same subject, and in a haphazard sequence, conclusions based exclusively on the appearance of the endometrium may easily be misleading. However, in a limited but carefully controlled study of 24 subjects using the 300 ug norethisterone minipill, it was found that, irrespective of the ovarian function, the minipill significantly reduced the number of endometrial glands, diminished the grandular diameter, reduced the amount of deoxyribonucleic acid per cell nucleus and increased the number of capillary plasmolemmal vesicles and the proportion of venular endothelial cells showing contraction. Any, or none, of these changes may represent a predisposing factor for intermenstrual bleeding. Since, however, the above changes were not influenced by the presence of intermenstrual bleeding, or by the simultaneous administration of 50 ug ethynylestradiol for a week, it can only be concluded that the statistically significant endometrial changes in-

TABLE 1. Critical levels of hormonal indices characterizing normal follicular and luteal function in more than 90% of the normally menstruating women studied.

Hormonal index and No. of cycles studied	Characteristic mean level days 1 to 6		Mean level days LH-7 to LH3		Pre-ovulatory peak		Luteal maximum		Mean level luteal phase	
FSH*	>0.9	<4.0	>0.6	<5.2	>2.5	<16.0	--	--	>1.5	<3.3
LH*	>1.0	<3.5	>0.9	<4.8	>13.0	<36.0	--	--	>1.5	>3.3
Estradiol**	>0.15	<0.37	--	--	>0.7	<2.1	>0.48	<1.2	>0.3	<0.7
17-hydroxyprogesterone**	>0.6	<1.8	--	--	>3.2	<6.3	>5.5	<11.8	>3.2	<6.4
Progesterone**	>1.2	<4.4	--	--	--	--	>32.0	<96.0	>15.0	<42.0
20 a-dihydroprogesterone**	>0.5	>1.5	--	--	--	--	>7.3	<25.0	>4.4	<12.0

*IU/l in terms of the 69/104 International Reference Preparation.
**nmol/l.

Table 2. Classification of ovarian reaction to steroidal contraceptives.

Reaction type	Follicular maturation*	Luteal function**
A	None	None
B	Marked	None
C	Normal	Inadequate
D	Normal	Normal

*As reflected by the peripheral estradiol levels.
**As reflected by the peripheral progesterone levels.

dicated above were indeed induced by the norethisterone minipill and that the therapeutic value of estrogen therapy for improving the bleeding performance in women using low-dose progesterone formulations remains to be established. Several, but not all, of these minipill effects could be duplicated by the continuous premature release of small amounts (1.4 mg/24 h) of progesterone from vaginal delivery systems during days 7-11 of the normal menstrual cycle.

The relative paucity of relevant information underlines the necessity of greatly increased mission-orientated basic research on the complex relationship between endometrial bleeding and steroidal contraceptives.

EFFICACY

The efficacy of low-dose progestogens administered as minipills has been extensively studied. On the other hand, studies on the efficacy of progestogens released from vaginal delivery systems have not advanced as yet beyond the stage of a first Phase III study. Hence - with the exception of implants of the Norplant type, which are discussed in Chapter 12 - efficacy data are mainly available with various minipill formulations. The data shown in Table 3 are taken from the reviews of Fotherby.

TABLE 3: Cumulative results of trials of the efficacy of various types of gestagens administered as "minipills".

Compound	Daily dose (ug)	No. of women	No. of women months of treatment	Pregnancy rate (Pearl index)
Chlormadinone acetate	500	7359	44552	2.8
Lynestrenol	500	4731	37405	0.9
Ethynodiol diacetate	500	2420	24534	2.1
Northisterone	350	2925	26173	2.3
dl Norgestrel	75	2202	29006	2.4
Levonorgestrel	30	3218	36118	3.0

Although the efficacy of the progestogen-only formulations shown in Table 3 is clearly inferior to that of combined oral contraceptives, it should be emphasized that the overall failure rate is less than 3 per 100 woman years for any of the formulations, alghough in individual trials, pregnancy rates higher than this figure have been reported. The failure rate appears to be age-related, probably a reflection of the well known decline of fertility with age.

In view of their relatively short removal half-life, "missing" a pill or two represents a far greater hazard with minipills than with combined oral contraceptives. It is therefore important that minipills be taken at approximately the same time each day, which, wnenever possible, should be related to the pattern of sexual behaviour.

METABOLIC EFFECTS

Hormonal contraceptives have been associated with a variety of metabolic effects; the most frequently discussed ones are indicated in Table 4.

TABLE 4: Metabolic effects discussed in connection with steroidal contraceptives. Effects considered as possibly progestogen related are indicated by an asterisk.

Parameter	Effect
Coagulation factors	-
Fibrinolytic factors	-
Platelet function	-
Weight gain	*
Carbohydrate metabolism	*
Lipid metabolism	*
Mineral metabolism	-
Liver function	-
Renal function	-
Adrenal function	*
Thyroid function	-

A review of the literature reveals that, in most instances, these effects were attributable to the estrogen component of the steroidal contraceptive. Indeed, the relative paucity of metabolic effects seen following progestogen administration has been shown by a large number of studies with a variety of minipill formulations and was further underlined by the fact that large doses of progestogens administered during prolonged periods of time as long-acting injectable formulations, such as depomedroxyprogesterone acetate and norethisterone enanthate appear to have little or no effect on most of the indices indicated in Table 4. In addition to weight gain, the metabolic effects which have been discussed as possibly progestogen related (marked with an asterisk in the Table) are those on carbohydrate and lipid metabolism and on adrenal function. These will be considered only briefly and mainly on the basis of long-term studies involving exposure to large doses of progestogens administered as injectable formulations.

Carbohydrate metabolism

It would appear that - contrary to the findings of some earlier reports - contraceptive doses of depo medroxyprogesterone acetate (150 mg every third month) have little, if any, effect on glucose tolerance. On the other hand, and in contrast with most other studies, Spellacy continues to find changes in glucose tolerance also following the administration of the minipill; in a recent study of 50 women using continuously a 75 ug dl-norgestrel minipill for 18 months, a significant increase in blood glucose and insulin levels was found, and in 8 subjects the glucose tolerance became abnormal. Be that as it may, there is little doubt that the effect, if any, is rapidly reversible upon discontinuation of the treatment.

Lipid metabolism and transport

Minipills do not markedly affect the peripheral levels of cholesterol and triglycerides. On the other hand, it would appear that most currently

used synthetic progestogens decrease the levels of high density lipoprotein (HDL) cholesterol. However, the temporal and dose-effect relationships, the effects on HDL_2 to HDL_3 ratios and the correlation of these to ischemic heart disease remain to be established. Indeed, it is well pointed out in a recent review that "In the absence of a comprehensive assessment of progestin effects on the levels and composition of all lipoprotein classes it is premature to link isolated effects on lipids or lipoproteins to predictions of cardiovascular risk". At any rate, lipoprotein metabolism is an aspect of progestogen use which requires a great deal more systematic investigation.

Adrenal function

Progestogens, when given in very large therapeutic doses, are known to suppress adrenal cortical function. On the other hand, depo medroxyprogesterone acetate when administered in contraceptive doses has only insignificant or no effect on the circadian rhythm of cortisol; it has no effect on the circadian rhythm of a variety of other adrenocortical steroids or on the adrenal reserve capacity. In view of these data, it appears most unlikely that low-dose formulations of the progestogens indicated should possess a significant inhibitory effect on adrenal function.

OTHER CONCERNS

Neoplasia

There is a great deal of controversy at present about suitable toxicological models to be used in lifetime exposure studies to 50-times or more the human dose of various progestogens. This aspect (and the beagle issue), which has been considered elsewhere is beyond the scope of this review.

Concerning epidemiological studies, in 1978, a WHO Scientific Group concluded that "there are no adequate data from studies in women to assess whether progestogens used as contraceptives in the form of progestogen-only pills, or injections have any effect on the risk of neoplasia", WHO initiated a case-control study in 12 Centre on the association of oral and injectable contraceptives and the risk of cancer of the breast, cervix, endometrium, ovary and hepatobiliary system. More than 2,000 subjects and 4,000 controls have been enrolled so far, and the results are expected to be available in 1983. The proportion of controls who ever used injectable contraceptives will make it possible to detect a minimal relative risk of 2.0 or more with both combined oral contraceptives and depo medroxyprogesterone acetate. However, the limited number of subjects using minipill formulations will not permit a similar analysis.

Effects on progeny

Concern has been expressed about possible affects on the fetus in utero (because of method failure, or mother being pregnant when starting to use progestogen contraceptives) and about exposure of the infant to progestogens present in breast milk. These concerns, which relate principally to injectable progestogens, rather than to minipills, include a wide variety of problems, ranging from congenital anomalies following in

utero exposure to possible effects on physical growth and skeletal maturation, immunologic competence, hypothalamic and pituitary development, reproductive organ and psychological development. The data available to answer these questions are meager and not always consistent; however, "it is clear that any teratogenic hazard associated with in utero exposure to progestogens is small and the more reliable investigations suggest either no risk or an approximately two-fold increase in the risk of some abnormalities, such as cardiovascular defects, associated with a variety of contraceptive and non-contraceptive exposures'. Furthermore, children exposed to depo medroxprogesterone acetate in breast milk have been examined for physical growth and development up to 18 months of age; no adverse effects were found. It is also established that the quantity and quality of breast milk are not affected in an adverse manner by progestogens given as minipills or as long-acting injectables. A recent review of the available data suggests that the small amount of progestogen ingested by the infant through breast milk is unlikely to give rise to adverse effects on the child's development.

Ectopic pregnancy

A few reports have suggested an increased incidence of ectopic pregnancies in women using minipills. The mechanisms by which these ectopic pregnancies occur have not been elucidated, and this aspect requires continued investigations. At any rate, whenever women using low-dose progestogens present such symptoms, the possibility of an ectopic pregnancy should not be lightly dismissed.

Return of fertility

There is little, if any, reason to suspect that following cessation of the administration of low-dose progestogens, ovulation and fertility should not be readily re-established. Indeed, studies with prolonged exposure to large doses of medroxyprogesterone acetate do not indicate a significant difference in the return of fertility in comparison with intrauterine devices or combined oral contraceptives.

Bleeding irregularities

Disruption of the normal menstrual pattern is the major disadvantage of all low-dose progestogen formulations, administered as various minipills, implants or vaginal delivery systems. compared to combined estrogen-progestogen contraceptives, they do cause bleeding irregularities more frequently, and this fact constitutes by far the most important reason for discontinuation. The assumption that the bleeding performance will gradually improve with prolonged progestogen administration is a classic fallacy, since subjects experiencing menstrual irregularities will be the first to discontinue, leaving behind a highly selected population, with a bleeding profile which eventually may even approximate that seen in normally menstruating women in contradistinction to the effects of long-acting injectable formulations. Amenorrhea occurs rarely in women using low level progestogen formulations and the predominant menstrual irregularity is intermenstrual bleeding and spotting. The pathogenesis of this bleeding is incompletely comprehended. A recent Symposium organized by WHO carried out an in-depth examination of the available infor-

mation on the connection between intermenstrual bleeding and steroidal contraception and concluded that in this field the lacunae in our knowledge are deep and numerous and that it will be essential to intensify research in this critical area. Indeed, a limited morphometric, cytochemical and electron microscopic comparison of the "bleeding" and "non-bleeding" endometrium in minipill users underlines the problem, since - with the exception of a slight reduction in glandular diameter in "bleeders" - no difference was found with regard to any of the endometrial indices studied, including venular capillary size. Moreover, treatment with ethynylestradiol or with placebo exerted no effect on the frequency of bleeding, or on any of the endometrial indices studied.

A recent examination of the correlation of ovarian function to intermenstrual bleeding in women using vaginal delivery systems releasing low doses of various progestogens is also of considerable interest in this respect. The findings presented in Table 5 indicate that the number of days with bleeding and spotting was significantly higher in anovulatory segments compared to those in which a normal ovulatory-like hormonal profile was found. The reasons for this difference could not be related so far to endometrial morphological changes; and, to complicate matters even more, no similar differences were noted in two (rather limited) studies with the 300 ug norethisterone minipill used during a limited period of time.

TABLE 5: Relationship between ovarian reaction and the precentage of days with bleeding and spotting in women uisng vaginal devices releasing levonorgestrel and norethisterone, respectively.

Ovarian reaction*	Levonorgestrel 20 ug/24 h		Norethisterone 50 ug/24 h		Norethisterone 200 ug/24 h	
	No. of segments	Bleeding days (%)	No. of segments	Bleeding days (%)	No. of segments	Bleeding days (%)
Anovulatory	20	37.3	3	35.6	34	38.9
Inadequate luteal function (type C)	13	29.5	5	21.3	3	22.7
Normal ovulatory-like (type D)	36	27.7	26	22.0	9	27.0
Pre-treatment cycles	23	17.6	15	18.8	15	17.2

* According to the classificiation of Landgren & Diczfalusy, indicated in Table 3.

Last, but not least, it should be emphasized, that low-dose progestogens are by no means unique in causing bleeding irregularities and that improved bleeding profiles would have a significant impact on the continuation rates with a variety of fertility regulating agents, including i.e. intrauterine devices, injectable and implantable formulations, and even combined oral contraceptives.

CONCLUSION

During the past 15 years, a variety of low level progestogen contracep-

tive formulations have been developed and are still being developed. They do not invariably inhibit ovulation, and their sustained release formulations seem to be capable of interfering with fertility when administered at such low rates as 20-30 ug/24 h. The balance of evidence strongly suggests that the administration of such low steroid doses minimizes the possibility of inducing major metabolic alterations or adverse effects. However, the use of these formulations is associated with two major disadvantages; their efficacy is lower than that of combined estrogen-progestogen contraceptives, and they cause more bleeding irregularities, mainly in the form of intermenstrual bleeding. This last-mentioned fact constitutes by far the most important reason for discontinuation. The mechanisms by which progestogens induce intermenstrual bleeding are incompletely comprehended.

Since improved bleeding patterns would have a significant impact also on the continuation rates of a variety of other contraceptive methods, the importance of and necessity for a massive increase in mission-oriented basic research on the relationship between intermenstrual bleeding and steroidal contraceptives cannot be overemphasized.

Other areas requiring more research include the mechanisms of anti-fertility action of progestogens in those (numerous) cases in which they do not inhibit ovulation, their effect on lipoprotein metabolism and the possible connections, if any, between progestogen use and the risks of neoplasia, cardiovascular complications and ectopic pregnancies. In a broader perspective, it should be realized that progestogens do not represent a finished chapter in the history of fertility regulation, but rather the first act of an ongoing drama in which we have learned enough about the complexities of the problem in order to understand how much more remains to be learned.

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INJECTABLE AND IMPLANTABLE PROGESTINS: PROBABLE LACK OF FETAL EFFECT

Joe Leigh Simpson

Potential fetal risks of progestins include deleterious effects resulting from unwitting hormone exposure during a pregnancy associated with contraceptive failure (teratogenic effect), exposure of germ cells, manifested in progeny conceived years later (mutagenic effect). Various reports have claimed that medroxyprogesterone acetate (MPA), norethisterone (norethindrone) (NET), and norgestrel (NGT) exert both teratogenic as well as mutagenic effects. On the other hand, critical review leads one to doubt claims of mutagenicity and teratogenicity, excepting genital virilization by certain progestins administered in very high doses during susceptible embryonic periods.

I. TERATOGENICITY OF INJECTABLE/IMPLANTABLE PROGESTINS

The optimal scientific way to determine whether injectable or implantable progestins - medroxyprogesterone, norethisterone, or norgestrel - are teratogenic is to observe the outcome of pregnancies occurring as result of contraceptive failure. Because failures are fortunately rare, only limited data are available by which to assess directly the potential teratogenicity associated with injectable or implantable progestins.

The few groups commenting on fetal outcome after injectable MPA have not observed increased anomaly rates; however, the total pregnancies in all these studies is perhaps less than 100. Between 1975 and 1978, 190 of 8,816 infants born in ChiangMai, Thailand were anomalous. The mothers of

the 190 used MPA in the same proportion as mothers of the 8,626 normal infants, but whether any fetuses were exposed during gestation is not known. Even less direct data exist concerning injectables or implantable NET or NGT, but similarly no claims of teratogenicity exist.

The paucity of formal studies makes it necessary to seek relevant information from other sources. Samples useful in determining the teratogenicity of injectable or implantable progestins include pregnancies characterized by 1) administration of progestins for pregnancy maintenance, 2) administration of progestins for pregnancy diagnosis, judged on the basis of presence or absence of withdrawal uterine bleeding following five days of moderately high doses, and 3) inadvertent progestin exposure (1 mg/day) during unrecognized gestation, associated either with oral contraceptives or progestogen intrauterine devices. At present the former two indications are no longer appropriate. Nonetheless, available for our study are populations of fetuses exposed when those indications were valid.

Several different types of epidemiologic approaches have been conducted, and these differ widely in validity. Ideally one prefers prospective studies, either of entire populations or a cohort thereof. However, such studies are laborious, expensive, and sometime uncover only a few informative subjects. Case control retrospective studies have thus proved popular. In such a study, one matches women with a specified abnormal outcome (e.g. infant with a cardiac anomaly) with controls who, perhaps after multivariate corrections, differ only with respect to the variable under investigations (e.g., MPA or NET exposure). Is drug exposure cited more frequently by the mothers of cases than by mothers of control? In such a design one serious bias is that women whose pregnancies resulted in an abnormal outcome search much harder for factors potentially responsible. Case control studies inevitably yield spurious positive associations of recall biases. Studies conducted prospectively with respect to fetal outcome should mitigate this bias.

Yet, in some prospective studies patients were interviewed before pregnancy outcome was known, yet months after drug exposure so timing of drug exposure often would not be precisely recalled. Finally, in neither retrospective nor prospective studies has infant morphology ordinarily been systematically assessed.

Despite shortcomings in all the epidemiologic studies we shall cite, substantial data attest to the safety of injectable or implantable progestins.

A. Genital Virilization

In humans, the only proved teratogenic effect of progestins is genital virilization of female fetuses. This effect is actually not surprising because some progestins possess androgenic properties that naturally could affect androgen-sensitive organogenesis. Such an organ-specific effect provides no basis, incidentally, for extrapolating that teratogenic effects would be expected in non-androgen sensitive organ systems. Moreover, virilization is observed only with some progestins and only in doses exceeding those present in women receiving injectable and implant-

able progestins.

Medroxyprogesterone acetate (MPA). In high doses, MPA virilizes female monkeys exposed at susceptible times of embryogenesis in doses above 300 mg/day. However, MPA does not virilize mouse or rabbit fetuses. In rats contradictory data exist. One study showed an effect, but Andrew and Staples observed no virilization following 30 to 3000 mg/kg/day. On the other hand, virilization was observed in rat fetuses whose mothers carried medroxyprogesterone-containing intrauterine devices in both uterine horns. Fetuses born of control mothers (silastic device in situ without MPA) were not virilized but, interestingly, showed an increased rate of anomalies compared to animals without a device.

In humans there is no convincing evidence that MPA ordinarily virilizes female fetuses. Virilization has not been reported in the few human fetuses conceived while their mothers received MPA injections. Further supporting the lack of effect is the near absence of reported virilization despite MPA having been administered in high doses (10 to 40 mg orally daily throughout pregnancy) to thousands of women in hopes of maintaining pregnancies. Only a few anecdotal reports can be cited. Burstein and Wasserman administered 5 to 50 mg MPA daily to women prior to the 12th week of pregnancy (total dose 50 to 7000 mg per patient). Only 1 of 82 female offspring had clitoral hyptertrophy and none was more extensively virilized. Similarly, Rawlings observed no virilization among offspring of 72 women treated with large doses of MPA. Virilization has also been observed in prospective studies.

Norethisterone (NET). In constrast to MPA, norethisterone (norethindrone) (NET) in high doses at the appropriate stage of embryogenesis (2 to 10 weeks) definitely virilizes female human fetuses. Labioscrotal fusion, utrethral displacement and clitoral hypertrophy result. Women delivered of virilized fetuses usually received 10 to 40 mg/day for various intervals, but sometimes doses were much higher. As would be expected on the basis of teratologic principles, labioscrotal fusion occurred only when NET was administered within the first 10 embryonic weeks. Exposure later in gestation sometimes caused clitoral hypertrophy without labioscrotal fusion. Norethisterone also causes virilization in several animal species.

Interestingly, not all human females exposed in utero are virilized, presumably because of differences in genetic susceptability. In Jacobsen's study, 15 of the 82 female offspring whose mothers received NET were virilized; the remaining 67 were not. Differences in susceptability might be explained by differences in maternal absorption or catabolism. Such a phenomenon would be relevant to injectable/implantable systems because individual variability in NET plasma levels occurs following implantation of a given dose.

If high doses of NET cause virilization in humans, could implantable or injectable NET result in such a deleterious effect? Probably not, because virilization occurs only with exposures much higher than expected with implantable or injectable NET. After 1 mg oral NET, serum NET rises to 12 ng/ml. By 12 hours the level falls to 2 ng/ml. Assuming a normal response for steroids, a 10 mg oral dose would lead to 1 hour

peak of about 120 ng/ml and to a 12 hour level of 20 ng/ml. By constrast 200 mg intramusuclar NET results 5 to 7 days later in a peak serum value of 5 to 7 ng/ml. Thereafter, NET fails and remains for most of the next several months at 0.05 to 1.0 ng/ml. Total 24 hours exposure of NET with injectable systems would thus be less than that associated with daily oral contraceptive ingestion. Absence of virilization following inadvertent ingestion of oral contraceptives, many of which contain norethisterone, would thus offer support for the safety of injectable or implantable progestins. Indeed, Schardein tabulated 644 pregnancies in which NET exposure, sometimes with estrogens in addition, was followed by normal offspring. The most likely circumstance in which virilization might occur is negligent administration to a patient already six to eight weeks pregnant. At the time of greatest embryonic susceptability, the fetus would be exposed to plasma NET levels of 5 to 7 ng/ml. Vigilance in excluding pregnancies should minimize such exposure, but even here virilization would not be likely.

Norgestrel (NGT). Edgren showed that this 19-nortestosterone masculinized rat fetuses. Though relatively few data are available in humans, the compound would be expected to virilize if administered in high doses. But analogous to other progestins, inadvertent exposure in the lower doses present in oral contraceptives does not appear to have produced genital abnormalities. It follows that virilization would not be anticipated after NGT injections, based upon reasoning comparable to that discussed for NET.

Conclusion. Medroxyprogesterone (MPA) does not virilize human fetuses even in high doses. Moreover, not even anecdotal observations incriminate MPA in lower doses comparable to those that would exist after MPA injections. By constrast, norethisterone (NET) in high doses (10 to 40 mg/day) can virilize human fetuses if administered during the susceptible embryonic period, and norgestrel (NGT) probably could as well. However, virilization is unlikely to be associated with much lower serum levels in women receiving injectable or implantable NET or NGT.

B. Hypospadias

Aarskog claimed that progestins in general and medroxyprogesterone in particular cause penile or perineoscrotal hypospadias. Although Aarskog's data are uncontrolled, two other studies later supported his hypothesis. A Latin American case control study claimed a relative risk of 2.4 for hypospadias associated with exposure to all progestins. Of 314 cases, 24 (7.6%) were exposed; 12 of 319 controls (3.8%) ($P < 0.05$) were exposed. Few details concerning the time of exposure were published, and incidence varied widely among the countries. From Hungary, Czeizel reported that 28 of 294 mothers delivered of males with hypospadias received sex hormones, compared to 12 of an unspecified number of controls. This difference was said to be significant; however, there is no confidence that controls were well matched, and a high prevalence of hypospadias in the proband's male relatives suggested selection bias. Other large case control studies refute the hypothesis that MPA is associated with hypospadias. Among large studies failing to show significant associations are those of Bracken, Sweet and Avellan. Indeed, no prospective study has revealed a relationship between progestins and hypospadias.

Conclusion. Although a few studies have claimed a relationship between progestins and hypospadias, more extensive case control studies failed to confirm such an association, and no prospective study found an effect. Progestins in general and MPA in particular seem unlikely to affect adversely male genital development.

C. Cardiac anomalies

That progestins could be cardiac teratogens was claimed by Levy in 1973. A case control study revealed that 7 of 76 mothers delivered of infants with transposition of the great vessels received first trimester "hormones"; significantly fewer (0/76) controls were exposed ($p < .007$). Nora and Nora claim similar findings in a series of overlapping studies that were initially retrospective but later more prospective in design. In one case control study, 20 of 224 mothers delivered of infants with cardiac defects recalled receiving an estrogen/progestin compound, compared to only 4 of 262 controls ($p < 0.001$). Nora then began to study the question prospectively. No significant differences were observed between the first 60 mothers and their controls. Despite these negative findings, another study was commenced with 2 controls per subject. In this second study, 31 of 176 mothers with affected offspring received hormones, compared to only 21 of 352 control mothers ($p < .001$).

A few other case control studies have drawn similar conclusions. For example, Janerich identified infants with cardiac defects through birth certificates. Of 104 mothers of affected infants, 18 received hormones; 16 were for pregnancy diagnosis and 2 as a result of inadvertent contraceptive use. Significantly fewer controls reported exposure. Cardiac anomalies were also among the anomalies said to be responsible for Greenberg's finding a relationship between progestins and generalized anomaly rates.

With respect to prospective studies, both the Noras study cited above as well as the U.S. Collaborative Perinatal Project found a positive association. Of 1042 offspring said in the latter to have been exposed to "sex hormones" during their gestation, 19 had cardiac defects (1.82%); 385 of 49,240 (0.78%) unexposed offspring were affected (relative risk 2.3, $p < 0.05$). Strangely, continued contraceptive use during the second and third lunar months was associated with a relative risk of 2.4, but exposure to progestogens only with a risk of 1.5 and exposure to estrogens only with a risk of 1.4. Too few cases existed to allow analysis by specific hormones; however, overall progestins had a low but significantly increased relative risk for cardiac anomalies (1.8) ($p < .05$).

Spira followed 20,000 French women throughout pregnancy. Almost half (9,566) received hormones, usually for either pregnancy diagnosis or pregnancy maintenance. Anomaly rate in exposed cases did not differ from that in the unexposed. In a later tabulation of the same population (12,764 women) by Goujard and Rumeau-Rouquette, cardiac anomalies were no more frequent in exposed (43%) than unexposed (.41%) mothers. Also impressive is the failure of Nishimura to detect cardiac anomalies in 108 microdissected embryos exposed to hormones. By constrast, several controls had cardiac defects.

If the consensus does not implicate progestins as cardiac teratogens, why did a minority of studies arrive at ostensibly contradictory conclusions? Unavoidable statistical vicissitudes and differing genetic susceptibilities notwithstanding, methodological shortcomings seem likely to explain those studies purporting to show positive associations between progestins and cardiac defects. First, we have already alluded to recall biases inherent in all retrospective (case control) studies. Investigations of Janerich, Levy and the Noras, all potentially suffer from this bias. Second, reasons for the attempt to maintain pregnancies, often the reason for administering progestins, were not sought. Third, prior pregnancy outcome is rarely taken into account. In fact, the birth of one child with a cardiac defect confers an increased risk (1 to 4% in subsequent pregnancies). The increased risk might even pass unrecognized if a cardiac defect had unknowingly been responsible for a stillborn infant. What is more, occurrence of a previous stillborn infant, especially of "unknown" etiology, could tempt some obstetricians to administer hormones empirically. Fourth, hormones could have been administered to pregnancies already manifesting problems (e.g. bleeding) indicative of underlying defects. Indeed, Matsunaga and Shiota believe that not progestins but rather the bleeding for which progestins were administered was responsible for cardiac defects. Fifth, few studies restrict analysis to the interval in embryogenesis during which exposure could produce cardiac defects. For example, in the analysis of the U.S. Collaborative Perinatal Project, the first 4 lunar months were considered the interval during which exposure could have produced anomalies. However, the first lunar month includes the 2 weeks before conception and the 2 weeks after. During this interval (all-or-none period), anomalies cannot ordinarily be produced. By the fourth lunar month, heart formation is complete. Thus, exposures at this time are also not likely to cause defects.

Among the 19 infants with cardiac defects in the Collaborative Perinatal Project, a total of 4 were exposed only during the first lunar month; 3 were exposed only during the fourth month. Excluding these 7 cases would abolish any significant association with hormone exposure. In the only other prospective study claiming a positive association between progestins and abnormal outcome, namely that of Harlop, first lunar month exposure was considered to be a susceptible interval. Unfortunately, exposure intervals were not recorded precisely in this study. Finally, defects caused by chromosomal abnormalities or mutant genes were not excluded from analysis. With so many methodological shortcomings, it is not surprising that a few studies would spuriously show increased relative risks, even statistically significant ones.

Conclusion. Most retrospectively and almost all prospective studies fail to support the hypothesis that progestins are cardiac teratogens. Moreover, serious methodological flaws exist in the minority of reports claiming positive associations. The magnitude of the observed differences in the few positive case control studies seems consistent with recall biases. The few prospective studies claiming effects are marred by potential selection biases and by exposures not necessarily occurring during cardiac embryogenesis. A prudent conclusion is that progestins are not cardiac teratogens.

D. Limb reduction deformities

Shortening or absence of a limb, finger, or toe (limb reduction defects) has been alleged to be associated with progestin exposure. The possibility was first raised by Janerich, who reported that 15 of 108 women with an affected infant received hormones (inadvertent oral contraceptive exposure, hormone pregnancy test, or pregnancy maintenance). Only 4 of 108 controls were exposed ($p < 0.05$). Hellstrom recorded exposure by 7 of 32 mothers of affected offspring, compared to only 1 of 30 mothers with spina bifida. Greenberg claimed an overall increase in anomalies following progestin exposure, apparently contributed in part by limb reduction defects. However, several of the above studies invite invalidation on grounds of recall bias, interviews sometimes conducted as long as 10 years after birth. In the study of Janerich, some exposures also occurred only during the all-or-none period.

Other investigations have failed to show an association between limb reductions and maternal hormonal exposure. Bracken showed no statistically significant association in a large study. In an especially well-constructed case control study, Oakley failed to observe a relationship. Control in the latter study were women delivered of offspring with chromosomal abnormalities, a design presumably obviating recall biases.

Prospective studies have similarly failed to confirm an association. Moreover, missing digits or severe limb shortening should be obvious to even the casual observer, strengthening the value of prospective data in excluding a relationship with progestin exposure. Finally, Nishmura apparently did not observe limb reduction deformities in their microdissection of 108 embryos recovered from progestin-exposed mothers.

Conclusions. Despite initial concern generated by the well-publicized report of Janerich, later studies failed to confirm a relationship between progestin exposure and limb reduction defects. This reassurance is enhanced by its being based in part upon studies in which exposure levels were much higher than those expected with injectable/implantable progestins.

E. Neural tube defects (NTD)

Neural tube defects - anecephaly and spina bifida - were claimed almost a decade ago to be associated with hormone exposure. The claim is now almost completely discounted.

Using a case control design, Gal reported that 19 of 100 women delivered of infants with myelomenigoecele or hydrocephalus received hormones (estradiol plus ethisterone or norethisterone) for pregnancy diagnosis; only 4 of 100 controls recalled hormone exposure ($p < 0.01$). Unfortunately ignored in this study was prior pregnancy history, especially relevant because in the United Kingdom NTD recurrence risk is 5%. Also not considered was the stage of embryogenesis at which exposure occurred. The neural tube closed at 28 embryogenic days. This is earlier than attempts to diagnose pregnancy are usually made and, hence, earlier than hormones would ordinarily have been administered for this purpose. One later study showing a possible relationship to NTD was that of Greenberg.

Overall, the anomaly rate in the hormone-exposed group was increased, and 25 of 93 malformed infants had NTD.

Other case control studies showed no association between NTD and progestins. In the United Kingdom, Laurence showed no significant increase: 22 of 271 NTD pregnancies were exposed; 22 of 323 controls were exposed. Another large negative case study is that of Bracken. Not a single prospective study showed an association between progestins and NTD. Further significant in view of the tendency of NTD fetuses to abort and, hence, possibly fail to be detected, is the absence of NTD in 108 pregestin-exposed embryos microdissected by Nishimura.

Conclusion. The hypothesis that progestins cause neural tube defects currently receives no support. The few retrospective studies claiming a relationship are not only greatly outweighed by prospective studies showing no relationship, but can be criticized on grounds of recall biases and exposures occurring during inappropriate embryonic periods.

F. Generalized anomalies and the VACTERL complex

Is there an overall (generalized) increase in anomalies after progestin exposure? Although not illogical as a way of generating hypotheses, using overall anomaly rates as an end point is conceptually hazardous because of etiologic heterorgeneity. Moreover, it is almost inconceivable that a generalized increase would exist without one or more organ systems subsequently being identified as primarily responsible. Recall biases are especially invited.

Excess rates for anomalies of all types following progestin exposures have been claimed in some but not most case control studies. One study claiming an association is that of Greenberg, a work actually of uncertain validity because only a small and, hence, possibly unrepresentative proportion of eligible women participated. No significant associations were found in case control studies of Bracken and Oakley, and we have already noted the frequency of anomalies not to be increased in 541 "pill-failure" pregnancies pooled by Harlap and Eldor.

Among prospective studies, only 2 of 15 studies showed an association. The Collaborative Perinatal Project analysis by Heinonen showed a significant overall anomaly risk. There existed a significant association with "hormones, hormone antagonists, and contraceptives," but not with "progestational agents" alone. The prospective study of Harlap also showed a small increased relative risk. But criticism has already been made of both these data sets, and prospective studies fail to show an generalized increase.

One refinement of the claim that a generalized increase in anomalies exists is that of Nora and Nora, who believed that non-specific vertebral, anal, cardiac, tracheosophageal, renal, and limb (VACTERL) anomalies constitute a complex associated with maternal progestin exposure. Defects involving any 3 of the 7 organ systems are said to justify the diagnosis. A further variant is the claim by Lorber for an "EFESSES syndrome" (embryo-fetal exogenous sex steroid exposure syndrome), characterized by various dysmorphic features. Geneticists do not appear to

subscribe seriously to the EFESSES concept, but VACTERL deserves comment. Nora claimed a significantly increased frequency of progestin exposure in 30 VACTERL probands (11 exposures) compared to 60 controls (5 exposures). However, not only is the sample size small, but recall would surely be amplified in mothers whose infants had multiple malformations. Physician awareness of the purported relationship to progestin exposure may also have tempted them to diagnose the VACTERL association or its individual components. Even more importantly, we have already refuted individually claims of cardiac and limb reduction components of VACTERL. One should also note the failure of several case control studies to find a significant relationship between progestin exposure and other VACTERL components, such as esphageal atresia. In some prospective studies, investigators specifically searched and failed to observe VACTERL complex.

Conclusion. Little evidence supports the hypothesis that progestin exposure causes a generalized increase in malformations. In fact, such an omnibus search serves principally ot generate hypotheses, which have more specifically been tested by organ system with the negative findings already noted. The validity of the VACTERL association and its association with progestins seems highly doubtful.

III. ARE INJECTABLE/IMPLANTABLE PROGESTINS MUTAGENIC?

In addition to direct effect on the developing embryo, a deleterious agent can produce abnormalities by inducing changes (mutations) in individual parental germ cells. A child subsequently conceived with that germ cell could be anomalous. The two types of potential mutations - gene and chromosomal - will be considered separately.

A. Gene mutations

Genetic disorders associated with normal chromosomal complements result from mutation at one (Mendelian) or more (polygenic) loci, the latter sometimes interacting with environmental factors (multifactorial). Individuals with such disorders may be affected through heritable transission, or they may be affected through a mutation. Agents can induce gene mutations but not chromosomal mutations, and vice versa, and not infrequently a single agent can do both.

Whether progestins result in mutations responsible for Mendelian or polygenic disorders in progeny conceived months or years later should ideally be assessed locus by locus, for the mutability almost certainly varies. However, this is mathematically impossible, given even a large increase over baseline mutation rates of 10^{-5} to 10^{-6}/gamete/generation. As a result, analyses must be content to compare overall anomaly rates in women previously exposed and previously not exposed to hormones. (Actually most studies pool anomalies of Mendelian, polygenic, chromosomal, and environmental etiology.) This is obviously less than an ideal approach, for which reason it is fortunate that available data are sufficiently reassuring to minimize fears that more refined analyses will yield surprises.

Outcome of pregnancies by women conceiving after discontinuation of in-

jectable/implantable medroxyprogesterone (MPA) or norethisterone (NET) represent the obvious sample. Relatively few pregnancies have been monitored to date, but in those there is no evidence for increased anomalies. For example, women delivered of anomalous infants in Chiang Mai, Thailand, were no more likely to have previously received injectable MPA than were women delivered of normal infants.

Offspring of women who used oral contraceptives prior to conception constitutes a larger sample that should provide relevant information. In fact, cohort studies of over 20,000 offspring have failed to detect evidence for mutagenicity. Further verifying the safety is the failure of national surveillance reports to record an increase in any Mendelian disorder after the introduction of oral contraceptives. By constrast, a sudden increase in phocomelia first suggested that thalidomide cause tetraphocomelia.

Sometimes overlooked as a source of data concerning gene mutations is the sex ratio. Induction of lethal X-linked recessive mutations decreases the proportion of liveborn males. Mutations at any X-linked loci would contribute to the decrease. Moreover, observations would have general applicability because agents that induce X-linked mutations also induce autosomal mutations. Several large cohort studies provide no evidence of an altered sex ratio, contradicting two earlier studies of very small sample size.

Finally, neither MPA, NET nor NGT are representative of those classes of compounds known to be mutagens. For example, progestins do not yield mutations in the Ames test.

Conclusion. Definitive proof that progestins do not induce mutations would require locus-by-locus analysis, a truly impossible task. However, relative safety can be assumed on the basis of acceptable alternatives: 1) comparing the overall frequency of malformations in previously exposed and previously unexposed women and 2) searching for sex ratio changes. Neither approach suggests that progestins are mutagenic. Previous oral contraceptive users show no evidence for a mutagenic effect, nor do the few pregnancies occurring after discontinuation of injectable or implantable progestins show an increase in anomalous liveborns. Incidentally, failure of progestins to induce mutations causing anomalies offer reassurance against unexpected mutagenic effects (e.g., cancer) later in life.

B. Numerical chromosomal abnormalities

That prior hormonal exposure could induce chromosomal abnormalities has been the subject of surprisingly intense investigation. Actually the hypothesis is not unreasonable. Oocytes remaining in dictyate of miosis I until ovulation might complete meiosis sluggishly as a result of hormone exposure. Resulting abnormalities would be cytogenetic.

Almost all relevant data have been derived from women previously exposed to oral contraceptives. Systematic cytogenetic studies following injectable/implantable progestins have not yet performed. Clinical impressions are unfortunately of limited value because not all chromosomal abnormali-

ties manifest abnormal phenotypes at birth.

Initial concerns were generated by Carr, who reported an increase in chromosomally abnormal abortuses: 48% in abortuses of women previously using oral contraceptives and only 22% in controls. Most of the excess was due to polyploidy. However, these observations were not confirmed in later studies. Boue reported abnormal complements (16% polyploidy) among 243 previous contraceptive users, compared to 63% (18% polyploidy) among 604 controls. Lauritsen found a slight excess in those women previously using oral contraceptives (61% v. 49%). The insignificant increase was due to momosomy X and structural abnormalities, however, and not polyploidy as Carr had reported. Alberman observed 32% abnormalities in 524 prior users, compared to 26% in 428 controls. Dhardial found differences of a similar, but again, insignificant magnitude. In induced abortuses, Klinger similarly noted an insiginficantly higher frequency in prior contraceptive users (1%) than in controls (0.5%).

Failure to confirm Carr's initial findings is especially noteworthy because any of several biases would spuriously yield increased abnormality rates in exposed groups. First, unrecognized induced abortuses are surely more likely to be included inadvertently among controls than among women who ceased contraception in order to attempt pregnancy. Indeed, illicit abortions furnish a likely explanation for the unusually low (22%) frequency of chromosomally abnormal abortuses in Carr's controls. Second, ovulation may be delayed immediately after contraceptive discontinuation, unwittingly producing abortuses younger than controls, who are more likely to have normal cycles. The frequency of chromosomal abnormalities is inversely related to gestational age; thus, unrecognized earlier gestational ages would lead to ostensibly higher abnormality rates among prior contraceptive users.

Yet other evidence suggests that oral contraceptives do not induce numerical chromosomal abnormalities. First, if prior contraceptive use leads to chromosomal abnormalities, the absolute frequency of spontaneous abortions should increase after hormonal discontinuation because 50% to 60% of first trimester abortuses show cytogenetic abnormalities. To the contrary, several large prospective studies show no increase in abortion rates. Second, increased frequencies of liveborns with Down syndrome should be evident inasmuch as trisomy in both abortuses and liveborns is presumably caused by the same cytologic mechanism (nondisjunction). Neither a case control study nor prospective studies show such an increase. Down syndrome has on the basis of surveillance studies not increased in frequency since oral contraceptives were introduced.

Conclusion. Initial concern generated by Carr's observing an excess of polyploid abortuses following cessation of oral contraceptives has been replaced by a consensus that progestins do not predispose to chromosomally abnormal abortuses, and no study has suggested such an effect in liveborns. Injectables or implantable progestins should similarly prove safe.

C. Structural Chromosomal Abnormalities

Several in vitro studies claimed increased chromosomal breakage in lym-

phocytes of contraceptive users. Thus, the possibility that progestins could be mutagenic (clastogenic) needs to be considered. However, breakage studies are hazardous without rigorous "blind" analysis to guard against unwitting bias. Confounding experimental variables are also legend. Further attesting to lack of a clinically significant increase in structural chromosomal abnormalities is failure to observe increased structural chromosomal abnormalities in abortus studies. There is similarly no evidence for an increase in anomalous liveborns. Finally, structural chromosomal abnormalities in liveborns would be expected to contribute to an increased overall anomaly rate, a phenomenon we have already concluded does not exist.

Conclusion. Progestins may or may not induce chromosomal breakage in vitro. Irrespective, the possibility of increased structural abnormalities occurring in offspring of women previously exposed to progestins seems extremely remote.

IV. OVERALL CONCLUSION

Critical review leads this investigator to conclude that injectable or implantable progestins are very unlikely to exert teratogenic or mutagenic effects. Of course, prudent physicians must always be cognizant of potential deleterious effects, and should continue to gather data that can confirm this sanguine conclusion.

TABLE 1. Summaries of prospective studies evaluating effects of progestin during pregnancy. Use of different methodologies preclude meaningfully pooling disparate data bases. However, the clear consensus is that progetins in the doses received were not teratogenic.

Investigator	Sample	Control	Anomalies	Comment
Smithells (1965)	189 wommen receiving hormonal pregnancy tests (United Kingdom)	None	0-2/189	Anomalies ("patent ductus arteriosus" in twins; "systolic murmur") may or may not exist
Rice-Wray (1966)	321 women receiving oral contraceptives, 7 of whom received drug during pregnancy (Mexico)	None	0/7	
Peterson (1969)	15 women who used oral contraceptives during pregnancy (United States)		1/15	
		669 women who used non-steroid contraception	6/699 (0.8%)	
		427 women who used contraceptives before, but not during, pregnancy	7/427 (1.6%)	
Spira (1972)	9566 women, interviewed in the third month, who received hormones (mostly for pregnancy support or diagnosis) (France)		171/9566 (1.8%)	Anomalies equally frequent in exposed and unexposed pregnancies
		8387 not receiving hormones	168/8387 (2.0%)	

Investigator	Sample	Control	Anomalies	Comment
Harlap (1975)	11468 women, 432 receiving "hormones" (Israel)		47/432 (10.9%) all anomalies; 21/432 (4.9%) major anomalies only	Small increase (25%) ($p < .02$) observed but recall bias possible because interviews months after exposure
		11036 unexposed	925/11036 (8.4%) 426/11036 (3.9%) major only	
Kullander and Kallen (1976)	6376 pregnancies from which 194 mothers had abnormal infants (Sweden)		5/194 were exposed to progestogen (2.6%)	Exposure rates similar in both groups
		5002 women delivered of normal infants	98/5002 were exposed to progestogen (2.0%)	
Royal College General Practitioners (1976)	136 pregnancies conceived during oral contraceptive therapy		2/136 (1.5%)	No differences among groups
		11009 pregnancies non-users	177/11009 (1.6%)	
		5530 pregnancies in prior contraceptive users	86/5530 (1.6%)	
Goujard and Rumeau-Rouquette (1977)	12895 mothers interviewed in the first trimester, of whom 1165 were exposed (France)		5/335 (1.5%) "testosterone derivatives"; 15/830 (1.8%) "progesterone derivatives"	Chromosomal anomalies excluded from analysis no differences observed either overall or after separate analysis for cardiac and skeletal defects
	(Same population as Spira)	9822 non-exposed	160/9822 (1.6%) non-exposed	

Investigator	Sample	Control	Anomalies	Comment
Heinonen (1977)	Collaborative Perinatal Project (50282 women) 1958-66, of whom 1042 were exposed to "sex hormones" and 866 to progestogens only (United States)		19/1042 (1.8%) cardiac after any sex hormone exposure; 75/866 (8.7%) all anomalies after progestin exposure alone	No significant difference for total anomalies but significantly increased for cardiac anomalies alone (relative risk 2 $p < 0.05$). Relative cardiac risk 1.8 for progestogens alone ($p < 0.05$). However, some infants (e.g., 4 of 19 cardiac defects) exposed only during first lunar months, others exposed only during fourth lunar month.
		49240 not exposed to to any sex hormones; 49416 not exposed to progestogens	385/49240 (.8%) cardiac; 3172/49416 (6.5%) all anomalies	
Nora (1978)	118 women who received hormones in "first trimester" (United States)		16/118 (13.6%)	Probably not truly prospective for controls with bias toward unrecognized exposure in controls. Exposure interval not well defined.
		At time of delivery of exposed women, "control infant without....exposure ....selected"	4/118 (3.4%)	
Torfs (1978)	Over 18000 women of whom 203 had "hormonal pregnancy tests" (United States)		9/203 (4.4%)	No significant difference among groups
		689 with serum pregnancy tests;	30/617 (4.4%)	
		332 with urine pregnancy tests;	9/332 (2.7%)	
		17057 with no pregnancy tests	650/17047 (3.8%)	

Investigator	Sample	Control	Anomalies	Comment
Goujard (1979)	3451 women, of whom 133 used progestins (France)		5/133 (3.8%)	Four of five anomalies occurring in subset of 35 women who used testosterone derivatives
		76/3318 non-exposed	76/3318 (2.3%) overall	
Vessey (1979)	66 pregnancies conceived while on oral contraceptives (United Kingdom)	None	1/66 (1.5%)	
Savolainen (1981)	3002 mothers of malformed infants, of whom 38 conceived while receiving "pills" (Finland)			Anomaly rates similar in sample and control, both for prior or concurrent contraceptive usage
		3002 matched controls, of whom 39 conceived while receiving "pills"		
Michaelis (1983)	13643 pregnancies of whom about 10% received hormones for diagnosis or support		4/320 (1.3%) Progesterone alone; 11/610 (1.8%) Progesterone and Estradiol	No significant difference between exposed cases and their unexposed matched controls
		Matched controls within same population who were not exposed		

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BLEEDING PATTERNS WITH LONG-ACTING STEROIDAL CONTRACEPTIVES

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Progestins are used as long-acting steroid formulations mainly alone without the combination with estrogen. The most widely used is a crystalline suspension of depomedroxyprogesterone acetate (DMPA) which is given 150 mg every three months. The next important is an oily suspension of norethindrone enanthate (NET-EN) which is given 200 mg every eight weeks. Although NET-EN was the first injectable steroid contraceptive, the larger experience with NET-EN has been accumulated not until during the last five years. The pharmacodynamics and metabolism of these two progestins are different. The elimination of medroxyprogesterone acetate is slow therefore, by increasing the dose, a longer duration of contraceptive effect can be obtained. NET-EN is eliminated almost completely in ten weeks and after the injection high but rapidly declining plasma concentrations are observed. Therefore, an increase in the dose does not prolong the fertility regulating effect on this formulation. During the high plasma concentration of NET, the ovarian function is strongly suppressed. Then with medium levels of NET there is an activation of follicular synthesis of estradiol which results in an elevation of plasma estradiol concentrations. Further declining plasma levels of NET after ten weeks results usually in a normal ovarian function with the ovulation. This mechanism of action results in quite regular artificial cycles with bleedings from the withdrawal of estradiol. The profiles of bleeding with NET-EN cannot be regulated by increasing the dose as one

can anticipate from pharmacokinetics but by using a different schedule of administration.

The number of days of bleeding and spotting during NET-EN treatment after abortion is presented in Figure 1. The injection schedule of 8-12 weeks was used. Those women having the longest bleedings discontinued the method after the third injection. This could explain the good bleeding control during the last months of the years.

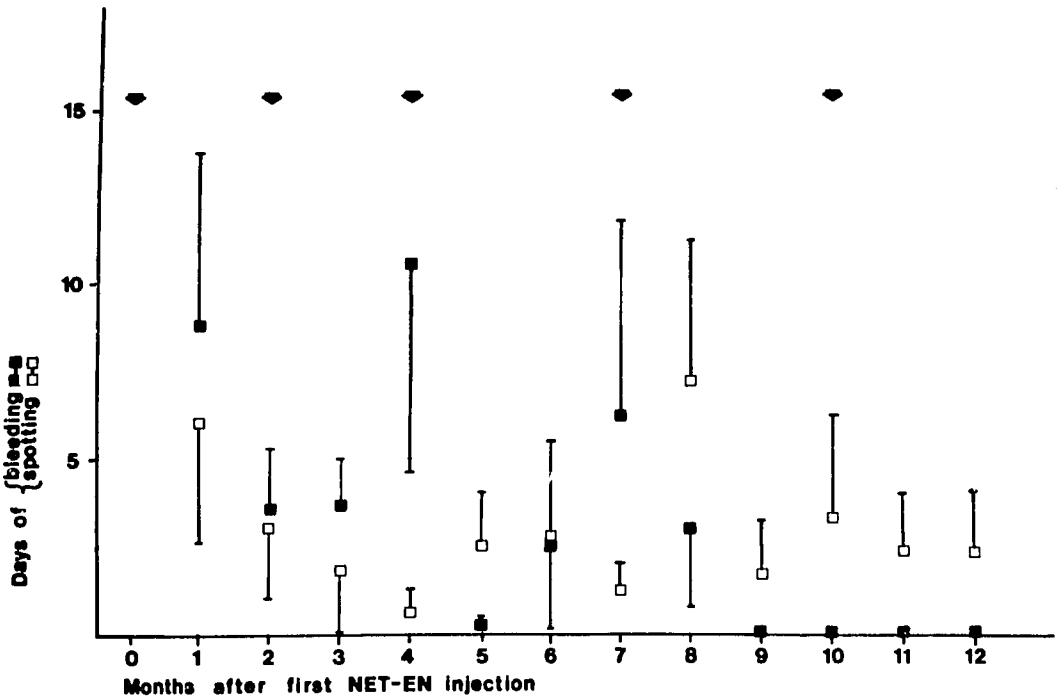

FIGURE 1. Mean number of days of bleeding and days of spotting during the first 12 months of use of NET enanthate 200 mg intramuscularly starting immediately after abortion.

If medroxyprogesterone acetate is given 150 mg every ninety days there seems to be a moderate suppression of the follicular function and complete suppression of the ovulation during the first 100 days. In the bleeding pattern during the first half year there is a complete disruption of the menstrual cycle. The profiles of bleeding vary from daily spotting to irregular bleding episodes for a few days. During the second half of the year there is an increased incidence of amenorrhea. Usually most of the patients are amenorrhoic after one year of use.

Experience using DMPA as a contraceptive has revealed a high discontinuation rate because of irregular bleedings. The number of bleeding and spotting days of those who continued the method is presented in Figure 2. The mean number of bleeding and spotting days was calculated for every 30-day period of bleeding days. The number of bleeding days is low during the first month after the injection and increases until the subsequent injection. After the third injection there seems to be a clear cumulative effect of the drug. The average number of spotting days is highest usually during the second month of injection. This

analysis seems to support the view that higher plasma concentrations are associated with lower average number of bleeding days. It could be that giving an injection every 6 weeks during the first 6 months could result in a sharp reduction of the number of bleeding days and an earlier introduction of amenorrhea.

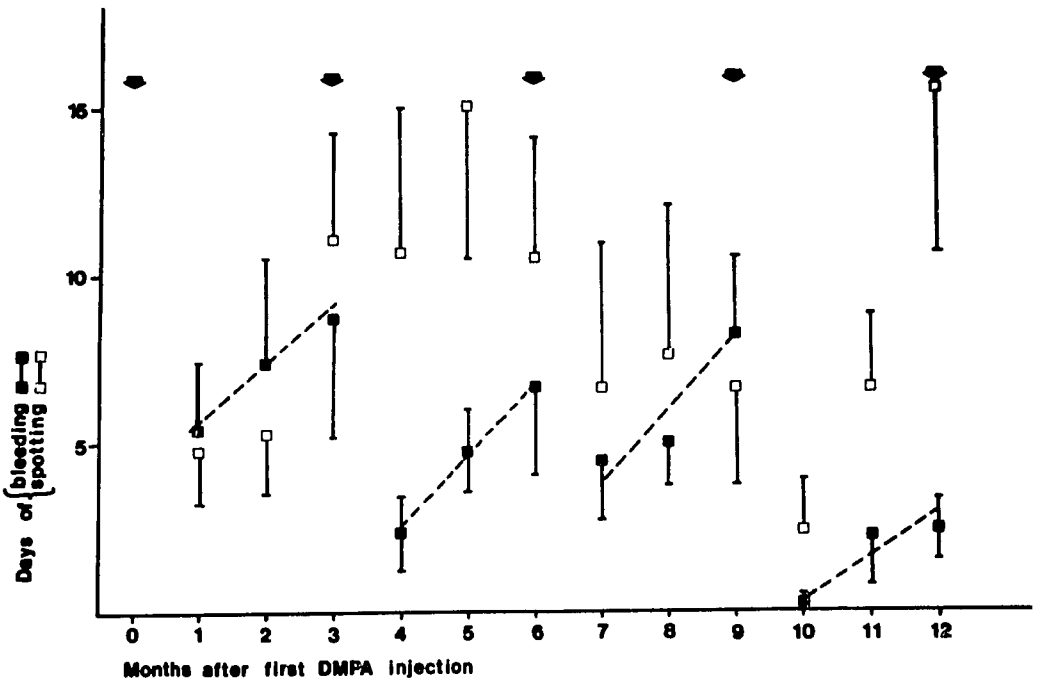

FIGURE 2. Mean number of days of bleeding and spotting during the first 12 months of use of depomedroxyprogesterone injections every 90 days.

Medroxyprogesterone acetate can also be administered immediately at the abortion and during the full lactation between 6 to 8 weeks after the delivery. The comparison of bleeding patterns varies from clinic to clinic mainly because the recording and the definition of bleeding and spotting has been different from center to center. Therefore, it seems that for the analysis of the clinical results on bleeding problems a comparative study should be initiated so that the results of various clinics could be compared. In studies with long-acting steroidal contraception our laboratory has used the insertion of a copper-releasing IUD as a control method against which the bleeding patterns and side-effect of new methods have been evaluated.

The problems with injectable contraceptives are connected with the decline in circulating steroid levels. This limits the duration of the action and affects the bleeding control. The main reason for the discontinuation of the use of injectables is the irregularity of the bleeding pattern. In the Thai National Family Planning program, the menstrual problems were the main reason for the termination of the use of DMPA. The pharmacokinetics of the injectables make it impossible that the duration of action could be prolonged by using higher doses. It seems that the real sustained release can be achieved only by using semipermeable mem-

branes. This principle has been used in subdermal implants, vaginal rings and in steroid-releasing IUDs and ICDs. The membrane which regulates the release of steroid from the reservoir eliminates the high burst at the beginning and, depending on the chemical properties of the steroid and the membrane, different release rates and duration of efficiency can be obtained.

A subdermal implant which releases levonorgestrel, Norplant™ will serve as effective contraception for 5 years. The correct counselling results in a very low rate of discontinuation because of menstrual problems. Sivin reported annual cross event rates for menstrual problems to be between 6 and 7 during the first two years and thereafter the rate was 3 per year. Cumulative net event rate for menstrual problems was 14.1 at four years. Nilsson and Holma measured the amount of menstrual bleeding before implant insertion and during the first year of use and found that the amount of bleeding was significantly reduced during the use of norgestrel-releasing subdermal implants. Kurunmaki studied the contraception with levonorgestrel-releasing subdermal implant after abortion and found that the average number of bleeding days during 30-day period was higher during the months 3, 4, and 5 than the mean number of bleeding days of copper-releasing IUD (Nova-T) users, but after month 6 there was no difference. The standard deviation in the number of bleeding days of implant users was significantly higher, showing that in implant users there are women with frequent spotting and women with oligomenorrhea. The continuation rate with Norplant™ at one year was 91.7 and the discontinuation because of menstrual problems was 6.0. In the control IUD group the continuation rate was 74 and discontinuation because of bleeding and spotting 17. The last mentioned study clearly demonstrates the usefulness of a randomized comparative approach using copper-releasing IUD as a control for the evaluation of long-acting steroidal contraception. This study further demonstrates that the hemoglobin concentration is significantly increased in women using the Norplant™ subdermal implant for one year. The low discontinuation because of bleeding problems reflects a good counselling of the women. The reduced bleeding will cause feeling of well-being because of the improvement of hemoglobin.

Another promising long-ating steroidal contraceptive subdermal implant contains a new progestin St-1435 (Merck, Darmstadt, Germay). The silastic subdermal implant longer than 30 mm will release so much steroid daily that the ovarian function is completely suppressed and the majority of patients is amenorrhoic from the beginning of the treatment. The high potency of the steroid makes it possible to use only one implant which gives effective contraception for 10 to 12 months. The ovulation suppression can always be reached if the plasma concentration of ST-1435 is more than 50 pg/ml, and therefore the final daily dose should be selected by giving at least this plasma concentration. The attractiveness of this method is its use during lactation because it seems that the steroid if given by oral route, rapidly metabolizes to biologically nonactive metabolite and no active steroid is detected in the blood stream. Preliminary investigations show that an acceptable bleeding pattern can be obtained with one implant of 20 mm, but no studies have yet been conducted during lactation. Also, the use of Norplant™ during lactation, requires further investigation. It seems that the ideal time for the introduction would be six to eight weeks after the delivery during lacta-

tion, and methods for the detection of steroid in milk have been developed.

The only commercially available progestin-releasing IUD, the Progestasert, has a reservoir of progesterone which releases about 65 micrograms of progesterone daily for slightly more than one year. The benefit of Progestasert is the reduction of menstrual bleeding but the other problems, such as the irregular bleeding and spotting and possible increased rate of ectopic pregnancies, remain.

The use of active progestin levonorgestrel in an IUD resulted in the development of a long-acting steroidal contraceptive method which strongly affects bleeding pattern. The clinical trials show the significant reduction of the average number of days of bleeding when compared to the copper-releasing IUD. However, the removal rate because of bleeding and/or pain was equal for the norgestrel-releasing IUD and for the copper-releasing IUD as was the average number of spotting days. It seems therefore that the life-table method is not measuring the number of days of bleeding and the irregular spotting and bleeding is the main reason for the discontinuation which is recorded by the life-table. The number of spotting days is high during the first 90 days after the insertion of levonorgestrel-releasing IUD but it is well tolerated because the amount of spotting is very low. Adequate counselling will also decrease the discontinuation for spotting during the use of this method. A strong suppression of endometrium is observed during the intrauterine release of levonorgestrel. In many women this makes the endometrial cavity totally insensitive to estrogens and amenorrhea develops. During the use of the levonorgestrel IUD there is an increased incidence of this symptom. Other women will have very regular scanty bleedings, suggesting that a small part of the endometrium is not under the complete suppression of levonorgestrel and therefore responds to the normal ovarian function.

The insertion of the levonorgestrel-releasing IUD immediately after abortion results in good bleeding control. The performance is even better than with a copper-releasing IUD during the first 90-day period. Thereafter there is a significant reduction in the average number of days of bleeding and also in the days of spotting. It seems therefore that for those postabortal patients who are dissatisfied with other methods of contraception but are highly motivated for family planning, there should be levonorgestrel-releasing IUDs available for contraception.

The insertion of the levonorgestrel-releasing IUD during the full lactation demonstrated, during the first month after the insertion, almost daily spotting and scanty bleeding. The bleeding was minimal from the second month after the insertion and spotting decreased sharply and was well tolerated. It seems therefore that the levonorgestrel-releasing IUD can be inserted during the menstruation, during lactation and immediately after the abortion. There is a sharp reduction in the number of days of bleeding and in the amount of bleeding. This is also seen as a positive effect on the serum ferritin, which reflects the body iron stores. Women should receive counselling for increased spotting during the first months after the insertion and for increased incidence of amenorrhea during the long-term use. During amenorrhea ovarian and pituitary function is normal.

The preliminary experience with intracervical device releasing norgestrel has shown reduction in the number of bleeding days, regular scanty bleedings, and no occurrence of amenorrhea. This could be explained by the intracervical residence of the device and therefore the local effect of endometrium is suppressive, but complete suppression is never observed.

The bleeding pattern can be altered by administering the long-acting steroidal contraception immediately after abortion or during full lactation. The discontinuation of injectables during the first year of use may be decreased by more frequent administration of injection during the first six months which in turn will increase incidence of amenorrhea. From the programming point of view, the treatment of bleeding problems is not recommended. The proper counselling of women will decrease the discontinuation of use of subdermal implants or the intrauterine progestin-releasing IUD because bleeding is never heavy. For the health personnel on the field, an effective method of treatment of spotting and in case of injectables heavy bleeding can sometimes be very valuable for the individual patient. It could be that if an effective method of treatment is found this could enhance the acceptance of long-acting steroidal contraception, because the main problem of discontinuation can then be controlled.

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STEROIDAL CONTRACEPTION AND ABNORMAL BLEEDING: WHAT ARE THE PROSPECTS FOR IMPROVEMENT?

I.S. Fraser,
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Modern steroidal contraceptives are far from perfect, but they are effective and often highly effective contraceptive agents. Among the many reasons for women failing to use these agents, one of the most important is a disturbance of the normal menstrual rhythm. In some cultures major disturbances such as amenorrhea or prolonged breakthrough bleeding are quite unacceptable at the present time. The progestogen-only contraceptives tend to produce the most disturbances of bleeding patterns, but they do have some major advantages in that they contain no estrogen, may release very low quantities of steroidal per day and may have the great convenience of an injection only once very 2-3 months.

A scientific solution must be sought, and it seems clear that a prerequisite for a rational approach is a greatly increased knowledge of basic factors influencing initiation and prolongation of bleeding under various circumstances. At this stage there appear to be few simple correlations with the occurence of breakthrough bleeding and the identification, and quantitation of factor involved in the process may not

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be easy. There are many who are pessimistic about the possibilities for early improvement, especially of the long acting injectable formulations, but there have been several encouraging advances in knowledge within the past few years.

THE ENDOCRINE PERSPECTIVE OF THE NORMAL CYCLE

The endometrium is a unique tissue. It shows duration cycles of striking growth, differentiation, functional change and regression of a type which is not seen in any other tissue. These changes are accompanied by a dramatic development and then regression of blood vessels. The cyclical events in the normal endometrium are dependent on a specific sequence of endocrine events. In the first 6 days of the cycle there is an estrogen dominance with a high plasma estradiol-progesterone ratio, and this is followed by a striking surge of estradiol prior to ovulation. In the luteal phase there is a further estradiol surge accompanied by a major increase in the plasma levels of progesterone. These endocrine events produce a morphological picture in the endometrium which has been extensively studied.

The normal endometrium has an in-built "self-destruct" mechanism which allows a coordinated breakdown and partial shedding of tissue following the combined fall of plasma estradiol and progesterone to low levels. Under these circumstances the occurence of intermenstrual bleeding, except of microscopic amount, is uncommon.

THE ENDOCRINE PERSPECTIVES OF STEROIDAL CONTRACEPTIVE-TREATED CYCLES

The exogenous and endogenous hormonal fluctuations with different steroidal contraceptives have been thoroughly reviewed by Johannisson and Landgren. With the combined estrogen-progestogen pill there is a variable early estrogen dominance and a simultaneous sharp rise in estroger and progesterone to intermediate levels which fluctuate markedly from day to day for three weeks until the sharp simultaneous fall to baseline levels. This pattern is associated with morphological endometrial and vascular changes which have been extensively described and which differ substantially from the normal cycle. There is usually a predictable withdrawal bleed and although breakthrough bleeding is more common than in the normal cycle, it is not a major concern unless the combined steroid dose is very low.

The progestogen-only minipills and the constant-rate progestogen-releasing devices, such as implants and vaginal rings, result in a variety of endocrine profiles, a variety of endometrial morphological appearances, which have not been extensively studied, and a variety of abnormal bleeding patterns. With these contraceptives there is never an initial estrogen dominance or a complete progestogen withdrawal. In general terms, with the low-dose progestogen minipill and with very low dose zero-order progestogen-release devices, regular withdrawal bleeding occurs; breakthrough bleeding is not good, but it is not too bad. As the progestogen dosage is increased, the incidence of amenorrhea, breakthrough bleeding and lack of withdrawal bleeding increases, but there is a great individual variation between women. It is worthy of note that in some women a high anovulatory rise and fall of endogenous estradiol may not be fol-

lowed by a withdrawal bleed.

Monthly injectables containing an estrogen ester and a progestogen ester offer some hope of providing more regular bleeding patterns. Although the epidemiological information on bleeding patterns with monthly injectables is inadequate, there is evidence that some patients will develop breakthrough bleeding and amenorrhea. An estrogen and a progestogen are injected simulataneously so that high plasma levels are achieved fairly quickly. The rate of clearance of each steroid will depend on the pharmacokinetics of the injected ester. If longer-acting esters are used there may be a progressive accumulation of drug. A withdrawal bleed usually occurs some days after the fall in estradiol.

The long-acting injectable progestogens and the high-dose progestogen-only releasing devices results in the greatest disturbance of the menstrual pattern. With the injectables there is an enormous initial progestogen dominance followed by a gradual progestogen withdrawal. Ovulation is inhibited and endogenous plasma concentrations of estradiol and progesterone remain low until the exogenous progestogen has fallen to very low levels. With these agents, there is an initial rapid "maturation" of the endometrium through the secretory changes to suppression and finally atrophy by day 20. At this stage the epithelium has a low cuboidal appearance. From day 50 there is gradual reversal of the atrophy with increasing development of columnar epithelium, stroma and vascular elements. Normal proliferative appearances have usually been restored by day 90. Sometimes a pseudodecidual response is seen. The morphological appearances have been described by several authors but have not been extensively studied.

Uterine bleeding patterns may be classified into three broad types:

- that which occurs when the endogenous or exogenous hormone levels are falling and one would expect bleeding. This may be termed normal menstruating or, with contraceptive agents, withdrawal bleeding. It is again worth noting that withdrawal bleeding does not always occur with contraceptive agents when levels of the endogenous or exogenous hormones fall.

- that which occurs unpredictably and which may be termed breakthrough or intermenstrual bleeding. It is this which is of most importance to the discontinuation of contraceptive use especially when it is frequent, heavy or prolonged.

- amenorrhea or complete absence of uterine bleeding for longer than an arbitrary period, often taken as 45 or 60 days, is common with some steroidal contraceptives. It can be a major source of concern to some women, especially in certain cultures.

From this evidence it seems that the bleeding patterns become worse when higher doses of progestogen-only agents are used, but it is obvious that no close correlation exists between endocrine factors and the initiation or prolongation of bleeding.

In the clinical stiuation with spontaneous menstrual disorders it is well

recognized that bleeding may begin when endogenous estradiol levels are constant or even when they are rising.

CURRENT STATUS OF KNOWLEDGE OF FACTORS RELATED TO ENDOMETRIAL BLEEDING

1. Patterns of bleeding

A large body of information is available on the epidemiology of bleeding patterns with many of the steroidal agents, but unfortunately many of these studies cannot be compared due to lack of standardized methodology. Knowledge about the bleeding patterns with progestogen-only contraceptives is much less extensive than for the combined estrogen-progestogen pill. The major problem with these studies is that large numbers of subjects must be studied prospectively, and in-depth assessment of the endocrine, endometrial and other factors correlating with their bleeding problem, or lack of bleeding abnormalities, has always been very difficult.

It has been established that many women specify menstrual disorders as the major reason for discontinuing use of steroid contraceptives, and that the extremes of amenorrhea and prolonged bleeding are least well tolerated.

2. Endometrial function

The paucity of basic scientific information about aspects of endometrial function which may be directly relevant to the study of abnormal bleeding is impressive.

Factors affecting development of the endometrial vasculature seem to be a major importance and some information is available about these. There is a good understanding of the three-dimensional architecture of the arterial and venous part of the vasculature of the endometrium during the normal cycle, but minimal information during steroidal hormonal treatment. There is a large literature concerning the light microscopic appearances of the vessels in normal and contraceptive-treated endometrium, but little about the ultrastructure or the perivascular tissues. An interest is now being taken in the proliferation kinetics of the endometrial cells and vessels, but the factors stimulating this have barely been considered. Estrogens have a strong influence on growth of the capillaries and the increase in blood flow through them, but progesterone appears essential for the full development of the spiral arterioles. Study of the endometrial enzyme content and its changes has given some functional insight into changes in vascular activity during this growth phase.

Lysosomal enzymes may be important during the early remodelling/regeneration phase of the cycle. However, information in this whole area is meager. It is perhaps relevant that lysosomes can be mediators of hormone action. In recent years, study of the steroid hormone receptors in endometrium has indicated the importance of an understanding of the way in which they mediate hormone action. However, knowledge of the way in which changes in receptors and changes in tissue concentrations influence endometrial and vascular growth is lacking. There is no doubt that some vascular tissue contain specific receptors for hormones, including estro-

and this must have some importance for the interpretation of vascular function.

There is no information about other factors which influence growth of the endometrial vessels. It has recently been demonstrated that LH-releasing hormone has a direct stimulatory effect on uterine growth in animals and this requires further exploration.

It is clear that many factors have a striking influence on function of the endometrial vasculature. There seems little doubt that prostaglandins have important actions on the endometrial vessels *in vivo*. For example, the concentration of prostaglandins E_2 and F_{2a} in human endometrium increases progressively during the menstrual cycle, infusion of PGF_{2a} decreases endometrial blood flow in monkeys and ingestion of prostaglandin synthetase inhibitors decreases menstrual blood loss. Steroids also have a direct vascular action and estrogens, particularly, have a rapid vasodilator effect which is probably mediated through synthesis of an intracellular enzyme. Several biochemical processes, involving substances such as histamine, bradykinin and prostaglandins may be involved in mediation of estrogen effects on vascular function.

Many factors may play a part in the regulation of blood flow through the normal endometrium and through different regions of the endometrium. Oxytocin and vasopressin stimulate vasoconstriction in the endometrium but the physiological significance of this unknown. It has been reported that PGF_{2a} secretion can be stimulated from the endometrium of non-pregnant sheep by oxytocin and this obviously requires further study in women. No *in vivo* studies have been reported on the action of angiotensin on endometrial vessels in non-pregnant women or animals, although angiotensin II has been shown to stimulate *in vitro* prostaglandin E secretion from human umbilical vein endothelium. There is some evidence that increased production of prostaglandin E may be associated with excessively heavy bleeding in women with spontaneous menstrual disorders.

Histochemical studies have demonstrated several active enzyme systems in endometrial vessles and the activity of most of these does seem to vary during the menstrual cycle. The most widely studied enzymes have been alkaline phosphatase and acid phosphatase and these do not develop in a normal pattern during treatment with contraceptive steroids. It is not entirely clear how these changes in enzyme activity are reflected in changes in function.

It is now obvious that receptors must be present to mediate the action of these hormones and study of the concentration and turnover of receptors is an important part of the interpretation of hormone function. Studies to date have mainly concerned steroid receptors and it seems that we are only just beginning to understand the complexity of these systems. The discovery that endometrial receptor concentrations vary depending on the site of sampling within the uterine cavity may indicate variable hormone responsiveness or even greater likelihood of breakthrough bleeding from certain areas. Of some importance is the observation that progesterone and progestogens inhibit the replenishment of estrogen receptors in endometrium and other uterine tissues. This may have implications for the ability of progestogen-treated endometrium to

respond to estrogens given to treat breakthrough bleeding.

It seems likely that increasing knowledge of the interaction between different hormones and receptor systems will begin to reveal the true complexity of hormone action in the endometrium. Few other hormone receptors apart from steroids have been studied in human endometrium. Endometrial oxytocin receptors have been investigated in the sheep and these show an increase to a peak at estrus, when the binding capacity of the endometrium is double that of the myometrium. Oxytocin enhances the release of prostaglandin F_{2a} from endometrium in culture and the degree of enhancement increases at estrus. It will be valuable to study the interaction of other hormones in detail under various circumstances.

If nonhuman primate models are to be used for future basic studies, much more comparative information on vascular function and blood flow to the uterus is required. Approaches such as the use of radioactive-labelled microspheres may be useful. It is noteworthy that basic reproductive processes have been studies so far only in few of the more than 200 subhuman primate species.

3. Endometrial breakdown

There is some knowledge of the events occurring during the breakdown of the vasculature and shedding of the endometrium, although there are still large gaps in the picture. Much of the present understanding still comes from elegant studies in menstruating subhuman primates by investigators such as Markee and Hartman, but unfortunately many of their feelings have been directly extrapolated, without qualification, to the human.

The one study which stands out above all others is the meticulous and extensive investigation of endometrial autotransplants to the anterior chamber of the eye of the rhesus monkey by Markee. This work indicates that an intense spasm occurs in the spiral arterioles immediately prior to the onset of menstruation and confirmation of this comes from histological studies. The vasoconstriction persists through menstruation but individual vessels show intermittent relaxation and bleeding. The spasm occurs particularly at the endometrial-myometrial junction and in the inner myometrium.

The cause of the spiral arteriole constriction is not known. It has been suggested that prostaglandin release may play a part, but loss of amine oxidase activity within the endometrium might sensitise the endometrial vessels to circulating catecholamines. Endometrial amine oxidase activity increases in the secretory phase, but it is not clear if a fall occurs at menstruation. The endometrium is not innervated by adrenergic nerve fibers but is capable of a significant uptake of adrenaline and non adrenaline. Release of vasoactive substances or precusors from lysosomes may also be involved.

Spiral arteriole constriction is associated with a rapid fall in endometrial capillary flow and hydrostatic pressure, a decrease in stromal edema and a rapid decrease in thickness of the endometrium. Withdrawal of estrogen probably also causes an increase in capillary permeability and fragility, but arteriolar constriction may lead to the appearance

of holes or breaks observed largely in the small vessels of the functionalis layer. Capillary fragility can be reduced by ethamsylate which also reduces bleeding time and menstrual blood loss. Ethamsylate apparently has an anti-hyaluronidase activity which decreases the rate of breakdown of mucopolysaccharides in ground substance of the capillary wall. This suggests that a reduction in vessel damage in the endometrium has a beneficial effect on menstrual blood loss. It is not clear whether ethamsylate also has other actions.

It is probable that lysosomes and the lysosomal hydrolases are involved in the mechanism of menstruation, but it is not known whether or not their role is restricted entirely to remodelling of the tissue after breakdown. It has been suggested that relaxin, a water-soluble peptide of molecular weight about 8,000, is released from endometrial granulocytes as progesterone levels fall and may play a part in the dissolution of intercellular bonds.

The mechanism of haemostasis in the uterus is still not well understood, but it now clear that it differs from that in most other body tissues. Hemostatic plugs containing platelets and fibrin do appear to be important, although these may be partially inhibited by heparin, or prostacyclin release, or broken down prematurely by the very active fibrinolytic system in the endometrium. Studies of menstrual blood have given some insight into the processes occurring within the uterus at menstruation, but much remains to be learnt.

There is still controversy amongst morphologists about the exact extent of tissue shedding at menstruation. The traditional view was that the entire endometrium above the basal layer was shed at the end of each cycle, but more recent studies indicate that there is a very variable and often relatively small loss of tissue from the superficial "compact" and "functional" layers. On average this shedding is accompanied by a hemoglobin loss equivalent to 30-40 ml of blood.

This brief summary of the present understanding of some of the mechanisms involved in the breakdown of normal endometrium gives very little idea of the differences which may be present during the breakdown of contraceptive-steroid treated endometrium. In particular, there is very little idea of the factors which precipitate and prolong intermenstrual or breakthrough bleeding.

4. Breakthrough bleeding

It is clear that there are abnormalities of the endometrial vasculature in contraceptive-treated women. These may include prominent dilatation of superficial stromal venules, inhibition of spiral arteriole development, endothelial proliferation and, occasionally, localized intravascular thrombosis.

In order that breakthrough bleeding may begin there must be vascular damage in some form. At a functional level this could just involve diapedesis with very small amounts of blood loss, but in most cases it is more likely that actual breaks will occur in vessels. It is not known whether these occur in arterioles, capillaries or venules and there are few clues

to the underlying cause of the damage. There may be increased "fragility" of the capillaries with abnormal changes in the perivascular supporting tissues, but some precipitating factor such as release of lysosomal enzymes, hypoxia or trauma may need to be postulated.

Once vascular damage has occurred, local defects of coagulation, vascular function and tissue repair may contribute to the prolongation and volume of the blood loss.

5. Present treatment methods

In this state of knowledge the actual options for treatment of established bleeding have been greatly restricted. The options have been restricted to discontinuation of the method, reassurance and explanation, a number of arbitrary estrogen regimes or rarely, curettage. This limited and uncertain situation obviously requires urgent clarification. It ought also to be emphasized that at present there are no realistic ideas on how this abnormal bleeding may be prevented in steroidal contraceptive users.

FUTURE STRATEGY

Future strategy should include the simultaneous pursuit of 3 distinct and complementary goals:

Mission-oriented basic studies to elucidate the factors contributing to abnormal bleeding. Since it is the very nature of basic information that there are always new and exciting ideas involving many workers and that data collection never comes to an end, there must always be an emphasis on the mission-orientation.

Well-planned clinical studies must always be emphasized in order to follow up present leads and new findings whenever they appear.

Long-term development of improved steroidal contraceptive methods which may minimize the occurrence of menstrual disturbances. Long-term development of improved methods of treatment and of non-steroidal agents to prevent bleeding problems may also be rewarding.

BASIC STUDIES

Basic investigations may be extremely complex and may need to take into account some or all of the following conditions:

(i) Steroid-treated endometrium and the factors which may influence it.
(a) under therapy with different steroidal agents and different durations of use.
(b) with and without breakthrough bleeding.
(c) during the use of therapeutic agents.
(d) during the recover period following withdrawal of steroid-contraceptive use.

Some attention ought to be directed towards an understanding of the factors which cause predictable amenorrhea, since this may be acceptable in some communities and could have significant health benefits in terms

of reduction of body iron loss.

(ii) Normal endometrium and the factors which may influence it for comparison with the abnormal sitution, preferably in the same laboratory using the same method.

This whole area is one in which particularly fruitful collaboration might be initiated with bioengineers or other basic scientists who have expertise in the use of modern electronic techniques which may be applied to the in vivo situation. Many of these problems may initially only be amenable to study with in vitro techniques. The importance of in vitro techniques should not be underestimated, but the problems of interpretation must be appreciated. The hormone-releasing intrauterine devices (IUD) provide a special case where care in studying different areas of the endometrium reveal unexpected and relevant information concerning abnormal bleeding. Consideration might also be given to the potential of modern electronic technology in developing IUDs carrying sensor devices for transmitting a variety of information from the uterine cavity.

Suggested areas for fundamental research

1. Morphology of the endometrial vessels

(a) Growth of the vessels. It is important that factors which stimulate vessel growth in the endometrium be studied specifically. There is good evidence to show that estrogens are important in the stimulation of proliferative activity of endometrial cells and vessels, but there is no information about the occurrence of other growth factors, perhaps of the type exemplified by platelet growth factors. There is no indication why the arterioles in the endometrium always take up a spiral conformation when stimulated by the specific sequence of endocrine influences in the normal cycle. This spiral conformation seems important in the mechanism of normal menstruation and requires further elucidation. It might also be rewarding to contrast the endometrium with the endosalpinx which also contains vessels which undergo spiral growth and regression each cycle. Why does the tubal mucosa have spiral arterioles yet not exhibit "menstrual" shedding?

(b) Vascular architecture. There is little knowledge of the three-dimensional vascular architecture of the endometrium during treatment with different steroid combinations. Information of the type obtained by Farrer-Brown et al, in the normal uterus might give useful clues for investigation of abnormal bleeding.

(c) Superficial dilated venules. A great deal more attention need to be given to the factors which influence the development and progression of the superficial dilated venules in endometrium treated with contraceptives, especially of the progestogen-only type.

These thin walled dilated venules may be etiologically important in the genesis of breakthrough bleeding. However, it requires to be established whether they really are venules, since formed blood elements are not usually seen in them. Are they perhaps dilated lymphatics which have picked up a few stray red cells within the endometrium?

(d) Perivascular tissues. Much more needs to be learnt about the components of the perivascular tissues, both cellular and non-cellular. These factors may be extremely important in terms of capillary and venule fragility.

(e) Cells containing "granules". Mast cells and granulocytes may be found in perivascular areas, and there is evidence that they may contain substances which will have an effect on vascular function, e.g. heparin, histamine or relaxin. Their true importance is quite unclear.

(f) Endothelial changes. Endothelial alterations, such as proliferations and protrusions, have been reported, but there is little idea of their importance in terms of function. This requires further detailed study to correlate morphology and function.

(g) Lymphatics. Knowledge of the lymphatic system in the human endometrium is negligible and much further work requires to be done to elucidate its extent in different situations and the part which it plays in endometrial breakdown and remodelling.

(h) General morphology of the endometrium. It is worth considering that uniformity of descriptive terminology and understanding of the basic morphology of the contraceptive-treated endometrium is still lacking. All future studies on morphology ought to bear this in mind.

2. Hemostatic mechanisms in the endometrium

(a) Arachidonic acid metabolism in platelets. The inter-relationship between the thromboxanes of platelet origin and their interaction with the prostacylin-synthetase system of the vascular endothelium within the endometrium will obviously be an area fro fruitful research for those who are prepared to take the necessary care with methodology. The place of specific inhibitors and potentiators requires exploration. Simple studies of bleeding time and malondialdehyde production with contraceptives and breakthrough bleeding are required.

(b) Sequence of endometrial breakdown. There is still considerable uncertainty about this sequence of events. It is now appreciated that the endometrial hemostatic reaction is deficient compared with other tissues, but why is this so? What events precede the initial vascular damage? What departure from normal endometrium is seen with contraceptives, and particularly with breakthrough bleeding?

(c) Fibrinolysis. The endometrium contains an active fibrinolytic system, but it is not certain which hormonal factors influence this or which organelles are responsible for synthesis of the plasminogen activator. Is this fibrinolytic activity merely a reflection of a generalized lysosome breakdown? How much fibrinolysis occur in the uterine cavity and how much fibrinogenolysis is there? How does this depart from normal with abnormal bleeding with contraceptives?

3. Other factors which influence the microcirculation of the endometrium

(a) Arachidonic acid metabolism in endometrium and endometrial vessels.

This requires further study in parallel with the metabolism of arachidonic acid in platelets (see above).

(b) Effects of prostanoids on vessels. Most of these substances are vasoactive but their relative importance within different phases of endometrial development requires a great deal of further elucidation. For instance, do the spiral arterioles become more sensitive to certain prostanoids in the premenstrual phase?

(c) Effects of other vasoactive substances on vessels. There is information about the influence of several hormones on blood vessels within the endometrium but it is by no means clear which factors, or how any factors, play a part in the regulation of blood flow within the endometrium under different circumstances. It is possible that blood flow may vary independently within different parts of the endometrium at any one time. An observation which requires further study is that blood flow can fall sharply in response to psychological influence, suggesting mediation through the sympathetic nervous system.

(d) Capillary dynamics. This area of study has been neglected in relation to the menstrual cycle and abnormal bleeding. There is some evidence that capillaries in the fingernail bed show changes at the time of menstruation, but this has not been well investigated. It is possible that study of capillaries in easily accessible parts of the body, such as the nail bed or retina, may give useful clues about vascular response in different circumstances and this is easily amenable to study. The interpretation of findings from direct observation of human endometrial vessels at hysteroscopy is fraught with great difficulties.

(e) Capillary fragility. A greater understanding of this feature of the endometrial circulation in contraceptive-treated women is a high priority. Studies of this area should place particular importance on the assessment of therapeutic agents which decrease fragility, as well as natural factors which may be responsible for increasing fragility. It is possible that nail-bed capillaroscopy might also be applicable here.

4. Hormones and their targets

(a) Plasma steroid levels. In recent years, endocrinologists have been greatly concerned with the measurement of plasma hormone levels under different circumstances. Plasma measurements of endogenous and exogenous steroids will continue to be important to provide a background for tissue studies.

(b) Tissue steroid concentrations. In many situations the availability of a steroid at a tissue level may be more important than gross fluctuations in plasma levels. This concept, as well as the possibility of interconversion of steroids in the tissues, requires closer attention in future studies.

(c) Steroid receptors. Receptors provide the cellular link betwen the hormone and its action and it has recently become increasingly clear that a knowledge of cytoplasmic and nuclear receptor concentrations and their turnover rate is crucial to the understanding of steroid action in dif-

ferent circumstances. This field requires much more detailed research in women treated with different steroids and particularly as part of the investigation of breakthrough bleeding. There is also little information on steroid receptors and the changing influence of steroids on the endometrial vessels in different situations.

(d) Non-steroidal hormones and their receptors. Plasma and tissue concentrations of non-steroid hormones and their receptors may be of greater importance than is currently realized. It is probable that interactions between these different hormones will also turn out to be important. The hormones which need to be studied may include prolactin, LH-releasing hormone, insulin, prostanoids, oxytocin, vasopressin, catecholamines, angiotensin and perhaps also compounds such as serotonin, histamine, bradykinin, etc.

(e) Endometrial lysosomes and enzymes. Further study of lysosomal function is a high priority in women with breakthrough bleeding since unstable lysosome function could certainly contribute to this problem. Lysosomes may contain many enzymes and it is likely that there are different populations of lysosomes containing different enzymes under varying circumstances. There is a great need for the development of improved biochemical and histochemical technology for studying the activity of free and bound enzymes in different cells fractions and new technology is required for the ultrastructural localization and quantitation of enzyme action within cells. Application of improved immunochemical techniques would be useful. A specific case can be made for a careful study of lysosome function in the endometrial vessels.

5. Animal models

Since primates are the only creatures who menstruate, subhuman primates are the only possible animals models for the study of true menstruation. It is also clear that some subhuman primates may be less appropriate models than others. Since much of current knowledge of the process of menstruation comes originally from subhuman primates, it is reasonable to presume that much more could be done in this field.

(a) Comparative study of endometrial morphology and menstruation. There is very little detailed information on the differences in endometrial morphology between the menstruating and non-menstruating subhuman primates. There is still controversy over the question of whether spiral arterioles are present in all those species which menstruate. It is suggested that careful comparisons may provide useful clues for further investigations in women.

(b) Direct visualization of endometrial transplants. It has been suggested that a great deal of sophisticated information could be obtained by the repetition, using modern technology, of Markee's experiments with autotransplation of small endometrial fragments into the anterior chamber of the eye in rhesus monkeys. However, there is increasing ethical concern about this approach. An alternative might be to use an immunologically privileged site, such as the hamster cheek pouch, for the transplantation of human endometrium. This would permit direct inspection of the tissue under different endocrine influence. Studies of this kind

are in progress in some laboratories.

(c) Repeated biopsy studies. The subhuman primate model may offer some advantages for multiple biopsy studies which would be ethically unacceptable in the human, but easy access to the uterine cavity must therefore be possible in the species chosen.

(d) Removal of normal uterus. Investigations where removal of a normal uterus is essential can appropriately be performed in subhuman primates. An example of this type of study is the use of radioactive-labelled microspheres for the measurement of absolute blood flow which could then be correlated with other parameters of endometrial function.

(e) Testing of new therapeutic agents. This may be the major value of animal models. Promising agents may be used in subhuman primates when toxicology testing is still insufficient for human usage. The most appropriate models at present still seem to be the baboon, rhesus monkey and stump-tailed macacque. However, there remains the problem of demonstrating whether breakthrough bleeding occurs with reasonably high frequency with contraceptive steroids in any of these animal models. Even if this does occur there is still concern about the lack of knowledge of comparability of the endocrine and endometrial profiles with the human situation.

CLINICAL STUDIES

Although less space will be devoted to these than to the ideas for basic investigations, the central importance of these clinical studies and their early initiation is obvious.

1. Epidemiology of patterns of bleeding

(a) Standardization of epidemiology methodology. This is an important aspect requiring further world-wide cooperation so that different studies may be comparable. Consideration should also be given to standardization of nomenclature.

(b) Epidemiology of bleeding patterns with monthly injectables. Phase II studies of the bleeding patterns of at least two of the available monthly injectables are required to give reasonable data to determine how satisfactory these agents may be in large scale use.

(c) Comparative study of different progestogens. There is anecodotal evidence that some progestogens, when given in low dosage, may be less inclined to cause troublesome breakthrough bleeding than others. This needs to be confirmed in a large scale trial using progestogen dosages of approximately equal efficacy in preventing pregnancy.

(d) Quantitation of blood loss. There is no information on the volume of blood loss during withdrawal bleeding or breakthrough bleeding with any steroidal contraceptive except the combined estrogen-progestogen pill. It is expected that total blood loss will be low in most patients, but no information is available.

(e) Identification of possible predictive factors for bleeding patterns. Recent evidence suggests that simple pretreatment measurements of follicular phase/luteal phase length ratios may correlate with the likelihood of disturbance of ovarian function while taking the 300 ug norethisterone minipill. This is a subject which has been given very little attention, but it is possible that patients with a particular menstrual cycle profile may be more likely than others to develop menstrual disturbances with progestogen-only contraception.

2. Treatment of established bleeding abnormalities

(a) Comparative evaluation of estrogen regimes. Estrogens have been used haphazardly for the treatment of breakthrough bleeding associated with combined oral contraceptives, the progestogen-only minipill and injectable contraceptives. There is no clear indication that any one regime is better than another, and there is an obvious need to set up good comparative studies of different regimes for each different contraceptive method. These comparative studies should also contain a placebo-group as well as one or two groups treated with the non-steroidal compounds discussed below.

(b) Comparative evaluation of prostaglandin-synthetase inhibitors. These drugs, and particularly the fenamate, mefenamic acid, should be considered for inclusion in any comparative study of treatment for heavy or prolonged bleeding. There is good reason to expect a beneficial effect of these drugs on heavy bleeding, but there is anecdotal evidence to suggest that they may not be as effective for prolonged or frequent episodes of bleeding.

(c) Comparative evaluation of other non-steroidal agents. Other drugs mentioned previously in this volume may have a role in treating or preventing abnormal bleeding. Consideration should be given to including some of them in clinical studies or at least ensuring that further evaluation of their mechanism of action is carried out at a basic level. These drugs include the fibrinolytic inhibitors, ethamsylate, vasopressin analogues, anti-heparin agents and tamoxifen.

(d) Treatment of amenorrhea. Most investigators believe that if a patient cannot tolerate amenorrhea she should not be asked to use a long-acting injectable like DMPA. In this situation a monthly injectable may be preferable, but it is not certain that a monthly injectable will produce a predictable withdrawal bleed when it is started soon after the patient discontinues DMPA. This is amenable to investigation.

LONG-TERM DEVELOPMENT

Three areas may be considered at a philosophical level.

1. Remodelling of the steroid nucleus

Is it possible to produce a greater separation of progestogenic effects on the hypothalamo-pituitary unit and the endometrium by manipulation of the steroid nucleus, or is it possible to produce a reliable anti-implantation effect without a serious effect on endometrial vascular function?

Is this a vain hope? Might once-a-month anti-progestogens produce a reliable withdrawal bleed without disturbing the subsequent cycle?

2. Non-steroidal agents for the prevention of bleeding abnormalities

What are the chances of developing a simple non-steroidal agent which could be taken perhaps once per week and reduce bleeding problems, for example by an effect on capillary fragility?

At present there is no available agent to prevent breakthrough bleeding, except for the addition of frequent or prolonged exogenous estrogen to the regimen.

3. New agents or delivery systems for the treatment of bleeding

What are the chances of developing new and safe agents for treatment? This is likely to have to wait until more basic information or mechanisms is available. It is conceivable that simple microcapsule delivery systems may be devised which would allow vaginally-administered medication to migrate through the cervix and act specifically within the uterine cavity, but this requires a great deal of further investigation.

CONCLUSION

The etiology and management of disturbances of the menstrual cycle associated with the use of steroidal contraceptives have, until recently, been greatly neglected. Since there are also large areas of uncertainty in the understanding of the mechanisms underlying normal endometrial function and menstruation, useful solutions are likely to require a great deal of applied research. For some reason, applied research has always seemed relatively unglamorous, but, in the word of Sir William Bate Hardy, recalled by Sir Henry Tizard in his Haldane Lecture of 1955, "You know, this applied science is just as interesting as pure science, and what's more it is a damn sight more difficult!"

The scientific world is faced with a most difficult, complex and challenging problem if it is to eliminate these disturbances of bleeding patterns. However, there seems to be little doubt about the possibilities for intellectual satisfaction from the work which can be immediately initiated in this area, and there is no question of the immediate and major practical significance which new advances will have.

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MONTHLY INJECTABLE CONTRACEPTIVES

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Monthly injectables share the advantages and drawbacks of injectables in general, but they are associated with a better cycle control than that observed with formulations given every 2-6 months. On the other hand, the need for frequent injections every 4 weeks or 30 days represents a practical inconvenience that may be reflected on the acceptability and continuation rates.

Formulation

There are many formulations used as injectables which differ from each other in many respects. The most relevant difference relates to whether the injectable is made of a progestogen only or contains an estradiol ester as well. The second aspect involves the type of progestogen present, and its dose. A third difference relates to the mode of manipulating the steroid molecule to prolong its action, such as by esterification, crystal formation or mixing with biodegradable polymer. The last variable in this connection is the nature of the injection vehicle.

The first report published on monthly steroid injections for contraceptive purposes appeared in 1963 and dealt with the administration of a combination of 500 mg 17 - hydroxyprogesterone corporate plug 10 mg estradiol valerate. At around the same time in China a similar monthly injectable (but using half the dose) has been under clinical evaluation. It is estimated now that this combination monthly injectable (termed

in China "Injectable No. 1") is used by 1% of all contraceptive users in China.

Tables 1 and 2 show a tentative list of the monthly injectables that have been tested in humans. Most of these injectables have been used in limited trials to probe their potential value as contraceptive agents. Only a few formulations have been administered in sufficient number of cycles to provide a meaningful evaluation in clinical terms. The most common progestogens used were depot medroxy progesterone acetate (DMPA), dihydroxyprogesterone acetophenide and norethisterone enanthate (NET-EN). In the combination types, only estradiol esters have been used (cypionate, valerate, enanthate, benzoate, unducelate, benzoate butyrate and hexahydrobenzoate). Types containing DMPA aqueous suspensions having the progestogen in crystalline form while those with NET-EN were oily solutions (mixture of benzyl benzoate and castor oil in a ratio of 6:4).

TABLE 1. Combined estrogen - progestogen monthly injectables.

Progestogen	Estradiol ester	Commercial or Trial Name of Drug
(1) DMPA	Cypionate	Cyclo-provera
(2) 16-17 dihydroxyprogesterone acetophenide	Enanthate	Deladroxate or Perlutal or Tobasel
(3) 16-17 dihydroxyprogesterone acetophenide	Benzoate butyrate	Unimens
(4) 17 -OH Progesterone caproate	Valerate	Gravibinon
(5) Norgestrel	Hexa-hydrobenzoate	--------
(6) Superlutin caproate	Valerate	Lutofollin
(7) Norethisterone enanthate	Valerate or Unducelate or Cypionate	--------
(8) Norethisterone	Mestranol	
(9) Megestrol acetate	Cyclopentyl propio- or valerate	--------
(10) Chlormadinone caproate	Valerate	--------

It is apparent from the large number of monthly injectables listed in Tables 1 and 2 that the development of a proper formulation acceptable has not yet been achieved. Various estrogen - progesterone combinations and progestogen - only types have been, and still are being tested in a

Table 2. Progestogen and estrogen only monthly injectables

Progestogen	Estradiol ester	Commerical or trial name of drug
Progestogen only		
(1) Lynestrenol phenyl propionate	------	------
(2) 16-17 dihydroxypro-gesterone acetophenide	------	Deladroxone
(3) 17 -OH-Progesterone caproate	------	------
(4) DMPA	------	------
(5) Norethisterone enan-thate	------	------
(6) 17-OH-19 Norproges-terone caproate	------	SH - 582
(7) 20B-OH, 4,9 nor pregnane 3 one, 20B phenyl Propionate		
Estrogen only		
------	Estradiol Unduce-late	Progynon depot

wide range of doses to detect optimal formulations. Also, special delivery systems as gelatin or polyglycolic - polylactic microcapsules for controlled release may improve the clinical performance of the monthly administration schedule.

Mechanism of action

The mechanism of action of monthly injectables is partially known for only few preparations. Most of the available investigations in this connection were conducted in women who received only one or few injections, presenting changes which may not be identical to those present after many injections, hence there is a need for studies among long-term users.

The metabolic fate and excretion values of the two steroids in Deladroxate (150 mg dihydroxyprogesterone acetophenide = DHPA + 10 mg E_2 enanthate = EE) were studied in two women following an i.m. injection of H^3 EE plus non-eadioactive DHPA and in two other volunteers who received ^{14}C DHPA plus non-radioactive EE. The same experimental design was repeated after 4 to 6 cycles of Deladroxte therapy. The results indicat-

ed a higher excretion of the progestogen in feces while the estradiol ester was preferentially excreted in urine and no significant differences in the metabolic turnover were detected after chronic treatment with the drug. The mean plasma disappearance rate was 7.5 days for EE and 24 days for DHPA. However, traces of labelled EE were still detectable in the blood 60 days after the injection.

The reported endometrial effects of monthly Deladroxate injections were rather controversial; some studies showed a pattern similar to that seen with combined O.C.'s. While others concluded that the injections induced endometrial changes indicative of estrogenic predominance over the progestogenic component. Occasional hyperestrogenic endometrial picture, has also been reported. Moreover, other investigators found a confused and mixed endometrial picture. The changes induced by one injection were commonly carried over to the next cycle due to enough of the active agents remaining to alter the regenerating endometrium.

The main mechanism by which Deladroxate prevents pregnancy so effectively is by inhibition of ovulation, which has been documented in most studies evaluating this aspect. Also, the carry-over effect of the injections may contribute to the delay in the return of fertility observed in some subjects after discontinuation of use.

The monthly injectable Unimens contains the same progestogen as Deladroxate but differs with respect to the estradiol ester where E_2 butyrate-benzoate (10 mg) replaced the original E_2 Enanthate which was believed to remain in the body for period longer than desired. This new E_2 ester has a duration of action that approximates the aim of 3 weeks. Endometrial biopsies taken premenstrually following administration showed a secretory appearance indicating a progestational predominance.

The pharmacokinetic and pharmacodynamic data following injections of cycloprovera (25 mg depot medroxyprogesterone acetate = DMPA + 5 mg estradiol cypionate = EC) have been reported in a multicenter study undertaken by WHO. Twelve subjects from four centers were recruited and each one received three consecutive injections at 4 week intervals. There was no evidence of ovulation during therapy and for 7 weeks following the last injection. After the third injection, the plasma MPA levels are detectable for 28-62 days while follicular activity returned between 28-50 days in all the cases.

Endometrial biopsies performed during the first months of cycloprovera therapy revealed distinct phases of endometrial proliferation and secretion, but after 6 months, endometrial hypoplasia became the dominating feature. The karyopyknotic index of vaginal smears obtained from women using cycloprovera showed a definite shift towards progesterone dominance. One of the studies with cycloprovera indicated that the drug effect was cumulative and suggested that the interval between injections be increased, or that the monthly dose of progestogen be decreased after 3-4 months of ordinary dosage.

The effect of different estrogen - progestogen monthly injectable combinations on ovulation has been studied in the People's Republic of China. Eight milligrams of NET-EN plus 5 mg estradiol valerate inhibited ovula-

tion in all of the 100 subjects studied while megestrol acetate (2.5 mg) plus estradiol cyclopentylpropionate (5 mg) prevented ovulation in 73 out of 77 cases during the treatment cycle. Other preparations of megestrol acetate were shown to inhibit ovulation in 88% of studied subjects.

A combination of 50 mg NET-EN and 5 mg E_2 valerate has been shown to offer a promising potential following preliminary trials in two centers and was given the code name of HRP 102. Initial data indicated that this combination as well as cycloprovera (DMPA 25 mg + EC 5 mg) probably contain a dose of progestogen higher than that required since most subjects presented detectable plasma progestogen levels and ovulation inhibition for periods longer than one month. In view of these findings, ongoing studies sponsored by WHO are evaluating lower dosage combinations of both cycloprovera (DMPA 12.5 mg + E_2 2.5 mg) and HRP 102 (NET-EN 25 mg + E_2 valerate 2.5 mg). Moreover, these Phase I studies also incorporate groups of subjects given the progestogen alone (either DMPA 25 mg or 12.5mg or NET-EN 50 mg or 25 mg).

In India, monthly progestogen-only injectable contraceptives have been tried in different doses. DMPA was evaluated in a dose range of 10-20 mg given at monthly intervals. The 10 mg dose had a high failure rate, did not inhibit ovulation and did not have any effect on the target organs except the vagina since vaginal cytology showed a progestational pattern. With the 15 mg/monthly dose ovulation was not inhibited in many cases but cervical mucus showed atypical arborization at midcycle and no pregnancies were reported in a limited number of subjects. Raising the dose to 20 mg inhibited ovulation and the mid-cycle arborization of the cervical mucus but the menstrual cycle was severely disrupted. The authors concluded that the optimal monthly injections i.m. DMPA dose was 15 mg. A series of experiments with NET-EN given at monthly injections in doses of 10, 20 or 30 mg were carried out by the same group of investigators. The 20 mg i.m. monthly dose induced reproductive changes rather similar to the 15 mg DMPA dose, and the NET levels in the blood were still measurable 30 days after administration in six out of the seven studied cases. In three subjects ovulation was inhibited, two other cases showed delayed ovulation till 33-36 days post-injection and one subject had a normal ovulatory pattern. Addition of 0.5 mg estradiol enanthate to either injectable to improve cycle control achieved its aim but resulted in many pregnancies due to method failure.

The pharmacokinetic properties of three estradiol esters (Cypionate, Valerate and benzoate) were investigated to select the one with optimal profile for incorporation as a monthly injectable. An i.m. dose of 5 mg resulted in a peak plasma level of estradiol 4 days after the cypionate and 2 days following the injection of the valerate or the benzoate. Increased levels of estradiol were detected in plasma for 11 days with the cypionate, for 7-8 days with the valerate and only for 4-5 days with the benzoate. There were marked variations from one subject to the other but the valerate ester appeared to possess the most predictable pharmacokinetic bahavior.

It therefore appears from the above data, apart from the progestogen-only mini - injectable approach, that most of the monthly injectable combined

preparations in current use contain relatively higher doses of steroids, especially the progestogen component, than that required for a monthly contraceptive. Moreover, the optimal dosage of monthly injectable steroids that is neither associated with a high falure rate or a carry-over effect on subsequent cycles may be clarified when the results of the ongoing pharmacokinetic/pharmacodynamic studies carried out by WHO become available.

Contraceptive efficacy

The ability of monthly injectables to prevent pregnancy depends on the above variables. The combination types are highly effective contraceptives and their theoretical effectiveness approximates that of combined pills but concerning use-effectiveness, the available data speak in favor of the monthly injectables. Almost no pregnancies have been reported in association with the use of cycloprovera, Deladroxate and NET-EN + E_2 unducelate.

These three preparations offered a contraceptive efficacy of about 100% in more than 32 thousand cycles of use. Other combinations used in the People's Republic of China in a larger number of cycles had a Pearl index ranging between 0-1.44.

Monthly injectables containing a progestogen only had a higher rate of failure and most of these types have not been tested in large enough series to permit a conclusive opinion as to their protective value against pregnancy. However, the failure rate ranged between 0-28%. With respect to the mini-injectable approach, the use of i.m. 20 mg NET-EN at monthly intervals was associated with a method failure rate of 5 pregnancies (1 ectopic) during 2,892 treatment cycles. This regimen appears promising but needs further confirmation prior to use in large scale trials.

Cycle control

Women using monthly injectable preparations usually experience some disturbances in their menstrual cycles which may range from mild alterations up to complete disruptions of the cycle. These changes depend on the presence or absence of estrogens, on the type of steroid used and its dose, and certain individual variations. In general, monthly injectables provide a more acceptable cycle control than formulations administered less frequently. Among those given every month, the types containing estrogens provide more predictable bleeding patterns than those lacking estrogens.

Menstrual cycle disturbances were the most common complaint among users of Deladroxate injections. The general trend of cycle events was one of an initial shorter cycle with increased amount of bleeding followed by a gradual lengthening of the cycles and scantier bleeding episodes. The overall reported abnormalities in the study conducted in Alexandria are shown in Table 3. The lack of heavy bleeding in this study is contradictory to other studies where heavy and prolonged bleeding episodes occasionally requiring curettage, have been reported.

TABLE 3. Menstrual disturbances during Deladroxate therapy.

	No. of Cases	Percent	Average No. of Cycles Affected	Average Duration of therapy (months)
Polymenorrhea	26	84.0	10.5	15.0
Hypomenorrhea	22	71.0	3.0	16.0
Amenorrhea	2	6.5	4.0	15.0
BTB	17	58.8	2.5	16.6
Menorrhagia	--	----	----	----

BTB - Breakthrough bleeding.

Unimens combination injectable which contains the same progestogen but a shorter acting estrogen defied theoretical expectations since irregular spotting and shortening of cycles during treatment was commonly encountered. Also, there was a delay in resumption of normal cycles following interruption of medication. The discrepancy between theoretical assumptions and clinical results was attributed to a relatively low dose of the estrogen ester (estradiol butyrate-benzoate) in the vial.

Cyclo-provera appears to induce a better and more acceptable cycle control than the above mentioned two preparations. A high dose (double the one in current use) of both the progestogenic and estrogenic components led to marked disruptions of the menstrual cycle. Several studies compiled by the manufacturer include 6,021 cycles of cyclo-provera use in the recommended dose of 25 mg DMPA and 5 mg EC showed a breakthrough bleeding in 34% of subjects; half of these cases, however, experienced this event only once. Moreover, cycle length was within normal limits in at least 80% of cases. Trials using variable doses (15-25 mg DMPA and 3-5 mg EC) showed no differences overtime in the number of bleeding days per cycle up to 30 mohths. The occurrence of amenorrhea during cyclo-provera contraception increases with continued use being around 10% in the first year and 25% by the end of 2 years. Contrary to Deladroxate, heavy bleeding requiring curettage is rarely if ever, needed among cycloprovera users.

Gravibinon which contains 250 mg 17 - hydroxy progesterone caproate and 5 mg E_2 benzoate has a short duration and therefore the initial dosage requires 2 injections in the first cycle (together or 10 days apart), then once on the 10th to 12th day of the cycle. Very short cycles are liable to ensue while twice a month injections of half the doses did not improve the clinical outlook due to breakthough bleedings, though cycle length improved to 20-24 days.

Few studies evaluated other monthly estrogen - progestogen combinations and claimed an acceptable cycle control in 80-90% of cases, but the number of cases in each study was quite limited requiring further confirmation in larger groups of women. On the other hand, similar studies with monthly progestogen-only injectables were quite disappointing in this respect. Estrogen alone as a contraceptive injection induced a high frequency of amenorrhea that was occasionally associated with endometrial

hyperplasia.

Return of fertility after discontinuation

The consensus among most workers is that the carry over effect contributes to the delay in recovery of fertility following discontinuation of deladroxate use (Table 4). The duration of infertility, however, was variable and without permanent residual gonadotropin suppression and the delay was believed to be totally reversible. With cyclo-provera contraception, there was also a tendency towards some delay in the return of fertility after discontinuation, ranging between 1-29 months (mean of 7.25). Unimens use as a contraceptive in a small number of cases resulted in a delayed resumption of normal cycles following interruption of medication. The above data contribute to the general feeling at present that available monthly contraceptive preparations are probably overdosed and investigation of lower doses is warranted. This assumption is further supported by the data following discontinuation of low dose NET-EN monthly contraceptive (20 mg/month) where 100% of cases resumed normal menstrual pattern within 3 months and 82.2% got pregnant within 9 months after withdrawal of the injectable.

TABLE 4. Return of fertility following discontinuation of Deladroxate therapy.

No. of Cases	Parameter of Evaluation	Period of Infertility (range in weeks)
23	E.B.	6 - 14
94	B.B.T. and pregnanediol	4 - 42
33	Pregnancy	7 - 192

E.B. = Endometrial biopsy
B.B.T. = Basal body temperature

Nonmenstrual side effects and metabolic changes

Apart from cycle disturbances, other side effects such as breast tenderness, fluid retention and weight gain, hypertension, headaches, dizzziness, dysmenorrhea and decreased libido have been reported with various monthly preparations. These diverse complaints were inconsistent, generally insignificant and their true relevance requires careful assessment in comparative studies with different injectables as well as placebo. It is well known from studies of combined pills versus placebo that many of these side effects can occur in the absence of the active ingredients. An increase or a decrease in weight has been reported in association with deladroxate therapy, which diminishes the likelihood of a direct correlation with the drug.

Breast tenderness was relatively common but periodic breast examination revealed absence of local abnormalities. Two investigations revealed an elevation in B.P. in some cases receiving monthly Deladroxate injections

but this response was reversible following discontinuation. The effect of the drug on libido was controversial since some studies reported a decrease in libido during treatment while others reported no changes or even an increase in libido. Laboratory investigations (Hematologic, blood chemistry and liver, thyroid and adrenal functions) indicated the absence of a potential toxic effect.

Fewer studies reported on the minor side effects and laboratory investigations during cyclo-provera therapy. There were no significant changes in weight or in B.P. as a result of cyclo-provera treatment while minor side effects such as breast ache or tenderness, headache, dizziness, etc. were occasionally encountered.

With the other monthly preparations, the available information related to nonmenstrual side effects and metabolic changes is very scarce since few subjects were given each of these formulations. The low dose progestogen-only monthly injectable (NET-EN 20 mg) induced insignificant changes in body weight, arm circumference, fat fold thickness or in B.P. following 24 months of repeated injections. Also HB. concentration was not altered as a result of treatment.

Neoplastic potential

The tumor inducing potential of monthly injectables is an unresolved issue, particularly with preparations containing estrogens. Though the human data in this respect show no evidence of increased risk of neoplasia, yet the relatively limited experience with these agents and the lack of well controlled prospective and case control studies make a conclusion in this regard difficult at the present time. Moreover, animal toxicology data with some monthly injectables pointed towards a possible hazard of developing tumors in some animal species.

All vaginal cytologic studies during Deladroxate therapy revealed absence of abnormal findings except two studies that detected a few suspicious class smears. Even in the latter reports, the authors concluded that a correlation between the drug and the cytologic changes was unlikely and without any evidence to support it. With cycloprovera treatment, there were no abnormal Papanicolau among 6,021 cycles of use either at 6 or 12 months following the onset of cycloprovera administration.

The theoretical concern about using preparations containing estrogens is more valid when it is related to the endometrium. Endometrium hyperplasia has been reported in some cases using Deladroxate monthly contraceptive injections but there were no cases of endometrial atypia or carcinoma. These findings indicate a relative predominance of the estrogenic component and may carry a certain risk among long-term users. Combined formulations with progestogenic predominance such as cycloprovera or those containing no estrogens are probably safer in this respect.

The breast is another target organ at potential risk of developing tumors in response to steroid therapy. This is substantiated by certain toxicological studies in some animal species. Despite the controversy; about animal models as valid experimental tools in the study of tumorogenic potential of steroids, the fact remains that some studies in dogs reveal-

ed the potential risk of developing breast cancer with Deladroxate. However, none of the human trials with this injectable supported such a tendency. Data on cycloprovera use in women also seem to show no breast abnormalities.

Animal toxicology studies with Deladroxate also demonstrated some evidence of increased cellular activity in other organs such as pituitary hyperplasia in rats and uterine swellings in dogs.

Lactation

Monthly injectable preparations containing estrogens appear to have some adverse effects on lactation, both in milk yield and composition. However, in one study evaluating this aspect during Deladroxate use, the authors believed that lactation was not altered. It is more likely that such formulations would probably behave in a fashion similar to combined O.C. pills.

The use of preparations containing progestogens only during lactation seems to be more favorable than combined injectables, especially in developing areas where nursing of the newborn constitutes a major health and economic problem. Low dose NET-EN (20 mg/month) did not reduce milk output or alter the duration of lactation. There is a need for more studies in this area to document the safety and validity of using injectables during lactation.

Acceptability and continuation rate

These are two interrelated aspects that are difficult to assess unless carefully monitored data on large scale use are available. Most of the available monthly formulations were only tested in a small number of cases. A drug that may be highly accepted in one area may be totally rejected in others.

The monthly injectables tested in large enough samples of women to provide data on acceptability and continuation rates are Deladroxate, cycloprovera and the Chinese injectable No. 1 (Table 5). Most of these formulations were generally acceptable in clinical use but the different studies reported a wide range of continuation rates. The main advantage of monthly preparations as compared to the 3-monthly schedule is the better cycle control. The monthly regimen, however, has two drawbacks; these are the need for repeated visits to the clinic for monthly injections, and the theoretical hazard of long-term use of depot estrogens.

The discontinuation rate of Deladroxate use was about 40-60% by the end of 24 months, and the most common cause of dropouts was the menstrual irregularities. Cycloprovera appears to be more favorable in this respect, and both injectables seem to be more acceptable than the 3 monthly preparations.

TABLE 5. Efficacy, acceptability and main side effects of the three most commonly used monthly injectables.

Drug	Cycles	Pearl Index	Acceptability	Main side effect
Deladroxate	20,677	0	Moderate to excellent	Moderate cycle disturbances
Cycloprovera	11,229	0	Good up excellent	Minor cycle disturbance and delayed return of fertility
Gra'ibinon = (Chinese injectable No. 1)	54,196	1.44	Moderate	Marked cycle disturbances

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NORETHISTERONE ENANTHATE INJECTABLE CONTRACEPTIVE

H.K. Toppozada

Norethisterone enanthate (NET/EN) is now registered or being registered in 70 industrialized and non-industrialized countries as a long-acting contraceptive steroid. It has no life threatening side effects, and clinical evidence from 17 years of use as a contraceptive agent shows no additional and possibly fewer adverse effects than are found with other hormonal contraceptives. It has a higher continuation rate than orals, and a rate equal to or slightly lower than IUDs at the end of one year of use.

Norethisterone of norethindrone was synthesized by Schering, AG Berling laboratories in the late fifties, and its acetate ester was used orally as a contraceptive since then. NET/EN was available as a contraceptive since 1966; in 1975, Schering accepted a cost-sharing contract from the National Institute of Health (NIH), Center for Population Research to develop further this long-acting injectable contraceptive.

NET/EN is 17a-ethinyl-4-estren-3-one-17B-yl-keptanoate 200 mg in 1 ml of an oily solvent mixture of benzyl benzoate and castor oil at a ratio of 4:6. It is a C18 steroid belonging to the 19-nor testosterone group. It is commercially named Norigest or Noristerate in different countries.

Actions

It exerts its action in humans and animals differently, so animal models

are not suitable for the study of its toxicology. Though it is mainly progestational in humans, it is estrogenic in rodents. Its estrogenic activity in rats increases the secretion of prolactin which stimulates mammary growth and nodule formation in the breasts. No evidence of significant changes in human breasts or vagino-cervical smears exists with its long use in humans.

As NET/EN is given in oily solution, it has to be hydrolized after injection to the biologically active NET. The blood level increases rapidly to reach a peak within 5 days, then it declines rapidly. The steroid is usually undetectable in the blood after 70 days.

It acts on the hypothalamus and depresses the midcycle pulsatile LH surge, while the tonic release is not affected, as the pituitary remains responsive to exogenous LHRH and TRH up to 8 weeks. This central mechanism is mainly exercised in the first half of the period between injections, and the peripheral action in the second half.

NET/EN may also have a peripheral action on the ovaries, because when it is injected premenstrually it inhibits progesterone secretion and leads to withdrawal bleeding. A high frequency of ovarian cortical fibrosis and occasional thickening of tunica albuginea have also been reported.

The cervical mucus was always found progestational, thick and viscous with lack of sperm penetration and/or sperm capacitation. The endometrium becomes poorly developed and atrophic, and this results in impaired implantation of any fertilized ovum as its capacity to support and nourish the blastocyst is diminished. The tubal function is also involved in its contraceptive action, as the egg transport becomes impaired.

Modes of administration

NET/EN is either given alone or with an estrogen. It is given monthly, every two or three months, according to the following regimens:

1. Monthly injections. These contain NET/EN with an estrogen in one of the following compositions and dosages:
   a. 50 mg NET/EN with 5 mg estradiol benzoate,
   b. 100 mg NET/EN with 10 mg estradiol benzoate, or
   c. 50 mg NET/EN with 5 mg estradiol unducelate.
2. Two monthly injections. 200 mg NET/EN.
3. Two monthly injections 200 mg NET/EN for 6 months and then every 84 days.
4. Three monthly injections. 200 mg NET/EN every 84 days.

In all schedules, the first injection is given within the first five days of the menstrual cycle. It is most effective to prevent pregnancy when given according to schedule 3 above. In schedule 4, about 25% of women will ovulate within the first 60 dyas after injection, and within 90 days about 60% will have ovulated.

In Alexandria, we tried the 200 mg NET/EN on 164 women for 143.8 woman years. They were divided into three groups: (a) 43 cases every 84 days, (b) 67 cases every 60 days for 6 months, then every 84 days (shifters),

and (c) 54 cases every 60 days all through.

Two pregnancies occurred in group (a) during one year; both were estimated to have occurred ten weeks after the first injection. No pregnancies occurred in groups (b) and (c).

Side effects

1. Though menstrual cycle disturbances are the most common side effects of NET/EN, they have a significantly lower incidence than in women taking depot medroxyprogesterone acetate (DMPA).

   a. Bleeding and spotting were noticed more frequently one month after injection and again before the next injection. This biphasic bleeding pattern may be due to the initial peak of NET/EN plasma level just after the injection and to the resumption of ovarian function before the next injection. The basic mechanism of the bleeding is not fully understood, as the blood levels of the steroid and the morphology of the endometrium are not closely related to the bleeding patterns. Bleeding and spotting are important reasons for discontinuation in Moslem and Hindu women. The bleeding is always scanty and may be controlled by estrogens or rarely by curettage.

   b. Amenorrhea of more than 90 days was not found to be an important cause of discontinuation, as it accounted for 8.4% of discontinuers only. It is probably due to a carry-over of the effect of NET/EN on the hypothalamus, pituitary, ovary or endometrium, or any combination of these. When LHRH is given to the subjects, they can still ovulate so its effect is probably mainly through the hypothalamus.

      Amenorrhea is a cause of concern, as the women consider themselves pregnant until proved otherwise. Some of them cases are resistant to therapy and the amenorrhea may last for several months.

2. Weight changes. Most of these were reported from uncontrolled series, yet these changes could not be attributed to NET/EN alone.

   It may induce hyperinsulinemia and promote glycogen storage in the liver, and it stimulates deposition of body fat. In our series 63% increased in weight, 17.4% showed no changes and 19.5% lost some weight.

3. The unborn fetus may be affected if the mother is given an injection inadvertently. It may cause defeminization in the female fetus as NET/EN is a 19-nor testosterone preparation. Experience shows no teratogenic risk on progeny and a twofold increase in risk of cardiovascular defects.

4. There is also some concern about using NET/EN in diabetic or prediabetic women, although it was never reported to cause diabetes in women, nor were there any changes in serum proteins. There were re-

duced seromucoid levels, and these were attributed to a direct effect on liver function.

5. Liver function was not seriously affected. No changes in thymol and zinc turbidity tests, serum alkaline phosphatase, bilirubin, SGOT and SGPT tests were found. Although a significant decrease in prothrombin activity and an impairment in BSP clearance was found - which means an effect on the hepatocellular function - there was no change in the blood coagulation mechanism.

6. Although there is some evidence of a link between oral pills containing progestogens and estrogens on venous thrombosis, no changes were observed in the blood lipids or in the blood coagulation under NET/EN.

7. There is no proved risk of the development of neoplasia in the breast or in the genital tract.

8. Other side effects have been reported, such as decrease libido, headache, loss of appetite, backache, nausea, skin pigmentation and breast flabbiness. All of these, however, are subjective symptoms that cannot be proved to be caused by NET/EN.

Failures

In the WHO multinational trials, the failure rate was 0.4 $\pm$ 0.3 per 100 woman years when given every 60 days. The rate was 2.0 $\pm$ 0.7 when given every 60 days for the first 6 months and then every 84 days.

The failure rate reported from South America was 1.5 and in almost half of the cases it occurred in the third month when ovulation appeared, as proved by pregnandiol assays. In Alexandria, we had two pregnancies in 86 women treated for one year. Our Ponderal index of pregnant and non-pregnant cases was significantly different ($\pm$ 1.468), and our pregnant mean weight was 5.20 kg less than that of non-pregnant cases ($P<0.01$).

Return of fertility

In South America, 93.38% of the cases became pregnant by the end of the year in which the injections were stopped. Another study from the same continent reported 25.5% becoming pregnant after six months since the injections were stopped.

Acceptability

We studied 400 women in Alexandria, who accepted NET/EN injections as a contraceptive. Their reasons for acceptability were:

1. Easy to use - 40.6%; Effective - 40.6%
2. Few side effects 16.3%
3. Regulates menstruation 12.3%

NET/EN users appear to experience an increasing proportion of normal cycles as time passes.

Continuation rates

In Alexandria, we followed up 164 cases for 1.87 years and found that the total discontinuation rate was 26.8%, and of these 8.5% were attributed to bleeding and 12.9% to amenorrhea. In another WHO multicenter study, one year continuation rates were 75.6 per 100 women; bleeding problems were the most common reason for discontinuation (35.3%), while amenorrhea was responsible for 8.4% only.

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THE INJECTABLE CONTRACEPTIVE DEBATE: AN UPDATE

Peter E. Hall

The only injectable contraceptive drugs currently available are depot-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). Currently, DMPA has been approved for contraceptive use in 84 countries, and NET-EN in 40 countries. They are both progestogens but belong to different groups of steroids, medroxyprogesterone acetate being a C21-steroid and norethisterone enanthate a C18-steroid.

Medroxyprogesterone acetate has been used since the 1950s for the treatment of a variety of conditions including endometriosis, threatened abortion, precocious puberty, acromegaly, endometrial carcinoma, renal cancer, breast cancer, premature labor; doses of up to several grams have been administered without apparent adverse effects. In the early 1960s, it was noted that in women receiving DMPA for premature labor the return of fertility following delivery was markedly delayed, and clinical trials of DMPA as a contraceptive agent were begun in 1963. Since then, an estimated 10 million women have received DMPA for contraception, and approximately 2.0 million are currently using it. Administered by intramuscular suspension, DMPA exerts its contraceptive effect by suppression of ovulation. However, its effects on the endometrium, the fallopian tubes and the production of cervical mucus may also play a role in reducing fertility. DMPA as a contraceptive agent is generally at a dosage of 150 mg every 90 days (3 months).

Norethisterone enanthate has been available as a contraceptive since

1966, although it has been used less extensively than DMPA. Administered as an intramuscular injection of an oily preparation at a dose of 200 mg, NET-EN also inhibits ovulation, but its effects on cervical mucus, tubal function and the endometrium may be more important for its contraceptive action than for DMPA, particularly towards the end of a treatment interval. Clinical trials have demonstrated that it is most effective in preventing pregnancy when administered every 60 days for the first 6 months and every 60 to 84 days thereafter (see Chapter 9).

Injectable hormonal contraception with these two long-acting steroid preparations can provide an effective method of fertility regulation, which has become an important addition to the current methods for family planning. DMPA and NET-EN have several advantages which make them particularly desirable by some women and acceptable by family planning programs. A single injection can provide highly effective contraception for two or more months; delivery is simple, independent of coitus, and ensures periodic contact with medical or trained ancillary personnel. Furthermore, progestogens, unlike estrogens, do not suppress lactation, which is an important consideration where there is a need for postpartum contraception and where infant health is dependent upon breast-feeding.

At a special meeting convened in 1978, the Toxicology Review Panel of WHO's Special Programme of Research in Human Reproduction, together with other scientists, and representatives of six national drug regulatory agencies, reviewed animal and human data on DMPA and NET-EN, and concluded that, for DMPA:

> "The available evidence does not indicate a risk of adverse effects associated with Depo-Provera (DMPA) which would preclude the use of this drug as a contraceptive. However, as shown by the experience with combined oral contraceptives, relatively uncommon complications may not be detected until a drug has been used on a large scale for prolonged periods of time. There is, therefore, a need to monitor the safety of Depo-Provera on an ongoing basis, and the Special Programme will continue to place high priority on such research."

Subsequently, for NET-EN:

> "In the light of the findings in the monkey, beagle and rat the Panel recommended that the current and planned clinical trials of norethisterone enanthate should continue."

Nevertheless, since then, considerable pressure has been put on governmental officials throughout the world to ban the use of injectable contraceptives, particularly DMPA. This is partly because neither DMPA nor NET-EN has been approved for use as a contraceptive in the U.S.A. This is a particular problem for DMPA, since many leading authorities in the world require registration in a drug's country of origin before they will give approval for use in their own country. DMPA was reviewed by the Food and Drug Administration (FDA) in 1978, and although approval was recommended by the FDA's Obstetrics and Gynecology Advisory Committee, a group of specialists who advise the FDA on technical matters, the FDA did not grant approval for its use as a contraceptive agent (7). Rather, a Public Board of Inquiry was convened to review the following issues:

Whether, in comparison with other drugs approved for contraception, the benefits of DMPA outweigh its risk under conditions of general marketing in the United States of America.

Whether data from beagle bitch and monkey studies on DMPA submitted by the Upjohn Company indicate a potential risk of breast or endometrial cancer in human subjects.

Whether the data submitted by Upjohn from studies in women can refute the risk of human cancer suggested by the animal data.

Whether approved use of DMPA for contraception under general marketing conditions is likely to increase use of the drug as a contraceptive under conditions not stipulated in the approved labelling or to increase its use for unrelated indications for which safety and effectiveness have not been established (e.g. for hygienic purposes in mentally retarded persons).

Whether, in the event of contraceptive failure, use of DMPA might increase the risk of teratogenic effects more than other systemic contraceptives.

Whether, in view of DMPA's adverse side effects or pharmacological effect, estrogen therapy is likely to be prescribed in addition to DMPA in a significant number of patients.

Whether there are conditions of labelling and distribution controls which would permit marketing of DMPA as a safe and effective drug on a limited basis. (There may be patients in the United States for whom benefits of DMPA for contraception outweigh the potential risks. This population may be very small and may not warrant general marketing of DMPA for contraception.)

Pressure has also been generated by certain consumer and women's groups. In particular, in the summer of 1980, an article entitled "Depo-Provera - a critical analysis" appeared in Women and Health, a journal published by the National Women's Health Network of the U.S.A. (7). This largely inaccurate article was distributed worldwide, and the resulting alarm has caused several governments to withdraw or consider withdrawing DMPA from both national family planning programs and private outlets, and has made many women reluctant to consider the drug for contraception. A detailed rebuttal, pointing out the many inaccuracies contained in this article, was published shortly afterwards by Benagiano and Fraser (2).

Particular concern has also been expressed regarding the potential for abuse by persons or agencies providing injectable contraceptives, including their administration without the woman's consent or knowledge. Several reviews have become available since 1981, in which all aspects of human and animal studies published on DMPA in particular, but also on NET-EN, have been assessed (3, 6, 8, 9).

In 1980, the International Medical Advisory Committee of IPPF considered the use of DMPA as a contraceptive, and concluded that "it endorses the recommendations of WHO, the AID's ad hoc consultative Panel on DMPA and

the Scientific Advisory Committees of USFDA, that it continues to be a responsible act to make DMPA available as a contraceptive. The Panel concludes that careful long-term monitoring, including case-control, cohort and clinical studies on all contraceptive methods, be continued" (5).

Because of these concerns and problems there has been a continuing demand on WHO's Special Programme of Research in Human Reproduction from various sources - governments, UNFPA, technical assistance agencies and other bodies - for guidance on the use of both DMPA and NET-EN. Because of this demand, and as part of its ongoing assessment of the safety of long-acting injectable agents through research coordinated by WHO in many countries, the Programme convened a meeting in October, 1981 involving members of the Programme's Toxicology Review Panel, representatives of the Drug Regulatory Agencies of India, Mexico, Sweden, Thailand, U.K. and U.S.A., representatives from the pharmaceutical industry manufacturing these products, and scientists working in this field. A review of the most recent data available from both animal and human studies was prepared and has subsequently been published by WHO (9). The concluding section of this document states:

> "Injectable contraceptives - both DMPA and NET-EN - offer several advantages as a method of contraception, and have been shown in a number of clinical trials to be effective in preventing pregnancy and acceptable to many women. Although animal data have raised concern about the safety and long-term side effects of DMPA and NET-EN, certain animal models and the doses used appear not to be appropriate for studying human effects of these steroids. Extensive clinical and epidemiological studies among women using these drugs have thus far demonstrated no life-threatening side effects, including any increase in the risk of neoplasia.
>
> The most common side effect is the disturbance of normal menstrual cycles, which occurs in the majority of women using injectable contraception, and is the primary reason for its discontinuation. Woman frequently report irregular bleeding, spotting, and amenorrhea, but heavy or prolonged bleeding is uncommon. Studies thus far have not shown any serious short or long-term effects of DMPA or NET-EN. However, both DMPA and NET-EN have been used for a relatively short period of time, and the potential long-term effects (more than 15 years) are not yet known. With regard to metabolic effects, the areas in which research should continue are on the effects and physiological consequences of long-term use of DMPA and NET-EN on carbohydrate and lipid metabolism. In addition, further research is needed regarding the risk of neoplasia among women using DMPA or NET-EN. Finally, the effects on the later development of infants who are epxosed to DMPA or NET-EN in utero or through breast milk are not known. Research should continue in these areas.
>
> In summary, DMPA and NET-EN appear to be acceptable methods of fertility regulation. Clinical evidence from more than 15 years of use as contraceptive agents shows no additional, and possibly lower adverse effects than those found with other hormonal methods of contraception. The particular advantages of DMPA and NET-EN as highly

effective, long-lasting and reversible contraceptives make them important as options for women desiring a method of fertility regulation."

Furthermore, at that meeting, the Toxicology Review Panel saw no reason to alter its opinion that DMPA is safe for use in human beings. With regard to NET-EN, the Panel recommended that it could be introduced into family planning programs.

At this time, a background paper on the use of DMPA as a contraceptive in the U.S.A. was prepared for the American College of Obstetrics and Gynecology by its Subcommittee on Reproductive Endocrinology and endorsed by its Committee on Gynecologic Practice. This paper stated that "a long-term injectable progestin contraceptive such as DMPA is appropriate and needed". The paper goes on to say that: "Our conclusion at this time is that current data suggest that DMPA does not produce adverse effects which should preclude the clinical use of this useful contraceptive modality in the United States."

Controversy still surrounds the use of these two long acting progestogen preparations. The U.S. FDA eventually appointed its Board of Inquiry, which held its first public hearing on 10-14 January, 1983. This was a full 5-day scientific hearing, at which all members of the pro and anti Depo-Provera lobby were able to submit written and oral data on this compound. There was considerable discussion on the issue of carcinogenicity, and the Board was privy to preliminary data derived from the WHO Collaborative Study on Neoplasia and Steroidal Contraception. Dr. Dallenbach-Hellweg of the Federal Repbulic of Germany presented information on the possible association of oral contraceptives and endocervical tumors and claimed, without substantive evidence, that the tumors seen in the two monkeys receiving DMPA and one receiving NET-EN are in fact endocervical in origin rather than endometrial. It is known that DMPA causes atrophy of the endometrium, and since its effect on the endocervix is not known, it was hypothesized that a possible hyperplastic effect on the endocervix might lead to neoplasia.

There was no evidence available at the time of the hearing to refute Dr. Dallenbach-Hellweg's statement. As a result of this statement, several other consultations and hearings have been held on this issue. The first was held in February, in the Federal Republic of Germany, at which there were 9 or 10 pathologists who reviewed all the slides from the monkeys treated with Depo-Provera and the monkeys treated with norethisterone enanthate. Except for Dr. Dallenbach-Hellweg and another pathologist currently working at her institute, the group of pathologists concluded that the tumors were not of endocervical origin. A similar conclusion was also reached at a subsequent consultation at WHO. It was also noted that the tumor arising in the norethisterone enanthate-treated monkey was identical to that seen in the two DMPA-treated monkeys. It had previously been stated that the tumors were different, but this was the first occasion on which all slides could be compared alongside each other.

A third pathology consultation was held by the FDA Public Board of Inquiry on June 3, 1983, at which the two tumors from DMPA-treated monkeys were reviewed. Five of the six pathologists stated that one of the tu-

mors was not of endocervical origin, and the sixth pathologist stated that it probably was not. While with the second tumor, four felt that it was very probably not, and two probably not. Another public hearing will be held by the FDA in August, to discuss the results of this pathology consultation.

The Bundesgesundheitsamt, the drug regulatory agency of the Federal Republic of Germany, held two one-day hearings, on March 23, 1983 on DMPA, and on March 24, 1983 on NET-EN. These hearing were held because under German law a public enquiry must be held on any drug for which there is any suspicion of risk of adverse effects. The hearings considered the metabolic effects, the risks of cervical and breast cancer, and the risks of cardiovascular disease for each of the two drugs. Considerable weight was given to the theory of Dr. Dallenbach-Hellweg that the monkey tumors were endocervical in origin, and also to the Zarfas study on the incidence of breast cancer in patients in mental institutions receiving DMPA in Canada. Apparently neither drug will be withdrawn from the market in Germany, but the package inserts are to be rewritten, and usage of DMPA is to be restricted to women for whom other methods of contraception had proved to be unacceptable.

Following the United Kingdom Ministry of Health's refusal to accept the Committee on the Safety of Medicines' qualified approval for use of DMPA as a contraceptive in the U.K., a panel of experts was selected following an appeal by the Upjohn Company. This panel of five experts met in London on April 25-29, 1983. The panel will review all written and oral material presented and submitted, and will write a report to the Minister. It is ironic that this panel of enquiry cannot make recommendations, but only summarize the data available and present an objective opinion, and that the Minister, who remains unchanged after the recent General Election, will still have the final say on this issue.

Thus, the debate continues, and it is unlikely that any decision will be made by the U.S. FDA before early in 1984. The prospects, however, in the U.S. for approval are not bright since, even if the FDA were to recommend approval of the drug, it is understood that Congressional hearings would immediately be organized and the present mood of the U.S. Congress in this area is extremely conservative. It remains to be seen whether governments around the world will follow the advice of the large number of expert scientists who have already met to consider the safety of DMPA, and continue to utilize this drug as a long-acting contraceptive, or whether political and other non-scientific considerations will sound the death-knell of something which some two million women are presently using as their chosen method of fertility regulation.

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POLY NET CONTRACEPTIVE SYSTEM

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The use of biodegradable polymers for the programmed delivery of contraceptive drugs is a relatively new technology whose origin stems from earlier work on nonbiodegradable subdermal implants. The various biodegradable systems under current development differ with respect to their method of administration, mechanisms of drug release, and duration of action. However, the rationale for their development is based on the same clinical principles; namely, controlled release offers a means of improving the therapeutic effect of drugs, minimizes their side effects by augmenting the amount and persistence of the drug in the vicinity of the "target cell," and reduces the drug exposure to nontarget cells. Steady release of steroids, which can be achieved using polymeric membranes, circumvents the problem of fluctuating blood levels of drug that occurs with oral dosages, thus permitting the use of lower doses to reduce the incidence of dose-related side effects. Another advantage is that steroids delivered directly to the systemic circulation do not pass through the gastrointestinal tract and hepatic portal system and therefore avoid first-pass clearance.

For contraception, the advantages of long-acting systems are particular-

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ly important, and it is not surprising that the state of the art in controlled-release drug delivery has advanced further in the area of human fertility control than in other areas. Women using chemical contraceptives are for the most part young and healthy. Contraceptive drugs are intended to control a normal physiological process. This stands in contrast to the kind of drug therapy that is intended to treat or control a pathological process and for which sickness is a prerequisite for treatment. There is a risk with the use of any medication, and when diseases present a greater risk than the medication, the distinction between benefit and risk is clear. The actual and perceived risks of conventional contraceptive therapies have prompted research for improved delivery systems that reduce the quantity of drug necessary to achieve the desired results.

The scope of this chapter is limited to a specific class of biodegradable contraceptive systems that use homopolymers and copolymers of poly(lactic acid) (PLA) and poly(glycolic acid) (PGA) as the polymeric platform or matrix for the controlled delivery of contraceptive steroids.

PROPERTIES OF PLA, PGA AND THEIR COPOLYMERS

The homopolymers, poly(lactic acid) and poly(glycolic acid) (also referred to as polylactic and polyglycolide, respectively), and copolymers thereof, poly(lactide-co-glycolide) (PLGA), are thermoplastic, biodegradable materials that are suitable for surgical implants. One of their earliest applications was for resorbable sutures. Since then, these materials have shown utility for dental, orthopedic, and protheses applications.

In the areas of controlled release, PLA and PLGA are used as rate-controlling membranes and erodible polymeric excipients for implantable drug-delivery systems. In this application these materials show much promise in providing efficacious pharmaceutical formulations. The design of such delivery systems involves the evaluation and optimization of the polymer's mechanical properties biodegradation kinetics, tissue compatabililty, drug compatibility, drug permeability, and ease of processing.

The combination of these polymers with contraceptive steroids in the form of tablets, films, and cylinders to achieve controlled delivery of drug has been studied. The use of these polymers as excipients for the delivery of contraceptive steroids is somewhat limited, however, if the release of drug is to be controlled solely by a diffusional mechanism. This is because PLA, PGA, PLGA are glassy rather than rubbery materials. Because of this morphology, they are relatively impermeable to steroids. For instance, the permeability of progesterone in silicone rubber is 2.6 x 10_{-9} g/cm/s as compared to 0.000033 x 10_{-9} g/cm/s in DL-PLA. These data suggest that the reported release of contraceptive steroids, even from 10-um films, is most likely due to drug being released through leaching, polymer erosion, or a combination of both mechanisms. Consequently, to achieve a suitable rate of drug release from a delivery system containing PLA, PGA, or PLGA, the rate-controlling membrane must be extremely thin and the surface area of the steroidcontaining microspheres can compensate for the low diffusion of the drug through the excipient.

PLAs with high molecular weights produce the quality films needed for controlled-release delivery systems. These highmolecular-weight polymers are generally synthesized by the ring-opening polymerization of the cyclic diesters, lactide and glycolide; steroregular D-PLA and L-PLA as well as racemic DL-PLA materials can be prepared. The properties of these polymers are quite different. Primarily, L-PLA and DL-PLA have been employed as excipients for controlled-release delivery systems. DL-PLA is more suitable for contraceptive steroid formulations because it is a highly amorphous polymer that forms better films than crystalline L-PLA. Furthermore, steroids are more soluble and permeable in DL-PLA. All of the PLAs dissolve in common organic solvents, so they are good materials that are easily processed materially, with respect to processibility, to afford polymer drug composites under mild conditions.

PGA,the major component of commercially available absorbable sutures, is the simplest of the aliphatic polyesters, but has limited use for controlled-release delivery systems because it is difficult to process under mild conditions. High-temperature melt processing degrades many drugs and PGA is practically insoluble in common solvents.

On the other hand, when glycolide is randomly copolymerized with DL-lactide, copolymers with up to 50 to 70% glycolide will dissolve in common solvents to facilitate fabrication of polymer/drug composites. The relative amounts of lactide and glycolide incorporated into the polymer chain can be varied to alter the crystallinity, solubility, biodegradation rate, and water uptake of the material. Of these properties, regulation of the copolymers's rate of of biodegradation has been one of the primary reasons for incorporating glycolide with lactide, particularly for controlled-release delivery systems.

PLA as well as PGA undergoes random, nonenzymatic, hydrolytic scissioning of ester linkages to form lactic acid, a normal intermediate in carbohydrate metabolism, and glycolic acid. The rate of biodegradation is influenced by several factors, for example, molecular weight of the polymer, number of carboxylic end groups, and surface area. DL-PLA for the most part completely resorbs in about 12 months. This rate can be accelerated appreciably by copolymerizing up to 50 mol percent glycolide into the polymer chain to achieve complete resorption occurring in as little as 2 to 3 weeks. Exceeding 50% glycolide reduces the biodegradation rate back to that of DL-PKA homopolymer.

The NET microspheres were prepared by a solvent-evaporation microencapsulation process described elsewhere.

The microspheres were a free-flowing powder of spherical particles with NET crystals homogenously dispersed throughout the polymer excipient. NET microspheres had good film coatings and there was no evidence of the presence of unencapsulated drug present.

In the biodegradation studies, rats were injected intramuscularly with 40 mg of NET microspheres. Evaluation of the biodegradation curves obtained from unsterilized microsphere formulations (63 to 125 um) reveals that increasing the quantity of glycolide in the copolymer excipient causes a corresponding increase in the rate of biodegradation of the micro-

spheres. The gamma radiation decreases the molecular weight of the DL-PLGA excipient, as reflected in the decrease in the inherent viscosity and increases the rate of biodegradation of the microsphere excipient.

IN VITRO STUDIES

As predicted from theory, the rate of release of NET from the microspheres, i.e., the slope of the tangent to the curve, decreased with time and was fastest for smaller microspheres. At 40 hours, NET was completely depleted from microspheres having diameters of 45 to 63 um, whereas in the same time period, only 40 to 50% of NET was released from larger microspheres 125 to 150 um and 150 to 250 um. An amount of unencapsulated NET equilavent to that in the microspheres (about 2.5 mg) tested under similar conditions dissolves in the aqueous-ethanol receiving fluid in less than 1 hour.

For microspheres of the same size, but different NET content, the *in vitro* rate of release increases with the core loading.

The 63- to 125-um microspheres that released all of their NET *in vitro* in little over 50 hours released NET in baboons for about 110 days. This difference indicates that the *in vitro* release model provides accelerated release and does not give a one-to-one correlation with the *in vivo* rate of release. (The *in vitro* method is based on a diffusional mechanism of release, so it will not give information with respect to the *in vivo* release of NET due to biodegradation of the excipient.)

Although the *in vitro* profiles generated by this method do not give a one-to-one correlation with the *in vivo* rate of release of the microspheres, the method can be used to predict in a relative manner the duration of release *in vivo* once one batch of microspheres has been tested *in vitro* and *in vivo*. The method does provide information about microsphere quality, batch-to-batch reproducibility, and the relative *in vivo* release of various batches of microspheres.

IN VIVO STUDIES

PLA and PLGA have been tested in animals in various forms including tablets, cylinders, films, powders and microspheres as biodegradable controlled-release delivery systems for contraceptive steroids. The injectable DL-PLA NET microspheres system is the only form that has been tested extensively *in vivo*.

The first study to investigate the contraceptive efficacy of a PLA microsphere system in a primate species was published in 1979. The prototype system consisted of microspheres of DL-PLA containing 20 wt percent NET. Following intramuscular injection in baboons, the microspheres released NET by diffusion for 6 months. After 6 months, 90% of the polymer remained at the injection site; it required 12 months for the polymer to undergo complete biodegradation.

Biodegradation kinetics were established using [^{14}C]-labeled polymer. Microspheres were injected in the hind leg of rats at various times following treatment. The serum NET profile was established by measuring the

levels of NET by radioimmunoassay at various times after treatment. Comparison of the biodegradation curve to the serum NET profile reveals that most of the drug was released while the polymer matrix is intact. On the basis of this, it was concluded that NET release from the prototype DL-PLA system occurs by diffusion and not by biodegradation of the excipient.

In baboons, the treatment inhibits fertility for 6 months, as evidenced by suppression of estrogen and progesterone production by the ovaries. The microspheres used for these experiments ranged in diameter from 10 to 240 um.

It was concluded that microsphere size distribution can be effectively used to adjust both the rate and duration of NET release from the prototype DL-PLA system. Reduction in microsphere size increased the rate of diffusional release in vivo and shortened the duration.

The identical DL-PLA system has been tested in women, and the performance of the system was similar to that described in baboons. However, the doses used in the Phase I human study were not high enough to inhibit ovulation for the full 6 months. Figure 1 shows the mean serum profiles of NET in seven women treated by intramuscular injection with microsphere doses that contained 80 ± mg of NET.

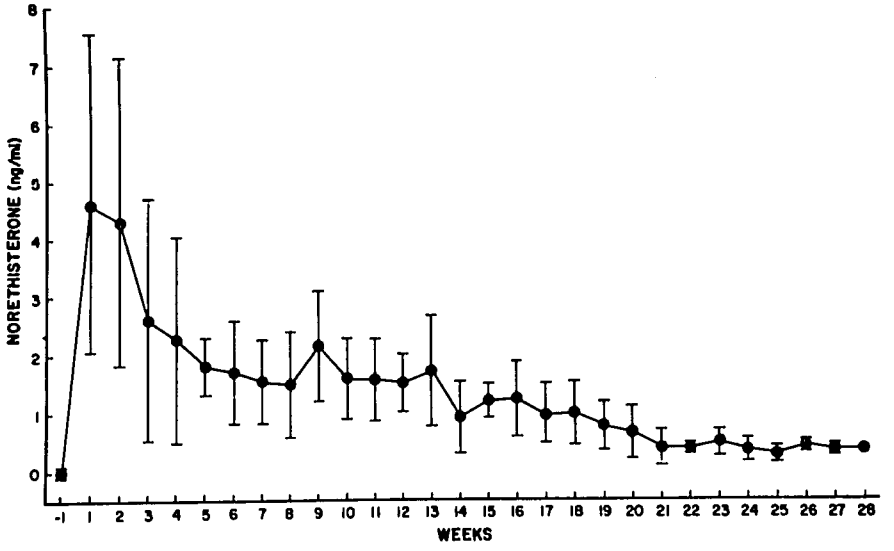

FIGURE 1. Mean serum level of NET ± standard deviations in women (N=7) treated by intramuscular injection with microspheres containing 80 mg of NET.

The serum NET profiles in baboons and women generated by the prototype DL-PLA microsphere system are typical of diffusional release. These

profiles are characterized by a gradual decrease in the serum levels of NET. This profile is not optimal in contraception because early serum levels of NET are significantly higher than necessary to suppress ovulation immediately following treatment and they decline to levels that allow ovulation during the last month. Diffusional release is complete by 6 months. However, it requires 12 months for biodegradation of the polymer to occur. Accordingly, the tissues at the injection site are exposed to the polymer for longer periods of time than necessary for contraception.

These two inherent weaknesses of the prototype DL-PLA microsphere system prompted further work to shorten the duration of biodegradation of the polymer excipient and to improve the NET release profile. To shorten biodegradation time, microspheres were made of DL-PLGA using different ratios of lactide and glycolide. The rationale for this approach is based on the knowledge that incorporation of up to 50% glycolide will increase the rate of biodegradation of DL-PLA. On the basis of the biodegradation described above, a formulation was selected for the second-generation NET system that biodegrades within 6 instead of 12 months. This polymeric composition was then used to manufacture microspheres containing NET.

Figure 2 shows the serum NET profiles in a group of baboons treated with the copolymer formulation. The biodegradation curve of the polymer is superimposed on the release curve. Comparison of the serum NET profile obtained from the DL-PLGA formulation to that obtained from the prototype DL-PLA formulation reveals a notable difference. The faster biodegrading system exhibits a two-phase release profile instead of a single phase. The release profile from the prototype system is characterized by a gradual decrease in the serum levels of NET, whereas the serum NET profile from the copolymer formulation exhibits an initial phase characteristic of diffusional release followed by a secondary increase in the serum NET levels. The secondary increase can be predicted on the basis of the biodegradation curve because it coincides with the time that the microspheres undergo substantial biodegradation. It can be concluded from this that the NET release from the copolymer formulation occurs by diffusion initially and then by both diffusion and biodegradation of the polymer. The bi-phasic release profile represents an improvement over the single-phasic profile because it maintains higher serum levels of NET during the second half of the treatment interval, thus reducing the chance of contraceptive failures that occur as the serum levels gradually fall below the amount necessary to inhibit ovulation (see Chapter 3).

As one might expect, smaller microspheres have faster rates of release and biodegrade faster as evidenced by higher initial bursts, earlier secondary release due to biodegradation, and shorter duration of release. These experiments illustrate the important principle that microcapsule size can be preselected to program the timing of the bi-phasic release profile by blending microspheres of different size fractions. It is therefore possible to maintain constant serum levels of NET over an entire treatment interval. This enables the use of lower doses and improves both the safety and acceptability of the injectable microsphere formulations.

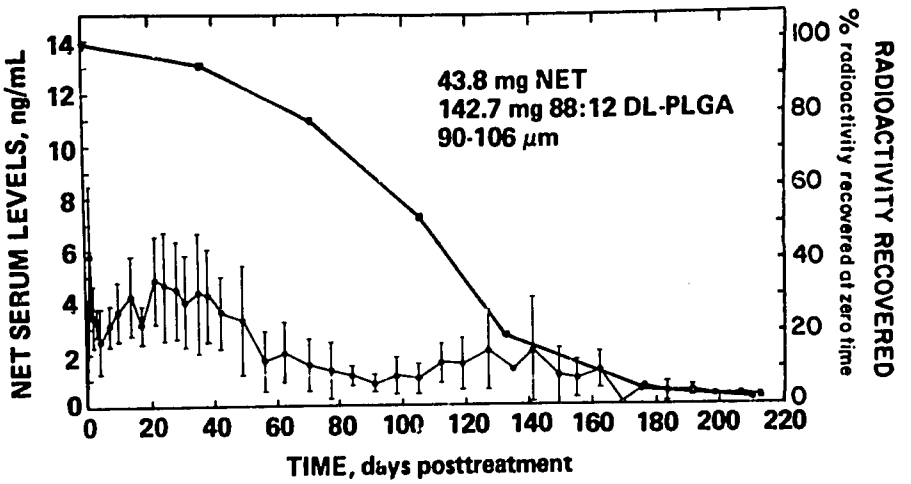

FIGURE 2. Biodegradation curve of copolymer superimposed on mean serum levels of NET ± standard deviations (vertical bars) in baboons treated with the copolymer formulation (88:12).

CONCLUSION

Biodegradable implants and injectable particulate systems offer greater drug selection because physical parameters of the delivery system can be changed to accommodate the drug. This flexibility in drug selection distinguishes the systems engineering approach from the pharmacological approach to drug delivery. No longer must we consider the usefulness of a new pharmacological agent on the basis of its rate of clearance from the body following conventional methods of administration. Theoretically, it is possible - using the systems engineering approach - to develop controlled-release dosage formulations for any drug that has a desirable biological effect. The pharmacological approach is limited to the extent that once a new drug is synthesized and is biologically characterized, its clinical usefulness depends on the rate of clearance from the body and the related side effects using doses high enough to achieve therapeutic blood levels. The ability to control the delivery of the drug precisely, thus keeping the systemic levels within the therapeutic range and below toxic levels, allows the safe use of a wider spectrum of drugs.

Contraception is but one example of the practical use of this newly emerging technology. The emphasis of this chapter has been on a specific class of polymers that have application for injectable and implantable drug-delivery systems. Other chapters considered depot formulations and biodegradable implants that use other polymers. There are advantages and disadvantages of injectables as opposed to implants. There is no basis to suggest that either approach is superior to the other. Acceptability will vary with each target population, depending on the social, economic, religious, and medical preferences. Suffice it to say that biodegradable injectable systems offer an alternative to implants, and both implants and injectables offer wider potential use of existing and new drug modalities.

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NORPLANT CLINICAL STUDIES - EGYPT

Fouad Hefnawi

Egypt was the first African nation to join an international effort to study the effectiveness, acceptability and side effects of Norplant, in continuation of an interest in contraceptive methods which dates back to the days when medical prescriptions were written on papyrus.

Planned as a multicenter project, the study pooled the resources of the universities of Al-Azhar, Alexandria, Assiut and Zagazig, each contributing a team of medical, paramedical, and social workers, statisticians and data-analysts. The four centers provided local data for making a comparison of clinical performance between a copper-loaded intrauterine device (TCu 380 Ag) and the subdermal implant, which releases capsuled levonorgestrel for an estimated period of five years.

Recruitment for the designed sample of Norplant and TCu 380 Ag cases began and ended at different times, as shown in Table 1. Follow-up data extending over a period of 12 months are available at present only for a part of the sample: 601 users of Norplant and 235 of TCu 380 Ag. Statistical analysis of data is also not yet complete in all respects. Therefore, findings given in this report cannot be considered a final outcome of research. The data base, however, is now wide enough to permit a number of tentative conclusions, presented in view of the national and international interest in the results of our investigation.

Egypt's interest in Norplant stems from two linked factors: an unsatis-

TABLE 1. First and last implantation/insertion by center and method.

Center	Norplant		TCu 380 AG	
	First	Final	First	Final
1. Al-Azhar	Dec. 1981	Aug. 1982	Nov. 1981	Sept. 1982
2. Alexandria	Jan. 1981	Dec. 1981	Jan. 1981	Feb. 1982
3. Assiut	Sept. 1980	May 1981	Sept. 1980	May 1981
4. Zagazig	March 1982	Sept. 1982	March 1982	July 1982

factory record of experience with methods adopted and advocated by the national family planning program, and cultural limitations imposed on the choice of methods by Islam, the religion of most Egyptians.

When the national program began in the early 1960s, it relied entirely on the two-steroidal oral contraceptive, a method binding the user over a period of years to a faithful daily regimen, and thus requiring a sustained high level of motivation. In rural areas, where tradition and opinion weigh against individual commitments to contraception, pill-use was predictably erratic and brief. As a subdermal contraceptive, Norplant cannot be forgotten or misplaced; termination of its use requires not only a positive decision but a discussion of that decision with the physician.

To solve the problem of irregular and discontinued pill-use, the national program tried to promote the Lippes Loop as an alternative. Its side effects of bleeding resulted in poor retention rates. The method was also disfavored by physicians because of the very high incidence of anemia in Egypt, a combined effect of high parity, poor nutrition and parasitic infestation.

Norplant enjoys some advantage over the IUD because its use often causes amenorrhea or scanty menstruation - beneficial side effects for the anemic. In its present state of development, it does not provide a full solution to the problem of blood loss but possibilities of reducing side effects by changing steroidal dosage can be explored, along the same lines used in control delivery systems described elsewhere in Chapter 3.

The religion of Islam does not forbid contraception and fully recognizes the parental right to control fertility when it is a source of hardship and stress (IPPF 1974). Yet, certain aspects of Islamic ethics and behavior tend to restrict the use of modern contraceptive methods. The most formidable barrier stands against sterilization. Despite its use in a number of Muslim countries, religious leaders have rejected the use of any contraceptive likely to destroy reproductive capacity. As a highly effective, long-acting and reversible contraception, Norplant can therefore meet the need of Muslim women who have already completed their family size but are averse to sterilization on religious grounds. Even without a religious rejection of sterilization, its use is often limited by

the lack of operative facilities in communities with a low level of development. Norplant can be implanted very simply in an outdoor clinic.

A disadvantage to the use of oral contraception by Muslims is the inhibition of lactation by its estrogenic component, as demonstrated in several Egyptian and foreign studies. Breastfeeding is viewed as an Islamic virtue. The Quran enjoins lactation, ideally for a period of two years (2:232). As an estrogen-free drug, Norplant can be expected to serve the needs of lactating women, if it is established that it will have no adverse effects on the development and health of the breastfed child.

Strong modesty norms of Muslim women limit the use of the IUD when female medical assistance is not easily available. Exposure of reproductive organs to male doctors is usually accepted only in the event of sickness or its likelihood. For this reason, Norplant promise to find greater acceptance than the IUD among the more traditional sectors of a Muslim community.

Although slightly less effective than sterilization, Norplant has the advantage of reversibility and simplicity of procedure; it is free of the estrogenic effect of oral contraceptives and of human factors contributing to their ineffectiveness and it is less hazardous for anaemic women than the IUD. Taking the points into consideration, the minister of health gave his approval to the study, on the recommendation of the ministry's board of research. The Islamic interest in the study was represented by the International Center for Population Studies and Research in the University of Al-Azhar, which performed a coordinative role. The broad aim of the study was to evaluate the reliability and acceptability of Norplant subdermal capsules, to study the side effects of the method in the Egyptian context, and to compare results with experience gained elsewhere. The study was undertaken in the hope of meeting the national need for a medically and culturally appropriate contraceptive, essential for achieving national goals in population planning.

MATERIAL AND METHODS

Each center recruited 250 acceptors of the Norplant and 100 cases of TCu 380 Ag device to compare the performance of Norplant with that of an established long-acting method, serving as a control. Criteria for enrollment, the schedule of visits, examinations and measurements were identical for both groups.

Patient selection conformed to criteria established by the International Committee for Contraception Research (ICCR): women under 40, not pregnant or breastfeeding, menstruating normally, non-diabetic, accessible for regular follow-up, with proven fertility, and without history of cardiovascular disease.

On admission, a complete medical history was taken and physical examination, including breast and pelvis, was conducted. Weight and hemoglobin concentration were recorded before and after the placement of Norplant or insertion of intrauterine device (TCu 380 Ag). Six Norplant capsules of Levonorgestrel were placed subdermally in the upper arm about 8-10 cm

above the elbow under local anesthesia, using 11-gauge trocar. Capsules were made from medical grade silastic (R) tubing of 34 mm total length; 30 mm contains approximately 36 mg of Levonorgestrel, and 4 mm is silastic medical grade adhesive A, with which the capsules are sealed -- 2 mm at each end. Follow-up visits were scheduled at 1, 3, 6, 9 and 12 months following insertion of Norplant and TCu 380 Ag. At each visit physical examination was repeated, and symptoms and bleeding episodes were recorded. In addition, side effects were noted, having been reported in response to the question, "How have you been feeling?"

Admission data presented in this report cover the entire sample of 1,000 Norplant and 374 TCu 380 Ag cases. Follow-up data for a period of one year are available for all recruited cases in Alexandria and Assiut centers, and in the Al-Azhar rural center for 101 Norplant and 35 IUD cases (Table 2). In the Zagazig center a period of one-year observation had covered only a few cases when this report was written, so follow-up data from this center have been excluded.

TABLE 2. Number of cases admitted and observed for one year by center and method.

Center	Norplants	No. observed (one year)	TCu 380 Ag	No. observed (one year)
1. Al-Zahar	250	101	94	35
2. Alexandria	250	250	100	100
3. Assiut	250	250	100	100
	750	601	294	235

The four research centers represented different cross-sections of the Egyptian population. The Al-Azhar center served an entirely rural group; Alexandria worked with a relatively modernized metropolitan community; Zagazig represented a mixture of rural and urban life-styles; Assiut, of upper Egypt is composed of a culturally distinct population, and is known for its traditionalism. Assiut also supplied most of the Christian case material to the study.

In addition to investigations relating to acceptability, effectiveness and side effects conducted in the multicenter project, research studies on metabolic and endocrine profile of Norplant use were performed by Alexandria, Assiut and Cairo Universities. The studied parameters were liver function, coagulation and fibrinolytic factors, lipids and lipoproteins, pituitary function, corpus luteum function, serum androgens, serum cortisol, serum total thyroxine and effect on lactation.

RESULTS

Characteristics of acceptors

As shown in Table 3, at the time of admission to the study, the experi-

mental and control groups did not differ significantly in physiological characteristics - i.e., weight, blood pressure, menstrual flow, hemoglobin, and incidence of pregnancy wastage. Any change observed later in these characteristics cannot therefore be attributed to a bias in the two samples. The table also reflects the anemic character of the population, with hemoglobin values ranging from 9.2 to 11.6 in different parts of the country.

TABLE 3. Physiological characteristics at admission by method.

Characteristics	Norplant (n = 1000)	TCu 380 Ag (n = 374)
Weight (kg)	69.4	70.4
Blood pressure mmHg		
- systolic	125.8	127.0
- diastolic	88.0	83.1
Hemoglobin gm/100	11.6 (9.2)*	11.7
Menstrual flow: *		
- heavy	11.0	9.9
- medium	77.9	78.3
- light	10.8	11.8
Last pregnancy outcome: **		
- live birth	91.0	91.2
- stillbirth/abortion	9.0	8.8

+ Based on 250 cases from Assiut center. ** Percent of cases.

Social and demographic characteristics of the two groups, displayed in Table 4, suggest the following conclusions:

- Method preference is not influenced by the age or religion of the acceptor, as the statistical differences are not significant.

- Preference for Norplant is strongly associated with a low educational level of acceptors and their husbands and also with their non-participation in economic activity. Among users of Norplant, 79.9% of the wives and 44.6% of the husbands were illiterate compared to 51.3% and 24.9% respectively in the TCu 380 group. Only 10.8% Norplant acceptors were employed, against 26.2% in the control group.

- Previous use of contraception tended to increase preference for Norplant. Almost 90% of the Norplant acceptors had tried a contraceptive method earlier against 73.8% of those who preferred the intrauterine device.

- Most women in both groups wanted to limit family size rather than space childbirth, but the proportion of women desiring no more

children was substantially larger among Norplant users: 95.2% against 80.5%.

TABLE 4. Social and demographic characteristics of accepters.

Characteristic	Norplant (n = 1000)	TCu 380 Ag (n = 374)
Age	32.2	31.3
Live births	5.2*	4.1
Percent desiring no more children	95.2*	80.5
Percent of previous users of a method	89.2	73.8
Percent of illiterate wives	79.7*	51.3*
Percent of illiterate husbands	44.6*	24.9
Religion (percent)		
- Muslim	91.6	93.8
- Christian	8.3	6.2
Percent of working wives	10.8*	26.2

* = $P < 0.01$

The profile of Norplant acceptors in Egypt is in many ways different from that of an international sample drawn from Brazil, Chile, the Dominican Republic, Jamaica, Denmark and Finland (ICCR, 1978). The contrast is presented in Table 5. Egyptian acceptors are more fertile, older, and more inclined toward a method which would limit rather than regulate fertility. Significantly, the level of hemoglobin found in the Egyptian sample was relatively low. The difference in educational levels, not presented on Table 5, is also significant. In the international study, education extended to 7-8 years of schooling, but 80% of the Egyptian users were illiterate.

TABLE 5. Comparison of selected accepter characteristics (Egypt - ICCR).

Characteristics	International data*	Egyptian data
Age	26.0	32.2
Number of live births	2.5	5.2
Percent desiring no more children	51.3	95.2
Weight (kg)	57.3	69.4
Systolic blood pressure (mmHg)	113.5	125.8
Diastolic blood pressure (mmHg)	71.0	83.1
Hemoglobin gms/100 ml	12.9	11.6 (9.2)**

* ICCR Study (1978). ** Assiut data based on 250 cases.

Acceptability

The research protocol for this study required that acceptability should be observed initially in terms of method continuation.

Net cumulative continuation rates using multiple decrement method have been tabulated only for the Assiut part of the sample, and are based on 250 Norplant and 100 TCu 380 Ag acceptors. Results presented in Table 6 show that the one year continuation rate of 88.3 compares favorably with the continuation rate of 85.5% found for an established method like the Copper T.

TABLE 6. NET cumulative continuation rates for first 12 months* (multiple decrement).

Termination reasons	Norplant	TCu 380 Ag
Pregnancy	0.80	1.16
Removals		
- bleeding/pain	7.20	6.80
- amenorrhea	--	--
- other medical causes	--	1.31
- planned pregnancy and other personal causes	1.99	2.50
- expulsion (IUD)		
Adjusted number at risk	210	78
Continuation rate	88.3	85.5
Standard error of continuation rate	1.9	2.22

* Based on Assiut data.

A comparison of the Egyptian rate with international data on the continuation of Norplant is shown in Table 7.

TABLE 7. Comparative continuation rates per 100 users of Norplant (first 12 months segment)

Center	Rate
Egypt (n = 250)*	88.3** (1.43)
Six international centers (n = 492)	74.6** (2.0)
- Brazil	79.8 (4.0)
- Chile	88.0 (3.2)
- Dominican Republic	59.9 (4.9)
- Jamaica	81.8 (3.9)
- Scandinavia	63.5 (4.5)

* Based on Assiut data. ** $P < 0.01$

Further information on continuation of the two methods, stated as percentages of women who terminated the method at any time during the first year of use, is given in Table 8. Although a very crude measure of continuation, it shows that the proportion of women who removed or lost the device was about twice as large as those who had the Norplant capsules extracted: 17.8% against 9.0%.

TABLE 8. Termination events by method and reason (first 12 months).

Reason	Norplant No.	TCu 380 Ag No.	Norplant %	TCu 380 Ag %
Pregnancy	4*	2	0.7 (0.34)	0.8 (0.58)
Expulsion	---	6	---	2.6 (1.04)
Menstrual disturbances	32***	16	5.3 (0.91)	6.8 (1.64)
Other medical	6	9	1.0 (0.40)	3.8 (1.25)
Planning pregnancy	2	5	0.3 (0.22)	2.1 (0.94)
Other personal	10	4	1.7 (0.53)	1.7 (0.84)
Total termination cases	54	42	9.0**(1.17)	17.8 (2.49)
Continuation cases	503	143	83.7**(1.5)	60.9 (3.18)
Loss to follow-up	44	50	7.3 (1.06)	21.3 (2.67)
No. of Acceptors	601	235		

Standard error in paranthesis.
* Including two pregnancies ascertained to have occurred before use of Norplant.
** P < 0.01 highly significant.
*** Three cases of amenorrhea.

Table 9 gives a broad classification of reasons of termination. "Menstrual disturbance" means frequent irregular bleeding, heavy menstrual flow, prolonged or heavy period-like bleeding, spotting amenorrhea, oligohypomenorrhea, dysmenorrhea and/or pelvic pain. These disturbances can be further subdivided into amenorrhea and different types of bleeding abnormalities. "Other medical reasons" covers headache, dizziness, nausea, depression, loss of appetite, weight gain, pain at implant site, pain in axilla, acne, other skin problems. Out of 32 Norplant terminations attributed to menstrual disturbances, 3 are related to amenorrhea and 29 to bleeding abnormalities (9.4% and 90.6% respectively).

TABLE 9. Removals due to medical/method-related reasons.

Reason	Norplant			TCu 380 Ag		
	No.	%	S.E.	No.	%	S.E.
Explusion	---	---	---	6	2.6	1.04
Menstrual disturbance	32	5.3	0.91	16	6.8	1.64
Other medical	6	1.0	0.40	9	3.8	1.25
Total	38	6.3*	0.99	31	13.2	2.2
No. of Acceptors	601	100		235	100	

* P < 0.01

Frequency of method-related reasons for Norplant termination (pregnancy, menstrual disturbance, other method-related or medical) are compared with corresponding frequencies reported in data pooled from six other countries (Table 10). Incidence of removal of Norplant because of menstrual

disturbance was significantly and substantially lower in Egypt compared to other countries: 12.2% against 5.3%.

TABLE 10. Comparison of Egyptian and international data on method related termination (first 12 months).

Reason	ICCR data (n = 601)	Egyptian data (n = 492)
Pregnancy	0.6%	0.7%
Menstrual disturbance	12.2%*	5.3%
Other medical or method-related	4.7%	1.0%

* P > 0.01

Contraceptive effectiveness

In the Norplant study, 4 women out of 601 were pregnant during the first 12 months of use (Table 8). Two pregnancies were diagnosed after 1 month during the first follow-up visit, one case during the 3 months visit and one case at the 6 months visit. In the TCu 380 Ag control group, two women out of 235 were pregnant during the 12 months of use; one case after 1 month and one case after 6 months had passed since insertion. The difference between the two groups in the incidence of pregnancy during the first year was not statistically significant.

Outcome of pregnancy

In the Norplant study, one out of the four pregnant women induced abortion in a private clinic. The three other cases continued the pregnancies had normal deliveries, and gave birth to full term babies showing no abnormalities.

Side effects

Table 11 describes incidence of menstrual changes among women who completed the first twelve months of use for both methods. The term "change" means a change in length of menstrual period, in amount of blood flow, or both. "Decrease" includes amenorrhea, defined as absence of menstruation for three continuous cycles. It was found that Norplant users experienced variability in blood flow or bleeding period more frequently than users of TCu 380 Ag, but increase in flow or length of the period was more often associated with use of the intrauterine device. The first difference was highly significant and the second significant at 0.05 level of confidence. It was also found that 23.3% of all users of Norplant suffered from amenorrhea after the implant.

Table 12 gives incidence of non-menstrual complaints: weight change, headache, dizziness, nausea, depression, skin problems, nostalgia, loss of appetite and libido, vaginal problems, and other complaints excluding pain at implant site. The proportion of such complaints was far higher among Norplant cases than among users of TCu 380 Ag and the difference was highly significant.

TABLE 11. Incidence of menstrual changes observed during a period of one year.

Menstrual changes*	Norplant No.	%	TCu 380 Ag No.	%
Increase	142	28.2****	55	38.5
Decrease*	193**	38.4	0	----
Variable	84	16.7***	7	4.9
No change	84	16.7***	81	56.6
Total continuation	503	100	143	100

* Includes changes in cycle length, blood flow, or both.
** Includes amenorrhea observed among 117 cases (23.3%) after use of method.
*** $P < 0.01$
**** $P < 0.05$

TABLE 12. Incidence of non-menstrual spontaneous complaints during one year of use.

	Norplant No.	%	TCu 380 Ag No.	%
Complaints (non-menstrual)	274	54.5*	52	36.4
No complaints (non-menstrual)	229	45.5	91	63.6
Total observed for one year	503		143	

* $P < 0.01$

Analysis of pain at site of implant associated with the Norplant procedure revealed highly significant differences between three centers, as shown in Table 13.

TABLE 13. Incidence of pain at implantation site by center.

	Alexandria No.	%	Assiut No.	%	Azhar No.	%	Total No.	%
Pain	16	7.9	2	1.9	24	25.5	4.2	8.3
Continuing users	203	100	206	100	94	100	503	100

All values significant at 0.01 level.

Changes in physical signs

Table 14 shows the changes in relevant physical signs reported by the Assiut Center, between admission and the end of the one-year treatment with Norplant. There was a statistically significant increase in hemoglobin concentration and weight, and a significant decrease in the systolic and diastolic blood pressure.

Table 15 compares Egyptian data with results of the international study (ICCR 1978) in respect to changes in mean values for hemoglobin, systolic and diastolic blood pressure and weight.

TABLE 14. Change in hemoglobin concentration, weight and blood pressure after one year of Norplant treatment.*

	Hb. conc. gm/100 ml	Weight kg	Systolic BP	Diastolic BP
Mean at admission	9.188	68.75	127.6	80.4
S.D.	0.833	5.19	7.8	6.1
Mean at one year	9.437	70.44	121.7	78.5
S.D.	0.812	4.29	3.7	3.3
t	3.169	3.819	10.71	4.23
p	< 0.001	< 0.001	< 0.001	< 0.001

* Assiut center data

TABLE 15. Comparative changes in physical signs with one-year treatment of Norplant (mean values).

	Egypt*		ICCR Study**	
	Admission	12 months	Admission	12 months
Hemoglobin (gm/100 ml)	9.19	9.44	12.9	13.5
Weight (kg)	68.75	70.44	56.8	58.2
Blood pressure (mmHg)				
- systolic	127.6	121.7	1.14	115
- diastolic	80.4	78.5	71	71

* Assiut center data (n = 210). ** Six countries (n = 468).

Metabolic and endocrine profile

The results of the metabolic and endocrine profile studies conducted in Egyptian institutions on a sample of Norplant users did not show any abnormalities during the follow-up period.

DISCUSSION

Social profiles of the two sets of acceptors were found to be very distinct for reasons which are not fully clear and need further investigation. Compared to those who chose the intrauterine device, women who opted for Norplant were less educated, married to less educated husbands, did not work for income and confined themselves to the traditional female role of bearing and rearing children. A possible explanation of the difference is that with education and wider social exposure women lose inhibitions against insertion of the device by male doctors, or they find it easier to overcome fears and suspicions relating to the presence of a foreign body in the uterus. If this interpretation is found to be correct, Norplant will tend to find greater acceptability than an IUD in more traditional communities and classes.

Almost all acceptors of Norplant (95.2%) used contraception for family limitation rather than birth spacing, compared to 51.3% in the international sample. It appears that in Egypt, with limited facilities for sterilization and religious barriers against its use, Norplant is likely to provide a substitute for the surgical method. This possibility is also suggested by the project report from the Assiut center which runs an active sterilization program. It was stated that after the introduction of Norplant the caseload for sterilization diminished to half the level prevailing in the previous three years.

Low value of hemoglobin found at admission suggests the need for the contraceptive with the least risk of blood loss. With adequate management of bleeding problems, Norplant is likely to meet this need better than an IUD. Its associated side effect of amenorrhea can also be viewed as beneficial in an anemic population.

In Egypt, amenorrhea was of little importance as a reason for termination. Out of 120 known cases of amenorrhea, defined as three consecutively missed cycles, 117 had continued with the method (Table 11), that only three women came for the removal of the implant (Table 8) demonstrates the high tolerance of this side effect among Egyptian women. It suggests that any other implant regimen which reduces bleeding abnormalities even at the cost of increasing amenorrhea may be more acceptable than Norplant, if it does not have other disadvantages.

The major advantage of Norplant over sterilization and an important factor in its acceptability is the reversible nature of the procedure. This study, as initially designed, did not attempt a follow-up of cases who had terminated Norplant without selecting an alternative method of contraception. No accurate statements can therefore be made about the restoration of fertility after termination of use. In the next phase of the study, it is planned to investigate this aspect of Norplant performance.

in induced abortion could be definitely attributed to a method-failure: menstruation was reported during follow-up visits. If the two cases with definite evidence of pregnancy occurence before the use of the Norplant are ignored, the pregnancy incidence would be half of what has been reported. The advantage of Norplant over IUD in terms of effectiveness could not be statistically established, perhaps because the data on Norplant failed to make a clear distinction between patient-failure and method-failure. Other studies report a significantly lower rate of pregnancy with Norplant (Sivin et al., 1980).

Analysis of side effects presented in this report is limited to perceived changes in menstrual flow and recalled length of menstrual period. More objective data on bleeding performance in terms of bleeding/spotting days will be presented in a later report. Data for 503 Norplant and 143 TCu 380 Ag cases (Table 11), who were followed-up for one full year, indicate greater variability of blood flow and length of period among Norplant users, but significantly lesser incidence of increase in both factors. Incidence of non-menstrual side effects (defined earlier) was substantially and significantly higher among Norplant users (Table 12).

Clinic factors account for the variation in incidence of pain at implant site, ranging from 1.9% at Assiut, to 7.9% at Alexandria and a high figure 25.5% at Al-Azhar's rural clinic, with limited staff and medical facilities. Any large scale use of the subdermal method should therefore allow consideration for the available level of professional assistance.

In conclusion, this report based on partial data suggests that Norplant compares favorably in effectiveness and acceptability with most other available methods. Its wide adoption, however, would depend primarily on reduction of associated menstrual disturbances, particularly problems of excessive and irregular bleeding, through an experimental adjustment of dose levels. The method promises to serve as a highly reliable and reversible substitute for sterilization. Substantial information is still in the process of collection and analysis and will provide the basis for more definite conclusions, to be presented in a future report.

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VAGINAL RINGS RELEASING STEROIDS

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It is well known since the beginning of this century that the vagina is capable of absorbing a great variety of substances. In addition, some thirty years ago Greenblatt demonstrated that steroids can be readily absorbed from the vagina when administered as a suppository. This observation led to a large number of investigations aimed at designing therapeutic systems based on vaginal uptake; these studies were prompted by the demonstration that absorption through the vaginal mucosa is a monodirectional phenomenon, which results in the rapid appearance of drugs in the blood stream, bypassing the liver.

Following the observation by Dziuk and Cook that steroids diffuse readily from polysilicone rubber (such as polysiloxane) membranes, Segal predicted that devices made of polysiloxane could be utilized for the sustained delivery of contraceptive steroid hormones. This led to the development of two new types of contraceptives based on polysilicone tubings releasing steroids. One such device is meant to be implanted subcutaneously over a period of months or years, whereas the other is to be inserted intravaginally.

The present chapter will attempt to highlight briefly the characteristics and clinical performance of the two types of vaginal rings developed for the control of human fertility.

RING STRUCTURE AND DESIGN

In the early stage of development the steroid was finely dispersed within the polymeric matrix; this was achieved by mixing together the steroid and the siloxane monomers; following the addition of a catalyst the silicone polymerized and was extruded and moulded. Subsequently, the rings were moulded around a stiff, flat metal spring similar to that used in some diaphragms; unfortunately the stiffness of such devices caused ulcerations and the procedure had to be abandoned.

The second type of vaginal ring was designed by Henzl who prepared devices measuring 55 mm in outer diameter and enveloped by silicone tubing of 0.127, 0.254 and 0.508 mm thickness. The space between the core support and the outer tubing was then filled with a mixture of steroid and silica gel.

The third approach was developed by Victor by moulding rings incorporating a groove 1 mm deep and 2.7 mm wide around the outer circumference; a collagen band impregnated with the steroid was then fitted in the groove. This approach, intended to produce rings with a lower steroid content, was abandoned when it became apparent that the collagen string had a tendency to loosen from the silicone rubber ring.

Three additional structures were developed by the Battelle Memorial Institute for the WHO Programme. The devices were toroidal in shape with an outside diameter of 55.6 mm and a cross section of 9.5 mm. They were all moulded using a multiple step procedure. In the case of models "A" and "B" the catalyzed, drug-loaded polysiloxane was pre-moulded to constitute the core of the ring; subsequently a drug-free diffusion layer of polysiloxane was moulded around the progestogen-containing core.

Devices fabricated according to model "C" were prepared by first moulding a polysiloxane core and subsequently producing two layers around this core, with the middle layer containing the steroid. All three designs were utilized in the experiments and trials carried out under WHO sponsorship, depending on the steroid used. More recent trials, however, are limited to rings delivering 20 ug of levonorgestrel per day, which are fabricated to model "A".

RINGS RELEASING ONLY A PROGESTATIONAL STEROID

Both the Population Council and WHO Programme have investigated rings releasing only a progestogen.

The clinical investigations conducted under the auspices of the Population Council utilized relatively high doses of the progestogen expected to inhibit ovulation; for this reason the ring had to be extracted every three weeks to allow a withdrawal bleeding. In the studies sponsored by WHO, on the other hand, the main purpose was that of achieving inhibition of fertility at a level peripheral to the ovary, thus enabling the woman to keep the ring *in situ* over a period of at least six months.

Ten years after these studies began, only one progestogen-releasing ring is still under development: that diffusing approximately 20 ug of levo-

norgestrel per 24 hours.

Release rates

The first steroid investigated in a vaginal ring was medroxyprogesterone acetate. In the early studies no in vitro release rate was measured and the in vivo diffusion and uptake were calculated from the amount of steroid remaining in the device after use. On the average the rings released 1 mg of medroxyprogesterone acetate every 24 hours (range 0.5 to 1.4). This rate of diffusion was later confirmed when investigators were able to measure plasma levels of the steroid.

Another steroid tested in the early days was chlormadinone acetate. Although no release rates have been calculated for this compound, plasma levels obtained indicate that daily diffusion from the ring must have been below 1 mg.

Mishell used rings releasing norethisterone at rates between 0.85 and more than 2 mg per 24 hours. Two additional synthetic progestogens tested at relatively high doses are ethylnorgestrienone and norgestrienone; the first was investigated at levels allowing in vivo release rates between 0.3 and 3.7 mg/24 h., whereas no release rate is available for the second, although one could guess from the plasma concentration that daily diffusion did not exceed 1 mg/24 h.

One study investigated a progesterone-releasing ring which provide plasma concentrations of around 5 pmoles/ml with release rtes of approximately 2.2 mg/24 h.

The most extensively studied rings are those releasing norgestrel (either in its racemic form or as a levonorgestrel). Most studies were carried out with rings releasing either one of the two forms at levels of 0.25 to 0.30 mg/24 h. (range 0.17 to 0.41). The insertion of these rings resulted in plasma concentrations ranging between 2.5 and 35 pmoles/ml. In an early study Mishell et al. tested rings with higher in vivo release rates (0.55 and 0.83 mg/24 h.), whereas Victor and Johansson utilized a ring releasing 0.13 mg/24 h. of norgestrel.

Vaginal rings utilized in the WHO studies release progesterone at the theoretical dose of 1.2 mg/24 h. Actual release rates before use were 1.33 $\pm$ 0.19 mg/24 h. and 1.4 $\pm$ 0.03 following in vivo insertion.

Two types of norethisterone-releasing rings were investigated by WHO; the first had a calculated release rate of 50 ug/24 h., with a rate before insertion of 38.8 $\pm$ 2.9 and after use of 49.4 $\pm$ 24.0 ug/24 h. The second should have released 200 ug/24 h. and in fact diffused before use 181 $\pm$ 20.0 and 196 $\pm$ 21.0 ug/24 h. after extraction.

Levonorgestrel was investigated embedded in rings with a theoretical release rate of either 10 or 20 ug per day; the 10 ug ring was quickly abandoned whereas WHO decided to go ahead with mass production of the device releasing 20 ug per day. Rings that should have diffused 20 ug/24 h. released before use 17.8 $\pm$ 2.2 and after 21.6 $\pm$ 1.4 ug/24 h.

Pharmacokinetics and pharmacodynamics

The ability of medroxyprogesterone acetate, released from a vaginal ring at rates ranging between 520 and 1219 ug/24 h. to abolish the hLH and hFSH midcycle peak was established by Mishell.

Endometrial biopsies obtained immediately after removal of the ring clearly reflected the progestational effect: glands were narrow, non-tortuous and widely separated, with a stroma pseudodecidual in appearance. Ovulation was inhibited in the vast majority of subjects.

Large variations were reported in plasma concentration of medroxyprogesterone acetate between individual studies and subjects. This, however may, at least in part, be due to the assay method used.

The chlormadinone acetate-releasing ring produced plasma levels of the steroid ranging between 0.25 and 0.74 pmoles/ml. These concentrations, however, were not sufficient to produce anovulation.

Studies with both chlormadinone and medroxyprogesterone acetate were discontinued when these compounds were shown to produce mammary nodules in beagle dogs.

The Population Council rings releasing norethisterone produced - when loaded with 100 mg of the steroid - anovulation in 10 out of 12 subjects and released on the average 1.04 mg/24 h. Rings loaded with 200 mg delivered the steroid at uneven rates: 1.5 mg/24 h. during the first cycle of usage, 1.1 and 0.48 during the second and third cycle respectively. The pharmacokinetics of ethylnorgestrienone were studied by Viinikka who found that the rings produced plasma concentrations declining with time: a total load of 200 mg resulted in levels of 55.4 pmoles/ml at the time of insertion which declined to 18.5 after only 20 days of use. Similar results were found with lower loading. Ovulation was inhibited in all four cases to whom a 50 mg loaded device was inserted.

Data obtained with norgestrienone indicate that a 50 mg loading produced plasma levels ranging from 2.7 to 6.1 pmoles/ml and anovulation in three quarters of the 12 subjects investigated.

Progesterone, when diffusing from rings releasing some 2 mg/24 h. produced plasma concentrations of between 4.8 and 6.4 pmoles/ml; this resulted in anovulation in approximately half of the 17 subjects studied.

In terms of ovulation inhibition the best results were obtained with norgestrel (either dl-norgestrel or levonorgestrel). Diczfalusy and Landgren have calculated that only 22 out of a total of 336 cycles studied were ovulatory in women treated with various discontinuously inserted rings. The pharmacokinetic profile obtained following the insertion of shell type rings loaded with 54 and 128 mg was studied by Mishell et al. The ring was capable of producing fairly stable plasma concentrations (4.8 ± 1.3 and 7.8 ± 1.8 pmoles/ml) and anovulation in all but two of the sixty subjects followed.

The pharmacokinetics and pharmacodynamics of the rings developed by the

WHO sponsored Programme were mainly studied by Diczfalusy and his collaborators.

In a investigation in which frequent plasma samples were obtained in subjects bearing norethisterone-releasing rings at the levels of 200 and 50 ug/24 h. respectively, Diczfalusy and Landgren demonstrated that only the higher release rate was capable of inhibiting ovulation.

Full plasma concentrations of norethisterone are attained approximately 24 hours following insertion. After this, levels remain constant over several months.

With the 50 ug rings ovulation and a normal luteal function was maintained in 83% of the 42 cycles studied, whereas only 21% of the women bearing a 200 ug ring ovulated normally over 48 cycles. In a study conducted by WHO, ovulation was seemingly maintained in 87% of women inserted with the 50 ug device and in 42% of those bearing the 200 ug device.

Insertion of the ring releasing 20 ug/day of levonorgestrel, produced plasma concentrations, on the average, of 0.528 pmoles/ml. Levels remained fairly constant and - 90 days after insertion - the decline in plasma concentrations was of approximately 20%. Following insertion, levonorgestrel reaches maximum concentrations in circulation within less than an hour. The device did not inhibit ovulation in the majority of subjects studied.

Data on the pharmacokinetics of the progesterone-releasing devices are more scanty. The constancy of in vivo release has been measured by removing rings at various time intervals. The data indicate a fairly constant diffusion over time.

According to a study conducted by WHO, a release rate of between 1.3 and 1.4 mg/day did not inhibit ovulation in the vast majority of cases (98%), although inhibition of sperm transport in cervical mucus occurred in 85% of the subjects.

Clinical studies

Medroxyprogesterone acetate released from a vaginal device has never been tested for efficacy. The only clinical data available relate to cycle control. When the rings were inserted on day 5 and left in place for 21 days, a high incidence of breakthrough bleeding and spotting occurred; this was interpreted as indicating an insufficient endogenous estrogen production. For this reason rings were inserted on day 10; when this regimen was tested, however, no improvement in the bleeding pattern was observed. An overall analysis of bleeding data from all investigators indicate that one third of the treatment cycles were complicated by breakthrough bleeding.

No clinical data are available on rings releasing chlormadinone acetate or progesterone. In the case of both ethylnorgestrienone and norgestrienone, in spite of the limited clinical experience it seems that the major problem was represented by irregular bleeding although Akinla et al. reported no breakthrough bleeding with ethylnorgestrienone.

The use of devices releasing norethisterone at high doses produced unacceptable episodes of breakthrough bleeding and spotting, associated with an offensive odor. For this reason further development of this ring was discontinued.

Norgestrel represents the steroid of choice both with discontinuous and continuous usage. However, when released in high doses in a discontinuous fashion also norgestrel causes unacceptable bleeding patterns: when either racemic mixture or levonorgestrel were studied over a period of six months, breakthrough bleeding occurred in one third of the women; in addition a low but sizable incidence of amenorrhea was also observed.

Following early clinical studies during which progesterone, norethisterone and levonorgestrel were tested at levels which proved to be ovulation inhibiting, the WHO Programme conducted, approximately 5 years ago, a multicenter comparative study of rings releasing progesterone at the dose of 1.2 mg/24 h., norethisterone at the doses of 200 and 50 ug/24 h. respectively, and levonorgestrel at the dose of 20 ug/24 h. Eight two women were investigated over a total of 217 woman-months of experience. Results of this study are summarized in Table 1.

After analyzing the results of this preliminary trial, the Programme decided to abandon any further development of the rings releasing progesterone and norethisterone at the dose of 200 ug/24 h.

TABLE 1. Summary of WHO-sponsored Phase I trial of vaginal rings.

Compound and Release Rate	No. of Subjects	Inhibition of Ovulation % of Cycles)	Inhibition of Sperm Migration (% of Post-Coital Tests)	Inter Menstrual Bleeding % Cycles
Progesterone 1200 ug/day	12	2	85	17
NET-200 ug/day	18	58	82	59
NET-50 ug/day	26	13	74	11
Levonorgestrel 20 ug/day	12	40	92	16

A new Phase II clinical investigation was then initiated to evaluate the contraceptive of rings diffusing levonorgestrel (20 ug/24 h) and norethisterone (50 ug/24 h.). A cut-off point was selected for unwanted pregnancies at 6 per 100 woman-years. The criterion for study termination was reached for norethisterone after 166 woman-months of exposure; for this reason, further development of this ring was also abandoned.

Results with levornorgestrel have been much more encouraging: no pregnancies, occurred over an exposure of 360 woman-months; clinical tolerance of the device was satisfactory with few complaints for unpleasant odors and only three subjects discontinuing because of menstrual irregularities, although there were some involuntary expulsions. After reviewing these data WHO decided to concentrate efforts on the development of the ring releasing 20 ug of levonorgestrel. Because of sufficiently

encouraging preliminary data with the Phase II trials, it was decided in 1981 to initiate a Phase III multicenter clinical evaluation. Results of this new investigation are expected by the end of 1983.

RINGS RELEASING BOTH AN ESTROGEN AND A PROGESTOGEN

Devices capable of diffusing at the same time an estrogen and a progestogen have been developed under the auspices of the Population Council in an attempt to improve bleeding performance.

Release rates

Only two progestational agents have been utilized in these rings: progesterone and levonorgestrel. They were coupled to estradiol in all instances, except for one study in which estradiol benzoate was used with levonorgestrel.

Victor embedded progesterone with a total load of 290 mg together with estradiol with a load of 20 mg in a ring of the core type. The release rates of the two steroids were 2.2 and 0.22 mg/24 h. respectively. The combination of levonorgestrel with estradiol benzoate with total loads of either 20.4 and 19.7 mg and 6.5 and 4.4 mg was also tested by Victor. *In vivo* release rates for the higher loading averaged 213 ug/24 h. for levonorgestrel; no data were given for estradiol benzoate. This level decreased to 130 ug/24 h. during the second cycle. The lower loading resulted in the daily diffusion during the first cycle of 74 ug of levonorgestrel.

Several pilot studies were conducted utilizing the combination of levonorgestrel and estradiol, although release rates were only reported in two of these studies.

Mishell reported that rings with a levonorgestrel load ranging between 39 and 77 mg and of an estradiol content between 29 and 66 mg produced *in vitro* release rates between 0.20 and 0.33 mg of the progestogen and of 0.18 to 0.25 mg of the estrogen. Jackanicz reported on rings utilized in the multicenter studies conducted by the Population Council. One type with a 58 mm diameter released *in vitro* approximately 500 ug of levonorgestrel and 300 ug of estradiol per day. From the calculation of average steroid loss during use, the observed *in vivo* release rate was 293 $\pm$ 54 ug/day for the progestogen and 183 $\pm$ 34 ug/day for the estrogen. A second type had a diameter of 50 mm; no *in vitro* data were reported for this ring, which diffused *in vivo* 253 $\pm$ 34 ug/day of the progestogen and 152 $\pm$ 21 ug/day of the estrogen.

Pharmacokinetics

The pharmacokinetics of rings releasing the combination of progesterone and estradiol were investigated in postmenopausal women. For this reason no pharmacodynamic data are available. The rings allowed fairly stable plasma levels of progesterone ranging between 5.8 and 6.4 pmoles/ml, whereas estradiol concentrations varied between 0.37 and 2 pmoles/ml.

The vaginal ring releasing levonorgestrel and estradiol benzoate resulted

in plasma levels of levonorgestrel ranging between 12.8 and 1.1 pmoles/ml depending on the initial steroid load.

Estradiol concentration usually remained at early follicular phase levels, although large variations and even an ovulatory peak were seen in one subject. A detailed pharmacokinetic and dynamic study of rings releasing levonorgestrel and estradiol was carried out by Mishell et al. who found that the rings inhibited ovulation in all 10 subjects studied. Similar results were obtained by other investigators.

Following each insertion, levonorgestrel plasma concentrations increased steadily reaching maximal levels within 48 hours of insertion and fell progressively from around 1 ng to less than 100 ng per ml during the seven days between removal and reinsertion. Estradiol concentrations, on the other hand, rose to a peak between 100 and 300 pg/ml within two hours of insertion, declining gradually between 50 and 100 pg/ml in the first days after insertion.

Clinical studies

No efficacy data are available on the ring releasing progesterone plus estradiol, although ovulation was apparently maintained in 70% of the 13 cycles studies.

Also in the case of the rings releasing levonorgestrel plus estradiol benzoate no efficacy data are available.

Clinical experience with vaginal rings releasing levonorgestrel plus estradiol covers 1147 users and two separate rings, the first with an outside diameter of 58 mm and the second of 50 mm. The rings were compared with a low dose oral contraceptive containing 150 ug of levonorgestrel and 30 ug of ethynilestradiol. The incidence of unwanted pregnancies and their outcome are listed in Table 2.

It can be seen that the 58 mm diameter ring produced a significantly lower pregnancy rate than the low dose oral contraceptive.

Gross termination rates at one year for all medical reasons did not significantly differ in the three groups ranging from 24.7 per 100 woman years for the oral contraceptive to 29.2 for the small ring. Termination for bleeding problems was more frequent among ring users, although the difference was not statistically significant. Both oral contraceptive and the rings were perceived by the users to reduce menstrual flow with approximately 20 to 25% of the ring users believing that intermenstrual bleeding or spotting had increased.

The overall acceptability of these vaginal rings was tested both in urban and rural areas of two Latin American countries. In each of the four location chosen, between 3 and 12.5% of total acceptors selected the rings. Acceptance rate fell after 6 months of use and recovered during the second year; it was higher in the rural areas. Women tended to remove the ring for intercourse and cleaned it frequently.

A series of metabolic studies were also carried out to evaluate the levo-

TABLE 2. Net pregnancy rates at one year and pregnancy outcome in the multicenter clinical trial sponsored by the Population Council.

	RINGS		PILL
	50 mm	58 mm	NOG + EE
First cycle	1.8 ± 0.6	0.7 ± 0.4	1.8 ± 0.6
All cycles	1.8 ± 0.6	1.0 ± 0.5	2.0 ± 0.6
Total pregnancies	9	5	10
Spontaneous abortion	1	0	1
Full term deliveries	2	1	1
Still pregnant	4	3	5
Ectopics	0	0	0
Voluntary abortions	2	1	3

norgestrel plus estradiol ring. Fasting glucose values and glucose tolerance were unaltered during ring use, although insulin response to glucose increased by 50% after one year of treatment. With the exception of a small, but significant, decrease in alkaline phosphate, all liver function tests remained normal.

The vaginal ring users had a significant reduction of cholesterol and the cholesterol/HDL-C ratio was significantly increased during treatment. Also the LDL/HDL ratio increased significantly.

CONCLUSIONS

Some 15 years after the initiation of work aimed at developing vaginal rings for contraceptive purposes only one progestogen-only-releasing ring and one device releasing both an estrogen and a progestogen are still under active development. In both cases the rings were developed by Public Sector Agencies, thereby underlining the lack of interest of the pharmaceutical industry for this type of activity. Both the ovulation inhibiting discontinuous use ring and the low dose continuous use device are reaching the Phase III level, thus raising the hope that this new type of vaginal contraception will become available within the next few years.

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NEW DEVELOPMENTS IN IUD TECHNOLOGY

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Apart from its obvious and well-known advantages, IUDs have some notable disadvantages, which are usually not perceived in the same way in different cultures. For instance, certain people strongly object to having "something" introduced inside their body. Also, changes in the quantity and duration of menstrual flow are considered differently in the various regions of the world, especially where prevailing social or religious mores prevent women from having intercourse during bleeding or spotting. For this reason, any serious attempt to improve IUD performance and acceptance must take these facts into proper consideration.

This chapter attempts to summarize recent developments in intrauterine contraceptive technology, with particular emphasis to those modifications or applications most likely to result in a more wide acceptance of the method. Some of these modifications relate to the shape of devices or to the time of insertion, other to the development of new agents to be incorporated in IUDs, that could become available within the next decade.

POST-PARTUM AND POST-ABORTION INSERTION

Even today, in many countries of the world, delivery is one of the very few occasions when women have a chance to get in touch with a physician and obtain effective contraception. The time of a voluntary pregnancy termination is another moment in which the average woman is most willing

and motivated to accept fertility regulating methods. This is the reason why there is great interest by family planning administrators and staff in devices that can be inserted right after placental expulsion or voiding of the uterus.

Experience with immediate post-partum IUD insertion was first gained in India and in the U.S.A. These studies produced results encouraging enough to overcome the considerable resistance of practicing obstetricians caused by a perceived danger of perforation in the soft post-partum uterus and of intrauterine sepsis, leading to the initiation in 1966 of the International Post-Partum Program of the Population Council.

Almost half of all acceptors of fertility regulation chose the IUD (405,346 out of 837,157) and the overall percentage rose from 11% to all family planning acceptors in 1966 to 21% in 1971. Even using the inert Lippes Loop-D, expulsion rate at 12 months was only 11.5% and the overall continuation rate at one year was 74.4%.

Removal for bleeding problems in post-partum acceptors was first studied by Banharnsupawat and Rosenfield who found an incidence of only 3.9% excessive bleeding among women to whom the device had been inserted immediately after delivery, compared to that of 6.3% among those inserted more than 6 weeks post-partum. These data have now been confirmed by additional comparative studies conducted in several countries of Europe, Asia and South America. Major features of results obtained in these trials are presented in Table 1.

Unfortunately, a different picture emerged from a multinational, comparative clinical trial conducted by WHO that, because of its nature can be considered more likely to represent a true "field" situation than previous studies. In this trial one of the 3 devices studies, the Lippes Loop, was expelled within 24 hours in as many as 8% of all women; of the remaining subjects, as many as 44.1% lost the IUD within one year. In addition, the WHO study indicated that a special device - the so-called Post Partum-T, developed by the Population Council - had a significantly higher expulsion rate than the conventional Copper-7 (41.3 versus 34.8 per 100 woman-year at 12 months). At the same time the post-partum device was more effective in preventing pregnancy, with a life table rate at one year of 5.6 $\pm$ 2.3 per 100 woman-year, compared to that of 7.2 $\pm$ 2.3 with the Copper-7 and of 12.1 $\pm$ 3.3 with the Lippes Loop. An important feature was advanced by the trial: complications varied considerably between individual centers; for instance, whereas in Santiago, Chile, explusions at one year were 9.6, 10.2 and 17.7 per 100 woman-years for the Copper-7, Lippes Loop and Post-partum-T respectively, the rates were 55.8, 77.0 and 83.6 in Brussels. This fact, which can only be explained on the basis of different medical conduct at the time of insertion or of the subsequent management of the patients, clearly points out to the need to develop especially designed devices which would make early expulsions less dependent from intangible factors.

In an attempt to improve placement of IUDs immediately post-partum, Newton manufactured a 25 cm long modified inserter, which - in the mind of the inventors - should have allowed better retention. Indeed, the authors reported in their original study with the LEM, Copper-7 and Pro-

TABLE 1. Overall performance of IUDs inserted immediately after expulsion of the placenta. (Results are expressed as event rate per 100 woman-years of experience at 1 year.)

Devices studied	Number	Pregnancy	Expulsion	Bleeding Pain	Infection	Other Medical	Continuation
Various IUDs	1008	2.8	23.5	5.5	1.2	0.7	61.8
Lippes Loop	274	1.9	7.8	----------	3.4	----------	82.1
TCu-220C	522	1.7	3.6	----------	5.3	----------	82.0
TCu-200	269	0.5	11.2	1.8	0	0.4	77.2
MLCu-250	293	2.4	9.9	3.6	0	0.9	77.3
TCu-200	136	3.4	5.2	5.7	0	0	82.2
MLCu-250	135	1.8	3.1	2.4	0	0	88.6
MLCu-375	134	0	4.6	4.8	0	0.8	84.4
Lippes Loop-D	272	12.1	44.1	4.6	----- 9.0 -----		39.1
P-p-Tcu	287	5.6	41.3	8.7	----- 5.0 -----		46.9
Cu-7	282	7.2	34.8	5.2	----- 1.8 -----		52.3

gestasert devices an expulsion rate at six weeks of 7.0%. However, when the same group participated in the above-mentioned WHO study, expulsion rates at one year were 39.1, 65,0 and 70.9 per 100 woman years using the Post Partum-T, Lippes Loop and Copper-7 respectively.

As already stated, termination of an unwanted pregnancy represents another ideal time for inserting an intrauterine device, because of the high motivation of women in that situation. Fear that the placement of an IUD may worsen post-operative conditions was greatly diminished when Tatum reported that the insertion of the device following elective first trimester abortion did not increase the severity of pain or of bleeding. Safety of this procedure was then established by several other authors.

Gillet have recently carried out a tri-center post-abortion study of the Copper-7 involving 259 women scheduled for pregnancy termination who were subdivided into 2 groups: in the first group the device was inserted immediately after the abortion procedure had been completed, whereas in the second group placement was delayed between 3 and 5 weeks. There were no significant differences in the discontinuation rates for medical reasons between the two groups; removal for bleeding or pain was higher - although not in a significant way - in the delayed insertion group (24.9 versus 16.9%). An important feature evidenced by the study relates to motivation: in the group of subjects who had agreed to have an IUD inserted and were told to return within 3 to 5 weeks, as many as 41% failed to do so. Several other studies have substantiated the rapid loss of motivation in women: for instance Echeverry reported that 55% of all post-partum acceptors who were told to return for an IUD insertion 6 weeks later, failed to come back, and Goldsmith found the percentage of IUD insertion rose from 20 to 80% when IUD insertion was offered before hospital discharge.

In view of the major impact that an early post-partum or post-abortion IUD insertion will have on the success of a family planning program, efforts have been made to design devices especially suitable for these conditions.

More recently, Family Health International developed another post-partum type of IUD by the simple addition to a Copper-T or Lippes Loop of biodegradable chromic suture extensions which can be biodegradable within 6 weeks. Preliminary results with the post-partum Lippes Loop indicate an expulsion rate of 13.7 per 100 woman years at six months, whereas the post-partum Copper-T gave a 6 month rate of 10.6.

Future developments in this area, will have to come from the possibility of designing IUDs which can be easily inserted and retained in the puerperal uterus, without risk of perforation, pain or excessive bleeding. The most promising lead in this direction is represented by the synthesis of rapidly biodegradable polymeric substances; IUDs could then be embedded in a polymer capsule having the proper shape. A device of this sort could be easily placed and retained in the large post-partum uterus and will shrink to its final size and shape within a 2 to 3 week period, following closely uterine involution.

POST-COITAL INSERTION

In 1976, Lippes proposed to utilize copper-releasing devices as interceptive agents for post-coital contraception. When Lippes and co-workers extended their original series, they observed no pregnancies in a study involving 299 women who had one or more unprotected intercourse once or more at a time when they were considered to be fertile. Tyrer calculated that, in a group of 42 women to whom a Copper-T was inserted within 7 days of an unprotected intercourse, at least 15 were fertilized, although no implantation occurred. Another series comprising 191 women was studied by Black; 80% of them were nulliparous and received a Copper-7; the remainder received either a Lippes Loop-D or a Copper-7. Insertion was carried out in the majority of cases within 5 days of coitus, although in 16 cases it was delayed up to 10 days. There was one case of missed menses, that - since amenorrhea in IUD users is exceptional - was considered as an indication of pregnancy. Unfortunately, no beta-hCG measurement was carried out and, therefore, since menses returned spontaneously, no confirmation that pregnancy had taken place could be obtained.

Considering the mechanism by which an IUD can act post-coitally, it has been postulated that the device will interfere with proper nidation, as is the case with all other insertions.

The use of an IUD as an interceptive agent presents several advantages over that of post-coital estrogens: it does not produce gastro-intestinal reactions, such as nausea and vomiting, it can prevent pregnancy up to one week after an intercourse (as contrasted to a maximum of 76 hours with estrogens); and does not cause long-term safety problems. For these reasons, the International Planned Parenthood Federation now recommends the use of IUDs over that of hormonal methods for post-coital contraception.

MEDICATED DEVICES

The most important development in IUD technology has been the discovery that an intrauterine device can be utilized as a carrier for agents aimed at enhancing contraceptive efficacy and/or decreasing the incidence of adverse effects. Research in this field has followed four major lines: the addition of metals, hormones, anti-fibrinolytic and spermicidal agents.

Metal-releasing intrauterine devices

Following the report by Zipper that metallic copper can act as an antifertility agent when placed in the uterine cavity, a large spectrum of devices were developed. Some of these devices can have a life-span of more than 10 years, although they have not, as yet, been tested for duration.

The superiority of copper-releasing devices over inert ones has been clearly demonstrated by several comparative studies. An evaluation of copper-bearing devices is beyond the scope of this chapter; discussion here will be limited to new leads for the improvement of the performance of metal-releasing devices.

Copper IUDs, like the non-medicated ones, produce an increase in the amount of blood loss during menstruation; they also prolong the duration of the menstrual period. Generally, blood loss doubles in users of non-medicated devices; with copper-releasing IUDs the increase in blood flow is of approximately 50%, probably because of the small surface area. Although total blood loss may be lighter in users of copper devices, bleeding is usually more prolonged.

An increased blood flow when using IUDs may represent a serious adverse effect in the developing world, where more than 50% of all women are either anemic or on the borderline. Indeed, WHO-sponsored studies have demonstrated that the insertion of copper devices resulted in a decline in serum ferritin, transferrin saturation and hemoglobin. For this reason the Organization decided to conduct clinical trials in which an attempt was made at reducing blood loss by administering non-steroidal anti-inflammatory agents: eight drugs have been compared each in at least two centers and in 12 women. Compounds have been taken orally for the first three days of menstruation. On the average, indomethacin reduced menstrual blood loss by 26%, flufenamic acid by 33% and alcofenac by 35%.

Indomethacin has also been incorporated into devices and tested in rats: it had no effect on ovulation, fertilization or ovum transport, although it might have slightly decreased the anti-implantation effect of the device.

Additional studies have evaluated the use of prostaglandin synthetase inhibitors to reduce blood loss: Davies utilized naproxen in a double-blind, crossover, placebo-controlled design. Two doses were employed; the higher dosage (1250 mg for 5 days) caused reductions in blood loss of 50% or more in a third of all cycles, whereas the lower dose (500 mg as a loading, followed by 750 mg for 5 days) produced the same reduction in about 10% of the cycles.

Guillebaud and Fraser used nefenamic acid and observed a highly significant reduction in mean total blood loss, which was more evident in heavy losers. Finally, Roy and Shaw employed ibuprofen in women bearing either the Lippes Loop or various copper devices, observing a reduction of between 25 and 39%. Those agents have also been used to reduce pain and dysmenorrhea.

Progestogen-releasing devices

The first suggestion that a progestogen incorporated into an IUD could improve its performance was made by Doyle and Klewe. Following this report, several groups have attempted the development of devices releasing either a synthetic or the natural progestogen.

In 1970, Scommegna published the first clinical data on the use of an IUD diffusing progesterone; they utilized a Lippes Loop-D to which a silastic reservoir containing the steroid had been attached. Initial results were promising, although the rapid release of the steroid from the polysiloxane tubing made the system impractical. Further advance in this area was made possible by the development of devices allowing continuous re-

lease for longer periods of time. Alza Corporation was the first to develop a commercial device with a duration of action of one year (the so-called IPCS-38), which contains 38 mg of progesterone and provides a daily release of 65 ug. The Company then developed a new device, the IPCS-52, releasing 25 ug per day which is loaded with 52 mg; it was estimated that this sytem would have a life span of three years. WHO decided to include this device in two comparative Phase III multicenter studies of copper-releasing devices. In the meantime, Alza conducted trials of their own which indicated that the pregnancy rate increased from 3 per 100 woman-years at 24 months, to some 10 per 100 woman-years at 30 months; also, depletion of the device reservoir occurred earlier than expected, suggesting that the daily *in vivo* rate might have been different from the calculated one.

An interim analysis of the WHO-sponsored studies of IPCS-52 indicates a significant increase in pregnancy rate at between 20 and 24 months. It seems therefore, that the device loaded with 52 mg of progesterone had a life-span of only one and a half years. In addition, out of a total of 9 ectopic pregnancies observed in the two trials, 8 occurred in women bearing the IPCS-52. This finding, although not statistically significant, is bound to renew the controversy on the possible increase in the frequency of ectopic gestations in users of progesterone-releasing devices that seemed to have been resolved.

The progesterone-releasing IUD has the distinct advantage of reducing the volume of blood lost during menstruation to almost half the pre-insertion levels, with a tendency to a further decrease with time. Several investigators have also stated that progesterone diffused *in utero* is effective in diminishing the incidence of cramps associated with IUD use, although no difference in the frequency of dysmenorrhea was found in a recent comparative study carried out under the auspices of WHO when the progesterone-releasing device was compared to a Copper-7.

In view of the relatively large quantities of progesterone required daily for proper contraceptive protection, further improvements in steroid-loaded IUDs must come from the use of potent synthetic progestogens. The most promising compound today is levonorgestrel. Devices diffusing this steroid are discussed in Chapter 16 and 17 of this book.

A norethisterone-releasing device was tested by the WHO Special Programme; following preliminary clinical testing; however, development of this device was abandoned because of the high doses required to produce a significant reduction in the quantity of blood loss.

There is one study carried out to evaluate the efficacy of a device diffusing retroprogesterone; the trial had to be discontinued at an early stage because 5 pregnancies were observed when only 500 woman-months of experience had been collected, and work on this IUD has been stopped.

Organon in the Netherlands are developing a device incorporating their new potent progestogen desogestrel.

Finally, in view of the very low uterotropic effect of estriol, Scommegna and his group felt that the steroid could be safely incorporated into an

IUD. Following promising results in rabbits and in baboons, a device capable of releasing estriol to the human uterus was developed by Baker. The device is under clinical testing at present.

Devices releasing antifibrinolytic agents

Among the factors that are considered of importance in the processes leading to menstruation, fibrinolysis occupies an important place. The normal uterus contains high concentrations of plasminogen activators which are localized in the vascular epithelium of the myometrium and in the endometrial cells during the luteal phase. The presence of an intrauterine device enhances fibrinolytic activity in the uterus. This undoubtedly influences uterine hemostasis.

It would therefore seem useful to utilize antifibrinolytic agents (aminocaproic acid, tranexamic acid), or protease inhibitors (traysol) to decrease bleeding-related IUD complaints.

Aminocaproic acid (EACA) was first utilized by Kasonde and Bonnar who observed a highly significant reduction in menstrual loss in 35 women. Shaw incorporated EACA into a silastic device and tested its effect in rhesus monkeys: they measured a doubling of the menstrual loss if using a non-medicated device and only a 33% increse when the EACA-releasing device was inserted.

The effect of tranexamic acid (AMCA) as an oral tablet was first tested by Westrom and Bengtsson in a double-blind study of 65 IUD users. It reduced the increase in blood loss from an average of 83 to only 11.5%. Similar results were obtained when AMCA was instilled in utero. This effect was confirmed by Ragab and Thomas who inserted devices loaded with AMCA (with a daily release of 4.3 mg/day) and observed a lower discontinuation rate at 6 months compared to copper devices (1.1% versus 9.9%), and by Hefnawi.

Finally, Trauber et al. have employed trasylol by intrauterine application observing an effect lasting for a period of some three months and advocated the development of a trasylol-releasing IUD.

Devices diffusing diamidines and guanidines

During the past 5 or 6 years, the WHO Programme has undertaken the evaluation of two classes of compounds that may present several advantages if incorporated into intrauterine devices: diamidines and guanidines. These substances have antifertility activity, can act as acrosin inhibitors and are effective in diminishing uterine bleeding. Studies in Rhesus monkeys indicate a reduction in blood loss ranging from 25 to 42% for the diamidines; with guanidines, a reduction up to 90% was observed in baboons, but only when the compounds were infused directly into the menstruating uterus. Work has therefore pursued mainly with diamidines along along four specific lines: screening of different compounds for their ability to reduce menstrual blood loss, antifertility testing in a mouse blastocyst culture, incorporation of drugs into polymer devices and toxicology. Of the 22 compounds tested, two have been selected for further development.

CONCLUSION

Research sponsored by various national and international agencies is apt to produce improved intrauterine contraceptive devices possessing not only high effectiveness, but also, a low incidence of adverse reactions and a duration of action up to ten years. These improved devices will be utilized in a variety of situations, such as after delivery, post-pregnancy termination and post-coitally.

One problem, however, cannot be resolved by simple technological advancements: as pointed out by Mishell, clinical factors such as the skill of the physician, the care at follow-up and proper instructions to prospective users, are more important in determining overall IUD performance than most of the improvements foreseen today. As an example of this, Wagatsuma cites the very low acceptance of IUDs in Singapore and Malaysia. When the National Family Planning Program began intensive post-partum and post-abortion recruitment in Singapore, there was a perforation rate as high as 0.8%. These events, which occurred over 15 years ago still influence acceptance of IUD in the area.

Multicenter studies have also shown very large differences in device performance between centers in different countries, once again stressing the overall importance of the clinical factor. For this reason, work aimed at identifying women at high risk for intrauterine contraception should be considered of paramount importance. Wheeler has attempted, through a computer program, to preselect subjects more likely to discontinue IUD use because of complications. If such women could be identified and advised to use other forms of contraception, a major improvement of the overall acceptability will probably result.

Finally, proper training of medical personnel will also result in a lowering of the incidence of procedural errors and in a better overall method performance.

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UTERINE GEOMETRY AND IUD PERFORMANCE

Harrith M. Hasson

The quality of IUD performance is essentially determined by the dynamic interaction between the geometric parameters of the host uterus and those of the resident device. The clinical outcome of intrauterine contraception in a particular patient is also influenced by other characteristics of the intrauterine contraceptive device system, the patient as well as the provider.

UTERINE GEOMETRY AND FUNCTIONAL CHARACTERISTICS

The human uterus is composed of three distinct segments with different anatomic and functional characteristics: an upper endometrial fundal segment, an intermediate isthmic zone and a lower cervical segment. There is general agreement concerning the existence of the isthmus as a functional sphincter found between the uterine corpus and cervix. The uterine isthmus should be recognized as a separate entity since the embryologic derivation of its muscles differs from that of the corpus and its general anatomic and functional characteristics are also different.

Anatomic - geometric features. At cross section, the uterus is found to be composed to three distinct geometric zones; an upper endometrial segment, having the general configuration of an isosceles trapezoid, an intermediate transitional isthmic zone and a lower cervical segment having the general shape of an elliptical cylinder.

The uterine cavity possesses a single axial and variable transverse and anteroposterior dimensions. Normally, the cavity is a shallow space capable of distention. In order to define the endometrial cavity in geometric terms, it is necessary to limit its confines to the uterine space bound inferiorly by an arbitrary horizontal line representing the level of 12 mm uterine width, superiorly by the top of the fundus and laterally by the lateral uterine walls. Total uterine length is differentiated into cervical and endometrial components on the basis of this dividing line. The axial distance between the external cervical os and the 12 mm uterine width level is considered the effective cervical length, which includes the isthmus. The distance between this 12 mm uterine width level and the top of the fundus is considered the effective endometrial length. Generally, the isthmus is defined as the area bound inferiorly by the histologic internal os and superiorly by the anatomic internal os. Although the 12 mm uterine width level does not necessarily identify the exact location of the anatomic internal os, it does indicate its approximate position within the uterine cavity; the diameter of a component sphincter does not exceed 12 mm. Thus, a geometric model of the endometrial cavity can be drawn with the top of the fundus representing the superior boundary of a trapezoid, the lateral uterine walls, the sides of the trapezoid, and the arbitrary fixed dimension of 12 mm the inferior boundary, (Figure 1). Although hysterographic studies have occasionally demonstrated other cavity shapes, it is believed that these shapes resulted iatrogenically from uterine overdistention and/or positional and other x-ray related distortions.

Anatomic-functional characteristics. Histologic and physiologic studies indicate that the upper uterine fundal segment provides the contractile expulsive force while the isthmus serves basically as sphincter. Schwalm and Dubrauszky demonstrated that the greatest concentration of muscle fibers was found in the upper segment with a progressive decrease caudally. Daels showed that the myometrium consists of two muscle layers: an outer active and an inner passive layer. The active layer of the myometrium was very broad in the fundus and narrow in the isthmus; the passive layer was arranged in the opposite way. Spontaneous motility patterns of the outer myometrial zone exhibited consistent, strong, regular, primarily rhythmic contractions; those of the inner zone displayed weak, irregular contractions or no activity. Berhman and associates noted definite fundus to cervix uterine muscle propagation waves during menstruation and Hendricks reported a great resemblance between the contractility pattern of labor and that of menstruation.

Dynamic cyclic changes in uterine shape and size occur normally in women during different phases of the menstrual cycle. These variations are based on a cyclic alternating inverse tonal relationship between the uterine fundal and isthmic segments. During menstruation, the isthmic segment is wide, short and hypotonic. Following ovulation, it becomes increasingly narrow, long and hypertonic. Changes in the uterine fundal segment occur in a reverse order. Myometrial activity is most pronounced during menses, at which time rhythmic contraction waves arise in the fundus and spread to the cervix. Uterine contractions during menstruation tend to compress the IUD and move it downwards, not upwards, as previously suggested (Figure 2). During the proliferative phase, on the other hand, only local unsynchronized contractions are demonstrated.

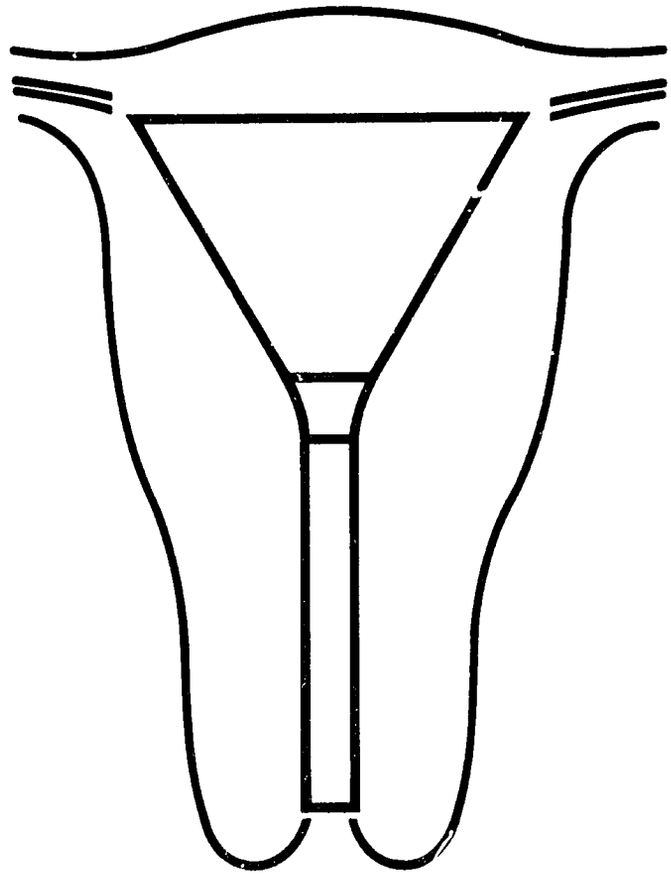

FIGURE 1. Geometric model of the uterus identifying its endometrial isthmic and cervical segments.

Abnormalities. Abnormal variations in uterine geometry occur as a result of congenital or acquired lesions. Developmental anomalies proceed from partial or complete failure of fusion of embryologic mullerian duct systems. During embryonic life, the mullerian duct system develops as a pair of ducts. Subsequently, the lower portions of the ducts fuse to form the vagina and uterus, while the upper portions become a pair of fallopian tubes. The resulting abnormality may range from a small rudimentary septum in the top of the fundus (uterus arcuatus) to complete separation of the uterus into two compartments (uterus didelphys). In a series of 125 hystograms performed after spontaneous abortion, I found a 4% incidence of congenital uterine anomalies. In patients wearing IUDs, the incidence has varied from 4% to 9%.

Leiomyomas are the most common form of acquired lesions that reduce the uterine space available for IUD development and cause distortion of uterine geometry. Anatomic investigations indicate that minor lesions of the congenital or acquired type do not change the basic geometric shape of the endometrial cavity; however, more extensive lesions do.

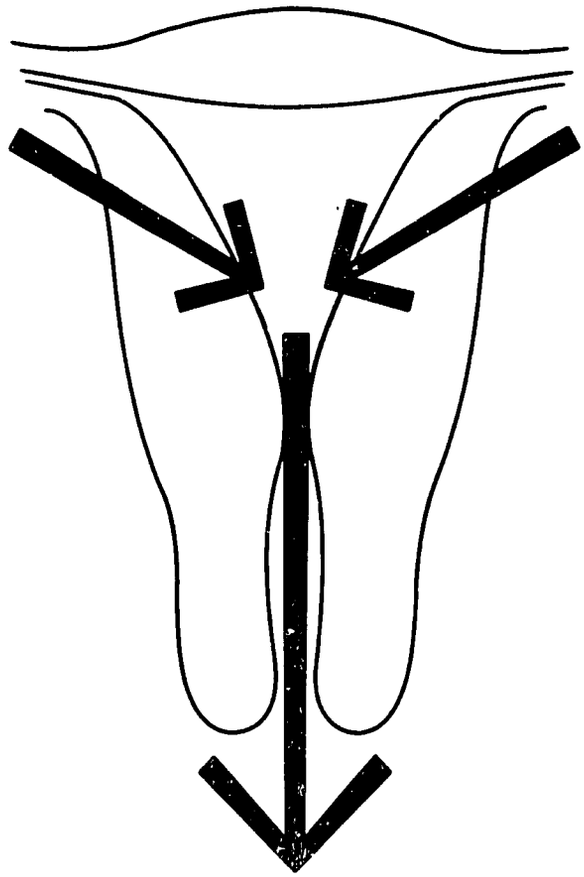

FIGURE 2. Effect of uterine contraction on an object placed in the uterine cavity.

Evaluation. The current method of estimating uterine size, with a bimanual pelvic examination and measuring length with a conventional sound, are not adequate for identifying uterine dimensions pertinent to IUD use. Studies show that the measurements of the external dimensions of the uterus do not reflect the internal dimensions of its cavity. Laboratory examination of uterine cross-section of fresh hysterectomy specimens reveals that occasionally the position of the anatomic internal cervical os extends significantly beyond the level of external junction between uterine body and cervix. Furthermore, existing evidence indicates that measurement of total uterine length is not predictive of endometrial cavity length. Uterine measurements obtained *in vivo* with the use of the Wing Sound, an instrument capable of differentiating total uterine length into cervical and endometrial components, show that different combinations of cervical and endometrial length are usually found among patients possessing the same total uterine length (Figure 3).

The Wing Sound is essentially a pliable probe formed with expandable wings and a scale (Figure 4). To obtain the desired information, the sound is introduced into the uterus and used as a simple probe to mea-

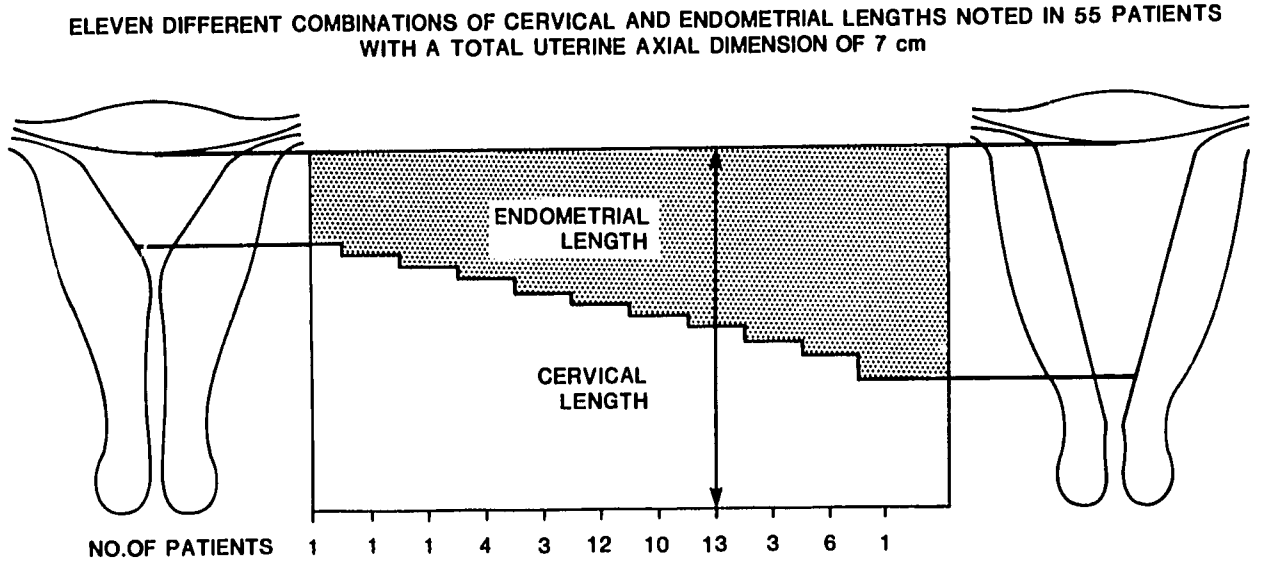

FIGURE 3. Various combinations of cervical and endometrial lengths in patients with a uniform total uterine length.

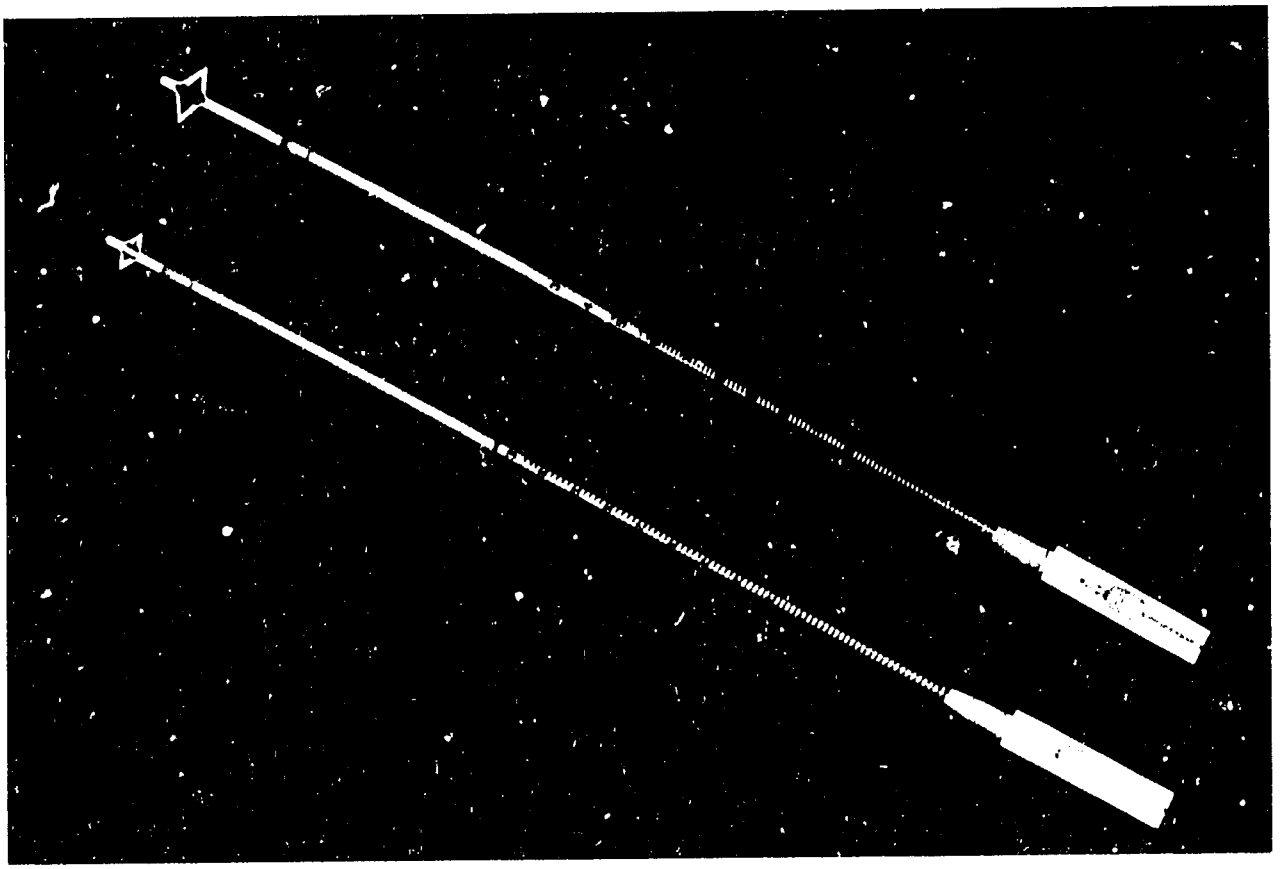

FIGURE 4. The Wing Sound II device with wing spreads of 12 and 18 mm.

sure total uterine length. While the sound remains in the uterine cavity, the wings are extended and the sound is withdrawn until firm resistance is encountered. This area indicates the approximate position of the anatomic internal cervical os. The measured distance is identified on the scale. This reading representing cervico-isthmic length, has to be corrected by subtracting 1.3 cm, a factor compensating for difference in end points of the measurements. The wings are then folded and the sound is withdrawn from the uterus. Endometrial cavity length is obtained by subtracting the corrected cervico-isthmic length from total uterine length. Should the sound slide out of the uterine cavity, upon withdrawal with its wings extended, cervical incompetence is diagnosed. Further assessments of cervical competence can be realized through graduated adjustments of the withdrawal force and/or the use of larger wing spreads.

The value of using the Wing Sound device was demonstrated in a study of patients wearing three different types of IUDs; the Copper-7, the Lippes Loop and the Dalkon Shield. Results of the study showed a positive relationship between endometrial cavity length and IUD performance regardless of IUD type. The rate of IUD events increased significantly when the length of the IUD was equal to, exceeded, or was shorter than by 2 cm or more the length of the endometrial cavity.

Devices used to measure transverse dimensions include the Battelle uterine caliper, the Kurz cavimeter, the Wang metrology device and the Wing Sound II. The Battelle, Kurz and Wang metrology devices employ similar concepts. Uterine transverse dimensions are assessed by releasing two outwardly projecting device members (arms) against the lateral uterine walls; the distance between the tips of the device arm is transmitted to a scale. Results of studies carried out with these instruments suggest that fundal width may be narrower than previously reported.

The concept of the Wing Sound II application is based on the assumption that the cross-sectional geometry of the endometrial cavity, as previously defined, is generally that of an isosceles trapezoid. In this case, it is possible to predict the specific shape of the cavity by identifying its singular axial dimension as well as two of its transverse diameters. Wing Sound II is essentially a pliable probe, formed with expandable wings and a scale. The wings of this sound can be expanded to two stable transverse dimensions of 12 and 18 mm respectively. Using the Wing Sound II, one can measure total uterine length and establish the insertion depth at which the width of the uterine cavity matches each of the predetermined wing spreads (Figure 5). Thus one can identify endometrial cavity length, as previously described, as well as the position of the 12 and 18 mm transverse diameters of the endometrial cavity. The information can easily be transmitted into a geometric outline of the endometrial cavity, using mathematical equations that define an isosceles trapezoid. The Wing Sound II instrument and method have been tested successfully in the laboratory, using fresh hysterectomy specimens. However, the ulitmate usefulness of the device awaits clinical confirmation.

The use of specialized metrology devices measuring uterine transverse dimensions is expected to be associated with an appreciable degree of discomfort as a result of increased uterine manipulation. Such measure-

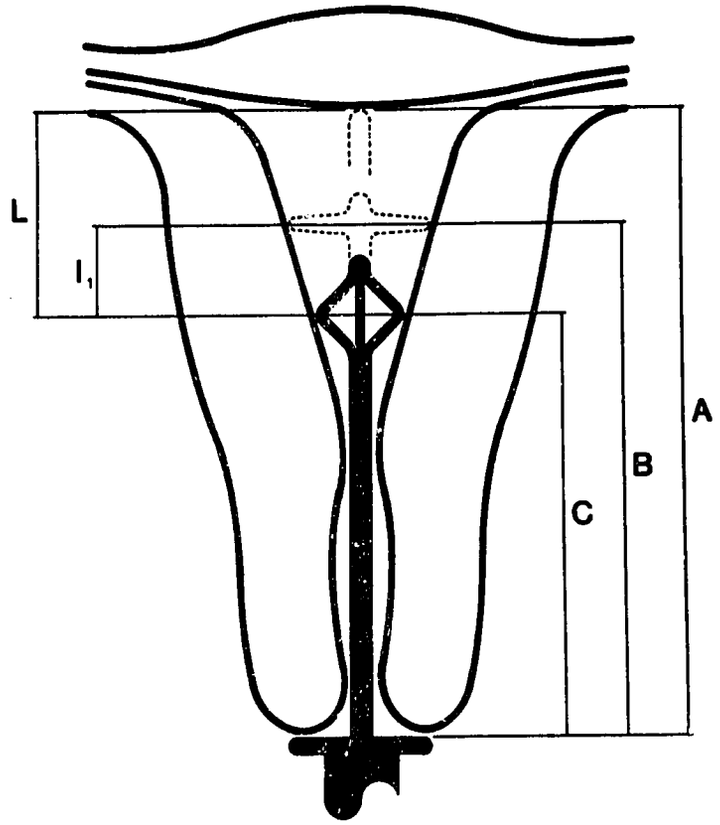

FIGURE 5. Application of the Wing Sound II. (A) Total uterine length. (B) Mid-uterine length (13 mm width level). (C) Cervico-isthmic length (12 mm width level).

ments may not be tolerated by nulliparous women, without suitable anesthesia. In order to relieve the discomfort associated with uterine measurements and IUD insertion, the author has introduced the technique of topical anesthesia and has used it successfully since 1974, in more than 500 patients. It is firmly believed that IUD insertion and/or uterine measurement should not be performed, especially in nulliparous women, without the use of topical uterine anesthesia or a paracervical block. The technique of topical uterine anesthesia is simple and safe: 2 to 3 ml of 2% Lidocaine are injected slowly into the uterine cavity, through a cannula formed with an acorn. The instrument is maintained in place, either automatically with a self-holding spring-loaded device or manually, for five minutes. Uterine manipulations are then carried out as indicated. It should be noted that topical uterine anesthesia is potentially dangerous if the proper anesthetic agent, dosage or technique is not utilized. Strict adherence to methods described in detail elsewhere is recommended in order to maintain the safety of this new application.

It is known that the uterine cavity is a shallow space that is capable of being distended. None of the available metrology devices is suitable

for estimating potential uterine capacity, defined as degree of distensibility. The uterine parameter has been evaluated with the use of an intrauterine balloon and with specialized hysterographic techniques using a balloon or free contrast material. The studies indicate that multiparous women possess a greater potential uterine capacity than nulliparous women. However, it is difficult to translate degrees of intrauterine balloon distention or amounts of injected contrast material into specific anteroposterior dimensions of the uterine cavity. Fortunately, the need to consider this uterine parameter in the design of IUDs has been virtually eliminated by the development of medicated IUDs, where the contraceptive effect is primarily dependent on the added medication rather than the thickness or physical bulk of the device.

Hysterography, ultrasonography, hysteroscopy, uterine cast preparations and dissection of surgical and autopsy specimens have been used to study the uterus. Hysterography can be employed in a clinical setting to verify IUD position within the uterine cavity. However, hysterography is not suitable for routine assessment of uterine shape or endometrial cavity dimensions prior to IUD insertion, as the procedure is subject to various positional and technical distortions. Over-distention of the uterine cavity with the injected contrast material is another problem. Cost and and patient exposure to radiation pose additional concerns. Ultrasonography has generally replaced hysterography as a means of identifying IUD position. This technique also is not useful for routine uterine assessment. The end point of axial measurement, the internal cervical os, is subject to unpredictable variations related to degree of bladder distention, length of cervix and uterine postion. Furthermore, measurement of transverse dimensions of a uterus that is not gravid or otherwise distended with fluid, is not possible without the use of an intrauterine device marker. Under such circumstances, the transverse dimensions of the uterus may not be easily differentiated from those of the device. Thus, it appears that the use of metrology devices remains the most accurate method of uterine assessment *in vivo*, to date.

DEVICE GEOMETRY AND FUNCTIONAL CHARACTERISTICS

The size, shape and consistency of an IUD jointly establish its design profile and determine the degree of its stability within the endometrial cavity.

Size. Custom fitting of IUDs requires knowledge of pertinent uterine parameters including cervical length. Recognition of cervico-isthmic length allows the health care provider to place the device exclusively in the endometrial cavity, above the level of the anatomic internal cervical os. It is logical to assume that IUDs that are fitted to the size of the endometrial cavity would yield a better record of performance than those that are inserted at random. In fact, it has been consistently shown that significant disproportion between the length, width or thickness of the IUD and the corresponding uterine parameter is associated with an increase in IUD complications.

Disproportionately large IUDs become wedged into the uterine isthmus and/or protrude into the cervical canal and cause endometrial injury, as well as myometrial distention. These mechanical effects trigger clinical

events of IUD expulsion, bleeding and pain. Disproportionately small IUDs may not cover enough uterine area to prevent pregnancy (if the IUD is inert), or they may gravitate downwards into the uterine isthmus and/or cervix. Bleeding and expulsion are predictable results. Disproportionately thick IUDs may produce endometrial injury and myometrial distention and cause clinical problems.

Shape. The shape of an IUD is an independent geometric determinant of IUD-uterine relations. For instance, devices possessing adaptive features making them capable of utilizing uterine space above the tip of a congenital fundal septum would perform reasonably well in patients with such minor fundal anomalies. On the other hand, devices lacking pertinent adaptive features would be deployed entirely below the tip of the septum. These devices are likely to become impacted in the isthmic segment or protrude into the cervix. Contraceptive efficiency is decreased and the probability of expulsion, bleeding, pain and infection is increased. Further, IUDs having adaptive features that resist descent of the device into the lower confines of the uterus, as a result of uterine expulsive activity, would tend to remain stable in their initial high position of placement. Conversely, devices lacking pertinent adaptive features are likely to be partially or completely expelled during menses.

Consistency. Adaptation of the IUD to dynamic cyclic variations in uterine shape and dimensions is necessary for the maintenence of favorable IUD-uterine relations. This is achieved through specific morphologic features and proper compliance properties of the IUD.

GEOMETRIC FACTORS ASSOCIATED WITH IUD EVENTS

Pregnancy. In the case of inert IUDs, contraceptive efficacy appears to be inversely related to bulk or surface area. Unfortunately, the greater protection afforded by increased IUD size is frequently associated with patient complaints of bleeding and pain. Ultimately the large IUD may be expelled leaving the patient unprotected. The contraceptive efficiency of medicated IUDs is essentially related to the amount found within the endometrial cavity. Medicated IUDs located partially in the cervix may not prevent conception.

Expulsion. Expulsion is a function of IUD size versus endometrial cavity size and IUD adaption versus dynamic uterine activity. The presence of a space-occupying lesion in the uterus, such as a fundal septal anomaly or myoma, reduces the uterine space available for IUD deployment and increases the probability of IUD expulsion and other clinical complications. Variations in uterine tolerance can modify the outcome.

Bleeding and pain. Abnormal uterine bleeding secondary to IUD use results from the mechanical effects of the device on the uterine tissues, namely compression and ulceration. The use of devices with pointed tips or sharp edges may cause localized penetration injuries. More extensive damage may occur with the use of excessively large IUDs. The uterine tissue and humoral responses to the IUD and the medication it carries are other important determinants of this problem. Pain is probably related to the degree of uterine distention and/or irritation of the isthmic region by the IUD. Patient complaints of bleeding and pain are affected

by psychological and socio-cultural factors and influenced by the attitudes of the health care provider.

Infection. Pelvic infections do not occur with an IUD in place unless the patient is, or has been, exposed to pathogenic organisms, usually of the sexually transmitted type. Interference with the cervical barrier and/or significant damage to endometrial tissues contribute to the development of a pelvic infection with an IUD.

Perforation. Uterine perforations occurring at the time of IUD insertion are due to inappropriate technique and/or unusual patient characteristics. Perforations occurring later result from the penetration of one or more device tips into the uterine wall. Perforations of the lateral uterine walls are caused by devices with pointed transverse arms. Retrograde penetration of the isthmic or cervical segments are caused by devices with a dependent vertical arm having a pointed tip.

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INTRAUTERINE RELEASE OF LEVONORGESTREL

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Clinical experience and research have shown that oral contraceptives have beneficial effects on the health of the users. These benefits include a reduction in the amount of menstrual bleeding, and protection against infection and ectopic pregnancy. Oral contraceptives have other problems than the widely published medical side effects, however. Recent trials have shown that oral contraceptives produce a higher pregnancy rate than expected, particularly in young women with low motivation for contraception and that the continuation rate of oral contraceptives is low as it is in the United States also.

The second modern reversible contraceptive method, the IUD, has been shown to have higher continuation rates than oral contraceptives. The basic problems with this method are the increased amount of bleeding and pain and the increased risk of infection.

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Development of a levonorgestrel-releasing IUD was initiated to eliminate some of the problems of oral and IUD contraceptives and retain some of the benefits of both methods.

Intrauterine release of levonorgestrel

In the first clinical experiments levonorgestrel was incorporated into a biodegradable matrix, polylactate, which released the steroid in the uterine cavity by hydrolysis. Levonorgestrel was well absorbed from the uterine cavity and measurable amounts appeared in the plasma. The polylactate was however unevenly hydrolyzed which resulted in high plasma levels during episodes of uterine bleeding and over a period of time rapidly decreasing average plasma concentrations of levonorgestrel.

It was possible to obtain a matrix from which the steroid was released at a constant rate in the uterine cavity by using a Silastic® polymer which was impregnated with levonorgestrel. By covering the levonorgestrel containing Silastic® with Silastic® tubing an initial burst in the release of levonorgestrel could be eliminated.

Levonorgestrel-IUDs with a daily release of 10, 12, 20, 30, 50 and 75 ug have been studied. The highest daily release of 50 ug and 70 ug caused inhibition of ovulation. These high amounts of daily release could not be achieved for longer periods of time, and therefore the use of these devices was discontinued. The low release of 10 to 12 ug per day resulted in one pregnancy in a small pilot series and therefore the use of this device was also discontinued.

The main experience is based on devices releasing 20 and 30 ug of levonorgestrel daily. Studies have shown that there are no merits when using devices releasing 30 ug over those releasing 20 ug per day. The device chosen to be used in further studies was therefore the one releasing 20 ug daily which has an effective lifetime of over five years.

Local effects of levonorgestrel

Histology. The levonorgestrel released by the intrauterine devices has a profound effect on the endometrium. Histologic evaluation of the effect of levonorgestrel on the endometrial morphology has been performed by obtaining endometrial biopsies during use of the levonorgestrel-releasing IUD and by examining the histology of uteri surgically removed because of uterine fibroids from women who have been using the steroid-releasing IUD. In addition to the published results, further knowledge on the long-term local effect of levonorgestrel has accumulated when biopsies have been taken after up to five years of continuous use of the levonorgestrel-IUD. The histologic appearance of the endometrium has in all cases been very uniform regardless of the treatment time. The mucosa is thin, about 1 to 3 mm, and shows a slightly swollen stroma with pseudodecidually enlarged cells. The endometrial glands are scarce and atrophic with an inactive, low epithelium and no signs of mitotic activity or irregularity. These changes can be seen throughout the endometrium and are not limited to the superficial layers. An inflammatory reaction of leucocytic infiltration is also present to an extent not greater than commonly seen with inert IUDs. The levonorgestrel released *in utero* causes a very strong

suppression of the uterine endometrium. The suppression of the endometrium by the progestasert IUD requires longer exposure and is less uniform.

Tissue concentration of levonorgestrel. The concentration of levonorgestrel in the endometrial, myometrial, fallopian tube and fat tissue of women using a levonorgestrel-IUD, has been determined. A comparison was made with an oral treatment of levonorgestrel. Healthy women scheduled for hysterectomy because of uterine fibroids volunteered for the study and had a levonorgestrel-IUD inserted postmenstrually between 39 and 49 days prior to surgery. Tissue samples were obtained immediately after removal of the uterus with the IUD still in place. There was no significant difference in the plasma concentration between the orally treated group with intrauterine treatment with levonorgestrel. A significantly higher concentration of levonorgestrel in fat tissue was however seen in the orally treated group than in the IUD group. In the IUD group, t e tissue concentration of levonorgestrel in the endometrium was much higher than in the orally treated group. This was to be expected, as the levonorgestrel is released directly into the endometrium. If the weight of the different organs in which tissue concentrations have been determined is considered, the total amount of levonorgestrel was lowest in the endometrium. The daily-release of levonorgestrel from the IUDs used was 30 ug. Thus the total amount of the steroid in the endometrial tissue represents only 0.6% to 2.2% of the daily release.

The concentrations of levonorgestrel in the myometrium and fallopian tube tissue were low and similar after oral or intrauterine administration of levonorgestrel. The daily oral dose of levonorgestrel was ten times higher than that of the intrauterine release of levonorgestrel.

The concentration of the cytosol progesterone receptor in human endometrium during the menstrual cycle has been found to be between 300 and 1500 fmol/mg of cytosol protein and the mean concentration of cytosol progesterone receptors in human myometrium was found to be 300 to 335 fmol/mg cytosol protein. The intrauterine release of levonorgestrel from the present IUD results in tissue concentrations which are high enough to saturate endometrial receptors. Levonorgestrel concentration in the myometrium is however so low that the myometrial receptors are not saturated with this concentration.

Bleeding patterns and ovarian function. High endometrial concentrations of levonorgestrel do explain the very uniform and strong suppression of the endometrium. The suppression of the endometrium results in a significant reduction in the amount of menstrual bleeding. This has been demonstrated by quantitative measurements of menstrual blood loss of women using the levonorgestrel-IUD. Studies in which the numbers of days of bleeding and spotting are recorded, show no significant reduction in the number of days of bleeding during the first three months of use but a significant reduction in the number of days of bleeding after six months of use. Determination of plasma ferritin concentrations show a significant elevation after one year's use of the levonorgestrel-IUD as compared with a copper-releasing IUD indicating an increase of the iron stores.

After one year's use of a levonorgestrel-IUD more than 10 % of the patients had no bleeding. The amenorrhea seems to be caused by local suppression of the endometrium which makes the endometrium insensitive to estrogens. Determination of the concentrations of estradiol and progesterone in the blood did show completely normal ovarian function in the amenorrhoic patients. The plasma concentrations of progesterone and estradiol show a normal cyclic ovarian function. The levonorgestrel concentration is low and stable. After a decline of the concentrations of progesterone and estradiol of the third luteal phase of the treatment, no bleeding was observed.

Clinical experience

A comparative randomized trial with a levonorgestrel-IUD and a copper-releasing IUD, Nova-T, now covers five years. A random assignment resulted in a very similar age and parity distribution in women accepting the levonorgestrel-IUD and the Nova-T. Table 1 gives the number of events during the 36 months of observation. The number of incomplete observations also includes women who have had their last observation before month 36. In this comparative trial the experience with the levonorgestrel-releasing IUD covers more than 7000 woman-months. The Pearl index for the levonorgestrel-releasing IUD is extremely low, 0.16, while the Pearl index for the Nova-T is 1.66. Table 2 gives the first segment gross rates at 12, 24 and 36 months of use. The gross pregnancy rate for the levonorgestrel-releasing IUD was 0.4 at 36 months which was not significantly lower than the gross pregnancy rate for the Nova-T ($p<0.09$). The net pregnancy rate of Nova-T was 3.9, which was reached during the second year of use. During the last year there were no more pregnancies with Nova-T. The termination rate of removals because of bleeding and pain was quite low after three years of use. The removal rate for both devices was around 10. The removal rate of the levonorgestrel-releasing

TABLE 1. Number of events and Pearl index of levonorgestrel-releasing IUD (Ng-IUD) and Nova-T during three years.

Event	Ng-IUD	Nova-T
Pregnancy	1	5
Expulsion	6	6
Bleeding and pain	25	14
Amenorrhea	32	0
Hormonal	18	2
Infection	0	1
Other medical	6	2
Planning pregnancy	19	10
Other personal	12	2
Released from study	0	0
Related terminations	119	42
Total terminations	119	42
Number entering first month	281	134
Number of incomplete observations	19	16
Number of completing last month	143	76
Woman months	7279.00	3604.50
Pearl index	.16	1.66

TABLE 2. The first segment net termination rates of levonorgestrel-releasing IUD and Nova-T at 12, 24 and 36 months.

	NET RATES					
	12 months		24 months		36 months	
	Ng-IUD	Nova-T	Ng-IUD	Nova-T	Ng-IUD	Nova-T
Pregnancy	0.4	3.0	0.4	3.9	0.4	3.9
Expulsion	1.8	3.0	1.8	4.7	2.2	4.7
Bleeding and pain	6.1	3.0	8.3	7.9	9.0	11.3
Amenorrhea	2.5	0	11.6	0	11.6	0
Hormonal	1.8	1.5	5.8	1.5	6.6	1.5
Infection	0	0	0	0.8	0	0.8
Other medical	0.4	0.8	1.5	0.8	2.2	1.6
Planning pregnancy	0.4	0	4.0	7.3	7.1	8.2
Other personal	0.7	0	2.2	1.6	4.5	1.6
Released from study						
Released terminations	14.0	11.3	35.5	28.4	43.6	33.5
Total terminations						

IUD because of amenorrhea was reached at the end of the second year. Counselling of the patients and doctors resulted in no discontinuation of the method because of this reason during the third year. In the present study there are no infections recorded with the levonorgestrel-releasing IUD and only one with Nova-T. Termination because of planning pregnancy is very similar with both IUDs reflecting the same age and parity distribution of women accepting the levonorgestrel-releasing IUD and the Nova-T. The monthly cumulative net rate of pregnancy demonstrates that the pregnancies with Nova-T were observed mainly during the first year. The only pregnancy with the levonorgestrel-releasing IUD occurred during the last part of the first year. The cumulative net rates of removals due to bleeding and pain are very similar with both devices.

The Nova-T had slightly increased number of bleeding and spotting days during the first month, thereafter the number is quite constant, approximately seven days per 30 day period. During the first three months the levonorgestrel IUD had more spotting and bleeding days. Thereafter the reduction is very dramatic and the decrease is observed until the end of the second year, whereafter, there is a small increase in the number of bleeding and spotting days.

During the first month after insertion, the number of bleeding are similar with Nova-T and the levonorgestrel-releasing IUD. After that there is a sharp reduction in the number of bleeding days with the levonorgestrel-releasing IUD until the end of the second year. During the first two years 32 women discontinued use because of amenorrhea. It could be that the increase in the mean number of bleeding days during the third year of use of the levonorgestrel-IUD is due to a selection of the patients. The mean number of bleeding days in women using the Nova-T is very constant during the three years of use.

The women with a levonorgestrel-releasing IUD had a higher number of spotting days than was observed with users of Nova-T during the first six months, thereafter the two curves run surprisingly coincidentally.

CONCLUSION

A daily intrauterine release of 20 ug of levonorgestrel results in very low plasma concentrations of levonorgestrel. Because the systemic concentration is low, the pituitary and ovarian function is normal even in patients who experienced amenorrhea for longer periods of time. Therefore, it seems that the amenorrhea is of a local nature and the endometrium is insensitive to circulating estradiol, because of the presence of high local concentrations of levonorgestrel. A low systemic concentration explains why the plasma lipoprotein profile is unaffected. In the series which is reported here, there was no infection during the three years use of the levonorgestrel IUD and only one infection with Nova-T. Our larger experience covers more than 25,000 cycles and during that time, three cases of endometritis and two cases of PID have been recorded. Women having PID had a positive culture of gonorrhea. As can be seen from the results of the present study, the number of days of bleeding is significantly reduced and this increases the body iron stores and a feeling of well-being among patients. Because of the number of spotting days is very similar with the Nova-T and the levonorgestrelj-releasing IUD after the first six months, it is not surprising that the life-table rate of removal because of bleeding and pain are very similar with both devices.

The problem with the levonorgestrel-IUDs seems to be the frequent spotting during the first three months. The proper counselling of patients diminished termination of use of the levonorgestrel-IUD during this period. Until now our efforts to find a way to eliminate the spotting problem have been unsuccessful but the clinical experience has shown that this spotting is well-tolerated.

As a summary, we can state that the levonorgestrel-releasing IUD has a very low pregnancy rate, sharply reduces the number of days of bleeding, increases the body iron stores and gives relief from menstrual pain. The mode of action of the levonorgestrel-releasing IUD is local. The levonorgestrel-releasing IUD could have a similarly protective effect against sexually transmitted diseases as oral contraceptives. Therefore we can conclude that the levonorgestrel-releasing IUD has the same beneficial effects as the oral contraceptives. It reduces the amount of bleeding, gives relief from menstrual pain and offers some protection against sexually transmitted disease.

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LEVONORGESTREL RELEASING CONTRACEPTIVE DEVICES

S. El Mahgoub

In theory the IUD is close to an ideal method of contraception. However, the major difficulty with the IUD is the high incidence of removals due to bleeding and pain. Furthermore, there is no doubt that IUD substantially increases the amount of menstrual blood loss. The development of levonorgestrel IUDs was initiated to overcome these side effects.

Since 1973, we have tried a variety of levonorgestrel IUDs. Our results confirm that intrauterine and intracervical levonorgestrel devices are an effective contraceptive in humans.

I. DEVELOPMENT OF NORGESTREL IUD'S

(A) Description: The platform is a Tatum T vector with an active layer of silicone homogenously impregnated with levonorgestrel, mounted on the vertical limb of the T, and covered by inactive silastic to act as controller.

(B) The in vivo and in vitro release rates were studies for devices releasing 2.5, 5, 8, 10 and 15 micrograms/day. The results indicated that all release levels were effective in fertility control. However, the 10 microgram devices revealed the best cycle control.

(C) The endometrium revealed a uniform pattern of glandular suppression in all specimens obtained 10 to 16 weeks following insertion of NGT 10.

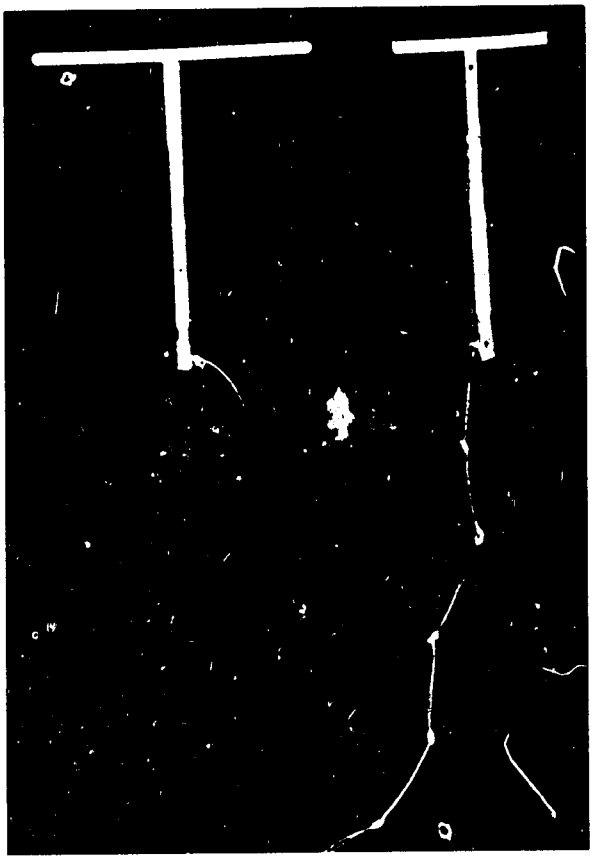

FIGURE 1. The improved Ng T and mini Ng T devices.

After one year both glands and stroma were suppressed and leucocytic infiltration was less marked than the one detected with copper devices. The endometrium regained its secretory activity 2 to 4 months following removal of the IUD.

With intracervical devices the endometrial changes were slower and complete endometrial suppression was detected after 6 months of use.

(D) When intracervical devices were used, hostile mucus and negative postcoital tests were encountered in all subjects after 3 months of use.

(E) Vaginal and cervical smears did not reveal any criteria suggestive of malignancy. In patients using the Ng ICD cervical device, biopsies showed mild leucocytic, plasma cell infiltration and reduction in number and size of the cervical crypts. Epidermidalization and squamous metaplasia were also encountered.

(F) Immunologic studies revealed an increase in immunoglobulin M.

(G) There were no significant changes in body lipids among the users.

(H) The basal body temperature and serum progesterone levels indicated that ovulation occurred in most cases with a 10 microgram releasing device.

(I) Menstrual blood loss for patients using T Cu 200 and NGT 10 devices was studied and results are summarized in Figure 1.

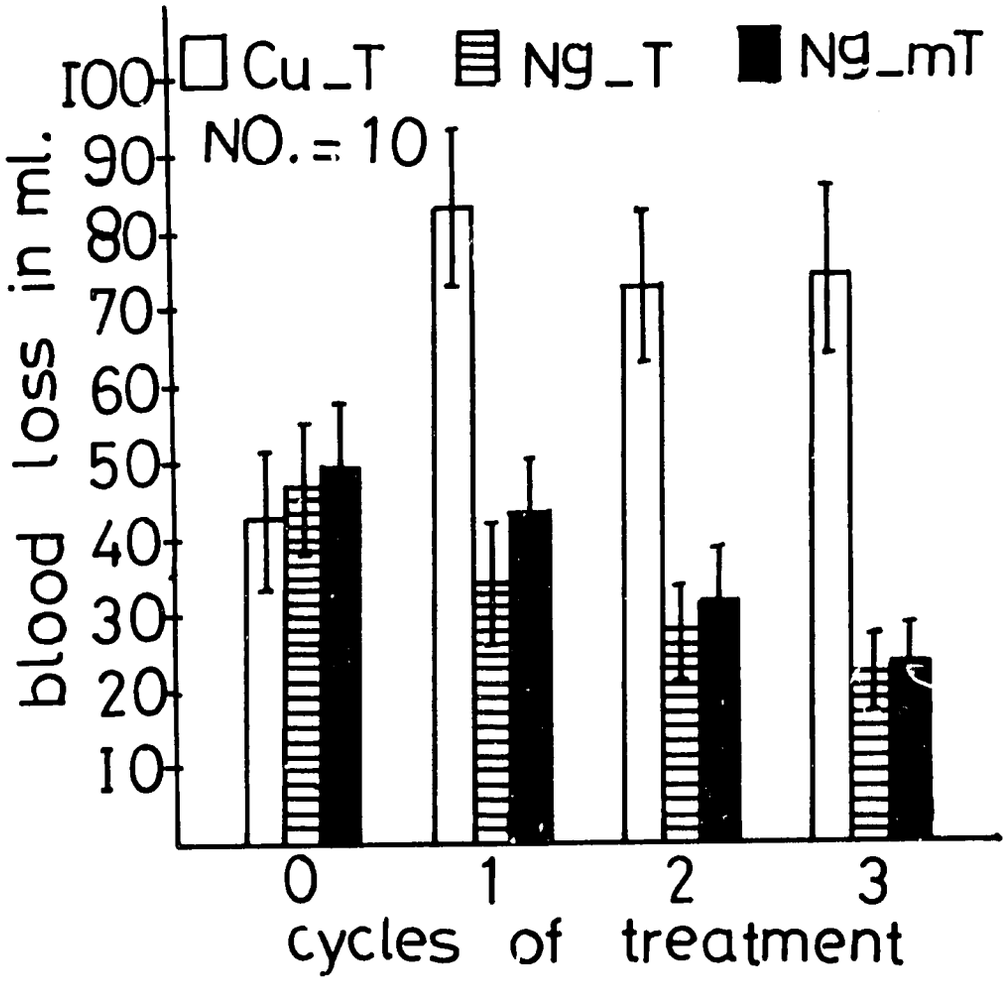

FIGURE 2. Comparative quantitation of menstrual blood loss for Cu T 200 and Ng T devices.

II. CLINICAL PERFORMANCE

TRIAL A

Comparative study of Ng-T-10, Ng-MT-10 and TCu 200. Three hundred multiparous, non-lactating women of proven fertility, were enrolled in this trial. All insertions were interval performed by the same clinician and included in the trial. One hundred women were randomly assigned to each device. The net cumulative termination rates are presented in Table 1.

(a) The continuation rates did not reveal any significant differences.

(b) No pregnancies were reported with Ng T while two pregnancies were found with Ng MT during the first cycle of treatment.

(c) Removals for bleeding and pain for Ng T were lower than for Ng MT and Copper T.

(d) Removal for oligohypomenouhea were lower for T-Cu than for Ng T or Ng MT.

The menstrual pattern. The number of days of spotting and bleeding calculated for the different trimesters are presented in Figure 3. During the first trimester patients using Ng T and Ng MT had a higher number of days of spotting and bleeding. However, from the second trimester onward Ng devices were associated with a lower number of days of spotting and bleeding.

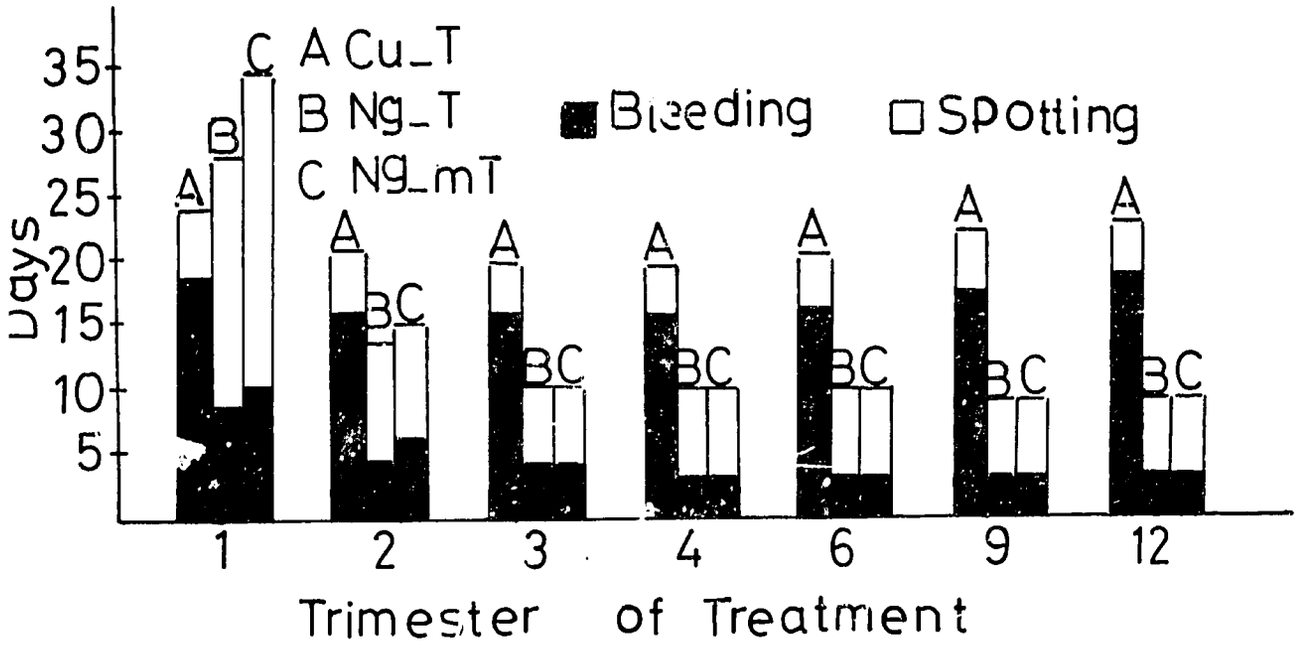

FIGURE 3. Total number of bleeding and spotting for Cu T 200 (A) Ng T (B) and Ng mT (C) during the different trimesters of treatment.

TRIAL B

A comparative study of T-Cu 380 Ag and Nova T Ng (20). This trial was conducted as part of a multicenter study conducted by The Population Council. The Nova T levonorgestrel device releases 20 micrograms per day. Insertions were performed by different health personnel.

Cumulative event rates are presented in Table 2.

From the two studies we can conclude the following:

1. Norgestrel devices are associated with marked reduction of menstrual blood loss.

2. In our experience, the retention mechanism of Tatum's T seems to be a better vector than that of Nova T which revealed a significantly higher expulsion rate.

3. Devices releasing 10 microgram levonorgestrel were associated with a better cycle control than those of 20 micrograms which were associated with high removal due to amenorrhea and oligohypomenorrhea.

TABLE 1. Cumulative event rates for T Cu 200, Ng-T and Ng-MT devices.

Event	Cu-T200 %	Ng-T-10 %	Ng-MT-10 %
12 Months			
Accidental pregnancy	3	0	2
Expulsion	3	1	3
Removals for B/P	9	1	7
Removals for other reasons	1	2	6
Continuation rates	84	96	82
Number of woman/months	1049	1153	1009
24 Months			
Accidental pregnancy	4	0	2
Expulsion	4	2	4
Removal for B/P	14	2	11
Removal for other reasons	4	7	12
Continuation rates	74	89	71
Number of woman/months	1984	2251	1898
36 Months			
Accidental pregnancy	6	0	2
Expulsion	4	2	4
Removal for B/P	18	3	14
Removal for other reasons	6	13	16
Continuation rates	66	82	64
Number of woman/months	2792	3259	2678
Primary insertions	100	100	100

TABLE 2. Cumulative event rates at 12 months.

Event	TCu 380 Ag	Nova T Ng 20
Accidental pregnancy	0	0.9
Expulsion	2.2	12.3
Menstrual Problems		
Bleeding	7.8	4.6
Oligohypomenorrhea	---	6.4
Other Medical	2.5	1.7
Infection	1.7	1.0
Planning pregnancy and other personal	4.4	2.2
Total termination	19.2	28.1
Continuation	81.8	71.9
Lost to follow-up	23	22
Woman/months	970	835
First insertion	175	165

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ANATOMICAL AND PHYSIOLOGICAL FACTORS IN THE FALLOPIAN TUBE

Carl J. Pauerstein

This chapter will focus on tubal anatomy and physiology as related to tubal sterilization techniques. We will also consider some clinical aspects of tubal sterilization procedures, including the concept of reversibility.

THE ANATOMY OF THE OVIDUCT

The oviducts are paired, hollow, seromuscular organs that extend from the superior lateral aspect of the uterine fundus to the ovaries. Each oviduct is supported throughout its length by a peritoneal fold, the mesosalpinx, and is bordered anteriorly by the round ligament and posteriorly by the ovarian ligament and mesovarium. Medially, the oviduct is attached to the uterine fundus and laterlly to the infundibular pelvic ligament and ovary via an elongated mucosal fold, the fimbria ovarica.

The extrauterine oviduct is sheathed throughout its length by a serosal covering consisting of a layer of loose connective tissue by a single layer of mesothelium continuous with the mesosalpinx. Beneath the mesothelial layer, smooth muscle fibers, distinct from those of the tubal muscularis, are present. The connective tissue is highly vascular and contains numerous lymphatic vessels. These originate primarily

along the mesosalpingeal border, extend parallel to the oviduct and branch extensively, penetrating into the muscular and mucosal layers of the oviduct.

The middle muscular layer, the myosalpinx, consists of smooth muscle arranged in layers, the orientation of which approximates their planes of contraction. The layers are not always clearly delineated from each other. Toward the uterine end of the oviduct, three muscle layers are present, an outer longitudinal layer, a prominent middle circular layer, and an inner longitudinal layer. The outer longitudinal and middle circular layers can be distinguished throughout the length of the oviduct. In contrast, the inner longitudinal layer becomes discontinuous within the distal two-thirds of the oviduct where it persists as scattered muscle bundles within and at the base of the mucosa.

The mucosa, or endosalpinx, lines the tubal lumen. It is composed of an epithelial layer resting upon a core of lamia propria. The lamipropria consists of loose connective tissue interspersed with numerous blood vessels and lymphatic spaces bound within a collagen fiber matrix. The mucosa is thrown into folds that project into the lumen. The height and complexity of the folds vary among the segments of the oviduct. The epithelium is made up predominantly of ciliated and secretory cells. The relative proportion of the cell types varies within different regions of the oviduct. Ciliated cells predominate in the distal oviduct and decrease toward the uterus whereas the inverse is true of secretory cells. Two additional cell types are seen occasionally. Wedge or conical shaped "peg" cells may represent depleted secretory or ciliated cells. Round "basal" cells may be the precursors of epithelial cells. The latter two cell types collectively represent less than 2% of the epithelial cell population.

The length of the oviduct varies from 6 to 15 cm with 11 cm being average. Length may also vary according to the organ's state of contractility, blood flow and lymphatic drainage - all of which may change in response to the organ's endocrine status. On the basis of its anatomy, the oviduct is divided into the infundibulary, ampullary, isthmic, and intramural segments.

The infundibulum is the short trumpet-shaped distal enlargement of the ampulla containing the fimbriated tubal abdominal ostium. This portion of the oviduct constitutes the normal functional connection between the ovary and oviduct and is responsible for ovum pickup. It contains the largest luminal diameter of any segment, up to 2 cm at its widest diameter. The cone-shaped ostium opens into the abdominal cavity. The epithelium is densely ciliated; the relative distribution of ciliated cells approaches 70% in fertile women. Ciliary beat is toward the uterus, as it is in cilia throughout the oviduct. The mucosa is complexly folded and completely fills the lumen. The myosalpinx is extremely thin.

The ampulla is the longest portion of the oviduct, constituting approximately two-thirds of its length. The lumen varies in diameter from 2 cm at its distal end to from 1 to 2 mm at its junctions with the isthmus. The endosalpinx is extensively folded. Numerous longitudinally oriented folds together with extensive secondary folds collectively fill the

entire lumen rendering it a potential space. Ciliated cells predominate in the distal ampulla and gradually decrease in numbers towards the isthmus. The thin myosalpinx is easily distended and easily collapsed. Peritubal adhesions, even if mild, may functionally occlude the lumen.

The isthmus makes up the remaining one-third of the extrauterine oviduct. The isthmic lumen is narrow, ranging in diameter from 1 to 2 mm at its junction with the ampulla to 0.1 mm at the uterine junction. The endosalpinx is composed of numerous low primary folds that run longitudinally. They describe a cruciform cross section near the uterine end and transition rather abruptly into the extensively folded endosalpinx at the ampullary-isthmic junction. Secretory cells predominate over ciliated. The isthmus is the most densely muscular segment of the extrauterine oviduct, with well developed longitudinal and circular muscle layers, as described above.

The interstitial segment of the oviduct traverses the uterine wall and is surrounded by thick myometrium. The longitudinal and circular muscle layers of the isthmus continue into the uterus. Vascular rings accompanied by uterine muscle bundles surround the intramural portion of the oviduct. An additional inner layer of musculature is arranged in spirals which encircle the intramural portion. The length of this segment varies from 1 to 3.5 cm. It has a narrow lumen variously described as ranging from "hairlike" to several millimeters in diameter. The path described may be straight or tortuous. As the endometrial cavity is approached, the lumen enlarges to terminate in the funnel-shaped uterine ostium. The mucosa lining this segment is more densely ciliated than that of the isthmus and is of a type intermediate between that of the endometrium and that of the oviduct. Mucosal folds are few in number, are longitudinally arranged and become continuous with the endometrial mucosa.

Blood Supply

The oviduct is a well vascularized organ. The blood supply is derived from the uterine and ovarian arteries. A major branch of each artery anastomoses giving rise to reduplicated vascular arcades. The magnitude of the contribution of the ovarian and uterine blood vessels to the oviduct may vary between individuals. The most commonly described pattern is that in which the uterine artery and its branches perfuse the interstitial and medial two-thirds of the oviduct, whereas the ovarian artery supplies the distal oviduct. The ability of the tube to autoregulate its blood supply can lead, under extreme instances, to either the ovarian or uterine artery alone supplying the entire oviduct. Venous drainage follows the arterial supply. Venous plexuses are present in the endosalpinx, myosalpinx and serosal layers. The three plexuses become confluent in the serosa and drain into extrinsic veins associated with the ovarian and uterine arteries.

Lymphatic Drainage

The oviduct contains a well-developed system of lymphatic vessels, more extensive in the isthmic region than in the ampullary segment. Lymphatic networks drain the endosalpinx, the myosalpinx and the serosa. Upon merging from each region, the lymphatic vessels combine to enter the

mesosalpinx and to drain into the para-aortic nodes.

TUBAL PHYSIOLOGY

The primary function of the oviduct is transport, initially to simultaneously convey the ovum and spermatozoa in opposite directions, then to transport the developing embryo into the uterus. A second important function is to furnish an appropriate milieu for gamete survival, fertilization, and early embryo development.

Gamete transport through the oviduct is a complex physiologic process which involves the conversion of metabolic into mechanical energy by smooth muscle, ciliated, and secretory cells. The relative importance of each of these components is not known. It is probably that there are regional differences in the contribucion and importance of each. In the infundibulum and ampulla with their thin myosalpinx, large lumen and complex, densely ciliated mucosal folds, ciliary activity may be of major importance in ovum transport with contractile activity a subordinate effector. In contrast, transport through the isthmus, with its prominent myosalpinx, narrow lumen, and sparsely ciliated endosalpinx, appears to primarily result from contractile activity.

Tubal Contractility

Because of the arrangement of muscle fibers in layers oriented in circular and longitudinal fashion, the oviduct is capable of generating a variety of contractile patterns, including peristaltic, antiperistaltic, and segmental contractions. Unlike the alimentary tract, the oviduct does not generate regular peristaltic contractions. It instead demonstrates segmental contractions that propagate simultaneously in opposite directions over short distances. Ovum transport therefore assumes a discontinuous pattern of reciprocal movements in which the ovum is forced out of areas of contraction into inactive regions. Thus, ovum transport appears to occur in a series of random movements that, over several days, acquire a gradual net bias toward the uterus.

The role of tubal contractility in sperm transport is less clear. Spermatozoa are motile and may actively participate in their transport through the female tract. The segmental contractions of the myosalpinx may compartmentalize the oviduct, randomly moving its contents throughout the tube. This mechanism, in concert with the spermatozoa's innate motility, may result in spermatozoa being transported to the vicinity of the newly ovulated ovum.

The oviduct exhibits continuous, spontaneous activity. Complete quiescence never occurs. Even during pregnancy, when the uterus is largely quiescent due to high levels of circulating progesterone, the oviducts remain spontaneously active, although at a reduced rate similar to that seen in the late luteal or early proliferative phases of the menstrual cycle. Two peaks of contractility occur: one at the time of ovulation, when estrogen levels are highest; the other during menstruation, when progesterone levels are lowest. The relative refractoriness of the oviduct to the inhibitory influence of progesterone may be important to insure that gamete transport can proceed despite rising progesterone

levels after ovulation.

Secretory Activity

The tube furnishes the environment for gamete survival, fertilization, and early embryo development. Tubal fluid is a complex derived primarily from hormone-dependent secretory activity of the tubal epithelium and selective transudation from the blood with varying contributions from the uterus, peritoneal cavity and, in the postovulatory interval, the ovarian follicle. Tubal secretory activity, a predominantly estrogen-dependent phenomenon, is antagonized by progesterone and is maximal at the time of maximum estrogen production.

Tubal secretory cells undergo morphologic changes during the ovarian cycle. During the early proliferative stage, under low-estrogen conditions, the tubal mucosa is thin, exhibiting a low cuboidal profile. Secretory activity is largely absent at this time. As the cycle progresses, rising estrogen levels result in progressive mucosal thickening. Secretory cells increase in height and become domed. Following the preovulatory estrogen peak, the mucosal epithelium attains maximal thickness. The domed, microvilli-covered apices of secretory cells protrude into the lumen above the tips of ciliated cells, rendering their cilia relatively inconspicuous. At ovulation, the secretory cells discharge their contents into the lumen. During the late luteal and menstrual phases of the cycle, the mucosa again thins, and secretory activity stops.

Quantitative difference in secretion exists in different segments of the oviduct. The major volume of secretions are produced by the isthmus is the primary site of production of mucin, a product that may be of importance in sperm and ovum tranpsort.

Ciliary Activity

The ciliated cell is characterized by the presence of 250 to 300 elongated, regularly arranged kinocilia at the cell apex. As noted above, ciliated cells predominate at the level of the fimbria. Their number diminishes somewhat in the ampulla and significantly declines in the isthmus. As the tube enters the uterus, there is a transient increase in the number of ciliated cells. However, this general pattern of distribution of ciliated and secretory cells may be interrupted in certain highly localized areas in which one or the other cell type predominates. In general, ciliated cells tend to be found in greatest numbers on the apex and sides of mucosal folds, whereas secretory cells occupy a more basal position.

Cilia exhibit a highly organized and synchronized pattern of contractility in which a propulsive power stroke is followed by a nonpropulsive retracting stroke. The cilia within individual cells are arranged in rows. The beating of cilia proceeds row by row within individual cells. Moreover, adjacent ciliated cells exhibit synchronized metachronal integration with each other so that waves of ciliary beating proceed in orderly fashion across large areas of endosalpinx. The rate of ciliary beating is relatively constant except for a transient increase during

the postovulatory period.

There is disagreement concerning specific changes in the morphology and distribution of ciliated cells during the menstrual cycle. It appears that human tubal epithelium does not undergo marked cyclic, estrogen-driven ciliogenesis. Some changes, such as increase in cell size and subcellular organization, may occur as the cycle progresses. Some renewal of ciliated cells does occur, but there is little evidence for the occurrence of cyclic deciliation/reciliation or the regular transformation of ciliated into secretory cells.

MECHANISM OF GAMETE TRANSPORT

We have integrated the above observations into a tentative schema of the mechanism of gamete transport. Following ovulation, ovum pickup occurs via contractile and ciliary activity involving the ovarian and tubal mesenteries that bring the surface of the ovary and the fimbria into proximity. Concurrently, spermatozoa, present in the upper vagina, have colonized the cervix, uterine crypts and possibly the proximal isthmus. In response to segmental contractility of the isthmus and their own flagellar movements, sperm ascend the oviduct. Estrogeninduced secretory activity of the isthmus mucosa and the increased height of the secretory cells protect the sperm from the prouterine ciliary beat. The production of thick mucin aids this process by agglutinating the cilia and by filling the isthmus lumen. The mucin plug may also enhance sperm transport in a manner analogous to that of mid-cycle cervical mucus. The ovum, slowly travelling down the ampulla, where secretory activity is sparse but ciliary beating is prominent, encounters the spermatozoa and is fertilized. During the fertilized ovum's three-day sojourn in the oviduct, increasing progesterone levels clear the isthmic lumen of mucin and cause retraction of the secretory cells, enabling the prouterine accelerated beat of the isthmic cilia to assist the pro-uterine segmental contractions of the tube in propelling the developing embryo through the isthmus into the uterus.

STERILIZATION PROCEDURES

With this background, let us attempt to ascertain which regions of the tube are critical to normal fertility.

Fimbriae

Tubal fimbriae function is a highly specialized and indispensable component of the ovum pick-up mechanism. Cohen described seven patients with idiopathic infertility whose major clinical finding was elongation of the fimbria ovarica greater than 4 cm. During a 12-month period of exposure to conception prior to surgery, only one patient conceived. The remainder underwent surgical plication of the fimbria ovarica and round ligaments to bring the fimbria in normal proximity to the ovaries. Five subsequently became pregnant. Three delivered at term and two aborted. From these data, he concluded that the excessive length of the fimbria ovarica had prevented the fimbria from being positioned close enough to the ovary to affect ovum pickup.

Although fimbriectomy is a very reliable sterilization method, spontaneous failures are not uncommon due primarily to formation of tuboperitoneal fistulas that re-establish distal tubal patency. Reversal of fimbriectomy sterilization has recently been reported with a pregnancy rate of 44% after transverse salpingostomy and cuff eversion using microsurgical technique. Therefore, it appears that absence of the fimbriae compromises fertility.

The ideal candidate for fimbriectomy reversal has an approximately normal length oviduct, an ampulla at least 1 cm in diameter, rugal patterns discernible on hysterosalpingography, and minimal peritubal adhesions. Most notably, successful reversal appears to be associated with spontaneous eversion of the endosalpinx at the time of surgery, and a tendency to form a neofimbria-like structure. All of these factors favor ovum pick-up and are usually absent or severely compromised in patients with hydrosalpinges.

Ampulla

The ampulla is the longest portion of the oviduct. Ampullary-ampullary anastomosis tends to be a among the least successful sterilization reversal procedures, with the exception of salpingostomy (Table 1). Because of its thin-walled anatomy, the ampulla is easily collapsed. Peritubal adhesions following tuboplastic surgery, even if mild by subjective appraisal, may be sufficient to place the ampulla on tension, resulting in functional occlusion of the lumen. The difficulty of accurately placing anastomosis sutures to avoid the endosalpinx may also interfere with the complex system mucosal folds, leading to partial or complete occlusion of the lumen or to the formation of blind passages. such architectural damage to the tube may be an important determinant in the occurrence of ectopic pregnancy. The post-tubal surgery patient is always at increased risk of ectopic pregnancy. The majority of tubal ectopic implants occur in the ampulla, a logical occurrence, since fertilization and early embryo development occur at this location. Derangement of the ovum transport mechanism or occlusion of the ampullary lumen may allow fertilization but deny passage of the developing embryo, with subsequent implantation in the ampulla.

TABLE 1. Restoration of fertility according to site of anastomosis.

Procedure	No. of Women	No. of Term Pregnancies	Pregnancy Rate
Cornual-isthmis	19	14	74%
Cornual-ampullary	39	21	54%
Isthmic-isthmic	28	19	68%
Isthmic-ampullary	72	40	55%
Ampullary-ampullary	30	15	50%
TOTAL	188	109	58%

Data complied from Winston, Silber and Cohen, and Rock et. al.

The importance of residual ampullary length has also been investigated. Silber and Cohen performed microsurgical reversal of sterilization in 25 women and examined their results according to length of ampulla remaining (Table 2). They demonstrated a positive correlation between length and pregnancy. However, pregnancy was possible even with only one cm of ampulla remaining, suggesting that the length of ampulla per se may not be critical. Instead, it appeared in their study that the overall length of the repaired tube was of paramount importance (see below).

TABLE 2. Relationship of length of ampulla to pregnancy.

	0-1 cm	1-2 cm	2-3 cm	3-4 cm	>4 cm
No. of women	2	5	8	5	5
No. of pregnancies	1	2	3	4	5
Pregnancy rate	50%	40%	36%	80%	100%

From Silber and Cohen

Ampullary-Isthmic Junction (AIJ)

Gomel reported the results of microsurgery performed in 14 patients previously sterilized by the Pomeroy or Irving technique in which the AIJ had been effectively resected. Eight of the patients experienced successful intrauterine pregnancies. Winston reported similar findings in 6 of 10 patients in whom the AIJ had been removed bilaterally. It would thus appear that removal of the AIJ compromises future fertility less than removal of the fimbria does.

The Isthmus

Shortly after ovulation, contractile activity predominates in the distal oviduct, while the major portion of the isthmus is quiescent. This inactive region acts as a passive "absorbing barrier" into which the ovum tends to migrate, since there are no contractions to push the ovum back to the active region. The gradual movement of this inactive region toward the uterus during the 3-day period of ovum transport, combined with the pro-uterine beat of cilia lining the fimbria, infundibulum and ampulla which actively impedes net movement of the ovum toward the ovary, thus constituting a "reflecting barrier," utlimately results in entrance of the ovum into the uterus. In the total absence of the isthmus, both its retarding function, via physiologic sphincter-like action or quiescence, and its ovum transport-promoting function, via propagation of active contractility toward the uterus, would be lost. This would be consistent with either premature or delayed entrance of ova into the uterus, respectively.

The clinical importance of the isthmus has not been clearly established,

primarily due to the lack of opportunity to examine a sufficent number of patients seeking reversal of sterilization in whom the entire isthmus, including the AIJ and UTJ, had been resected. Ampullary-uterine implantation results in about a 50% success rate.

In contrast, partial resection of the isthmus followed by isthmic-isthmic anastomosis yields about an 80% success rate (Table 1).

Utero-Tubal Junction (UTJ)

The report of successful pregnancy in about half of a group of patients with bilateral proximal tubal blockage treated with bilateral uterotubal implantation on the posterior aspect of the uterus suggests that the UTJ is important if restoration of optimal fertility is to be attained. This is strengthened by the observation that microsurgical rates as high as 74%. This technique, unlike implantation retains the UTJ.

Tubal Length

A minimum length of oviduct is necessary for restored fertility. The amount of residual tube deemed necessary for successful sterilization reversal ranges from 3 cm to 5 cm for end-to-end anastomosis and as high as 8 cm for salpingostomy after sterilization by fimbriectomy. Not only is the length of tube important, but also cornualisthmic anastomosis and isthmic-isthmis anastomosis, procedures which result in the maximum residual length of ampulla, are most successful. Pregnancy is possible even with only 1 cm of ampulla remaining, provided that normal fimbriae are present and that a total tubal length of 3 cm remains. When 3-4 of tube remain, about 40% of patients achieve pregnancy and when more than 6 cm of tube is present, pregnancy occurs in 4 of 5 women operated upon (Table 3).

TABLE 3.

	Tubal Length (cm)			
	<3	3-4	4-6	>6
Total no. of patients	7	18	26	9
Pregnant	0	7	19	7
Not pregnant	7	11	7	2
Pregnancy rate	0%	39%	73%	78%

Data compiled from Silber and Cohen, Winston and Wilson

Gomel also found that the length of tube following microsurgical reversal of tubal sterilization is inversely related to the length of time between surgery and pregnancy (Table 4). Nine women who conceived in the first cycle after surgery had 5.5 cm or more of tube remaining. Thus, the critical length of residual tube for optimal results appears to be at least 3 cm. Normal fimbriae are critical to high success rates, and isthmic-isthmic is the best site for anastomosis.

TABLE 4. Relationship of tubal length to pregnancy.

	Tubal Length	
	2.5 - 8.5 cm	4 cm or less
No. of women	118	36
Pregnant	76	22
Not pregnant	42	14
Normal intrauterine Pregnancy rate	64%	61%
Mean interval between Surgery and pregnancy (months)	10.2	19.1

From Gomel

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SURGICAL FEMALE STERILIZATION TECHNIQUES

John J. Sciarra

Voluntary sterilization is the most widely used method by which couples control their fertility, both in the developed world and in developing countries. In only twelve years, from 1970 to 1982, the number of couples choosing voluntary sterilization increased from 20 million to 110 million, and it is projected that by the year 2000, more than 400 million couples will have chosen sterilization.

It is unlikely that any method of fertility regulation will ever be ideal for every couple at any given stage of their reproductive life, because individual contraceptive needs vary considerably within a lifetime. Nonetheless, female sterilization techniques have been and are being developed that meet a number of the criteria of the ideal female sterilization procedure: that it is safe and effective, simple to perform, socially and personally acceptable to users, inexpensive, acceptable to large numbers of couples, applicable in an ambulatory setting with local or no anesthesia, and is potentially reversible.

Of the various methods for surgical sterilization available to women, tubal sterilization procedures performed by minilaparotomy or laparoscopy are the most widely employed. The present review will trace the development of the classic surgical sterilization procedures, will look at some of the contemporary laparoscopic approaches to female sterilization, and will consider briefly some of the most promising areas of interest for future sterilization options.

DEVELOPMENT OF THE CLASSICAL TUBAL STERILIZATION OPERATIONS

A historical review of surgical sterilization procedures is presented in Table 1.

While a procedure for tubal sterilization was suggested as early as 1834, the first such operation in the United States was not reported until 1881. The procedure, performed in Ohio by S.S. Lundgren at the time of a cesarean section, utilized a simple suture ligation and excision of the fallopian tube. During the late nineteenth century, many techniques for tubal sterilization were described in the European literature. Most of them were based on the principle of simple surgical ligation of the tube, and were performed in conjunction with a cesarean section or in the postpartum period.

TABLE 1. Selected chronology of tubal sterilization.

Year	Scientist	Event
1834	Blundell	First recommendation for incision and removal of portion of fallopian tube for sterilization
1881	Lundgren	First tubal sterilization by simple ligation
1910	Madlener	Technique for crushing, ligating fallopian tube; 1919, 89 procedures, 3 deaths, no pregnancies
1924	Irving	Ligation, division, and burial of proximal stump in myometrium; 1950, modified technique, 814 procedures, no failures
1930	Bishop & Nelms	Used Pomeroy's ligation and resection procedure; 80 sterilizations performed in original report
1934	Aldridge	Temporary sterilization technique; 1 successful reversal and subsequent pregnancy
1935	Kroener	Fimbriectomy; 1969, Kroener, Jr reported 200 fimbriectomies, no failures
1946	Uchida	Ligation, resection, and burial; 1961, 5000 sterilizations, no failures; 1976, 21,000 sterilizations, no failures, minimal complications

In the following section, we will describe the most important and successful of the sterilization techniques developed by the pioneers in this field.

Madlener. One of the sterilization techniques that received widespread acclaim, both in the United States and in Europe, was developed in 1910 by the German surgeon Max Madlener. The technique was simple in design, involving the elevation with a forceps of the midportion of the tube,

creating a loop. The base of the loop was then crushed, and ligated with nonabsorbable suture material. In practice, Madlener's technique has resulted in a considerable number of failures, owing to recanalization and tuboperitoneal fistula formation. In a review of the medical literature up to 1930, von Graff collected reports of 4279 Madlener sterilizations, with 19 known failures (a pregnancy rate of 4.4/1000).

Irving. Another procedure that has been particularly useful for sterilization immediately following cesarean section is that of Frederick C. Irving. In 1924, in introducing the procedure, Irving wrote, "An ideal method should be bloodless, should include division between double ligatures, and the burying of both cut ends at as great a distance from each other as possible." In 1950, Irving described a modification of the technique, and reported his experience with 814 procedures, with no failures. The Irving technique requires more time and skill to perform than most ligation procedures, but is highly effective. Because it requires a larger incision than other techniques, it is generally employed only at the time of cesarean section.

Pomeroy. The most frequently performed of all surgical ligation procedures is usually referred to as the Pomeroy technique, although no original paper by Ralph H. Pomeroy describing this procedure was ever published. The first reference to this procedure appeared in 1929, four years after Pomeroy's death, in a paper by E. Bishop and W.F. Nelms, delivered before the New York State Medical Society. These associates of Pomeroy described the technique that they had first seen used by Pomeroy, who had made no claim for originality although he had stated that he had never seen it done. Bishop and Nelms used Pomeroy's technique to ligate and resect the fallopian tubes of 60 women for sterilization purposes, with no known failures.

Although the Pomeroy procedure is similar to the Madlener technique, it differs in that the tissue is not crushed; rather, a loop of the ampullary portion of the oviduct is elevated and ligated with a single strand of absorbable suture material. Ligation and hemostasis are thus accomplished in one step, and a loop of oviduct is excised. No special surgical instruments are necessary. With the dissolution of the absorbable suture material, the proximal and distal ends of the oviduct return to their normal anatomical position, and tubal discontinuity with blind closure at both ends is achieved simultaneously. It is important that absorbable suture material be utilized for this technique. The operation has proven highly successful and is easy to teach. Today the Pomeroy technique and its many variations are popular worldwide. It can be performed both abdominally and vaginally.

Aldridge. In 1934, Albert H. Aldridge described a technique that he had devised for temporary, or reversible, sterilization, which consisted of burying the fimbrial end of the tube in a pocket beneath the peritoneum of the broad ligament, through an incision in the anterior surface. It should be noted that the idea of temporary sterilization by extraperitoneally embedding the abdominal ends of the fallopian tubes was not new; many earlier reports had appeared in the European literature. Procedures had been devised for occluding the fimbrial ends of the tubes by inserting them into the inguinal canals, the vagina, the anterior abdomi-

nal wall, the uterovesical space, the musculature of the posterior and anterior uterine wall, or the broad ligament. The Aldridge technique is mentioned primarily because of historical interest, and although it is rarely used today, new methods based on this technique are being devised.

Kroener. The fimbriectomy technique was proposed by William Kroener in 1935, and consisted of double ligation of the fallopian tube with silk sutures followed by excision of the fimbriated end of the tube. This technique can be performed either abdominally or vaginally. In 1969, William Kroener, Jr. reported on 200 cases of tubal sterilization using his father's technique, with no known failures. Fimbriectomy has had only scattered popularity, and may be complicated by hydrosalpinx formation, requiring surgical correction. Little information has been published on the failure rates with this procedure. Of 4300 fimbriectomies performed in Colombo, Sri Lanka, only two women are known to have become pregnant -- a pregnancy rate of 0.05%. Four of the sterilized women subsequently underwent surgery for fertility restoration, but did not have successful pregnancies.

Uchida. One of the most successful sterilization procedures to be developed was initially described by Hajime Uchida in 1961. This is a more complex procedure than most but it is highly effective, in terms of subsequent pregnancy rates. Special instruments are required to perform this procedure through a minilaparotomy incision. This is a destructive procedure and the distal tube is often excised. In 1976, Uchida reported having performed 21,000 sterilizations with no known failures and minimal complications. Failures have been reported by others, however. The Uchida technique is widely and effectively used in Japan and is also performed on a more limited scale in the United States and other countries.

SURGICAL STERILIZATION TODAY

Surgical tubal sterilization is performed in the immediate postpartum period, following pregnancy termination, or as an interval operation. Presently, the most widely used procedure, and the one generally considered the simplest and safest, is a modification of the original Pomeroy technique, in which a 4 cm loop of the ampulla or the ampullary-isthmic junction is isolated with a single suture or absorbable material. A 1 to 1.5 cm section of tube is then excised, providing adequate hemostasis, as well as surgical disruption of the oviduct. With the dissolution of the absorbable suture material, the proximal and distal ends of the divided oviduct separate, and at the completion of the healing process, anatomic discontinuity is achieved.

The major advantages of the Pomeroy procedure are that it is easily taught, simple to perform, highly effective, and can be offered to patients at a minimal cost. Its acceptance rates for both puerperal and interval sterilization are quite high. It can be performed either abdominally or vaginally, and the complications are minimal. General, regional, or local anesthesia may be used. When performed abdominally, it is usually performed by minilaparotomy. In the postpartum period, a small, infra-umbilical incision is used; when performed as an interval procedure, a suprapubic incision is used. The Pomeroy procedure has no major disadvantages.

The reported pregnancy rate, according to figures from Family Health International (FHI), is 3/1000 (Table 2). Using both traditional and microsurgical techniques, reversals of the modified Pomeroy procedure have generally been successful.

TABLE 2. Techniques of female sterilization.

Technique	Popularity*	Tubal destruction	Failure and/or pregnancy rates per 1000 women	Reversal potential
Uchida	1	50%	none reported	very poor
Fimbriectomy	1 to 2	40%	------	poor
Irving type	1	30%	------	poor
Laparoscopy electrocoagulation/ division	4	25%-50%	2 to 3	fair
Pomeroy type ligation/ excision	5	3-4 cm	3	good
Low temperature thermal coagulation	1 to 2	1 cm	------	good
Falope-ring	3	3 cm	6	good
Spring-loaded clip	2	1 cm	20	very good
Aldridge	rare	none	signifianct	excellent

* = Arbitrary scale of 1 (least popular procedure) to 5 (most common procedure).

ENDOSCOPIC STERILIZATION PROCEDURES

Laparoscopic sterilization procedures have had wide acceptance in recent years. Laparoscopy was developed in Europe at the beginning of the twentieth century, and was utilized for tubal occlusion in the U.S. for the first time in 1937. Endoscopy is particularly useful for interval sterilization. Endoscopic procedures fall into two categories: those that employ electrocoagulation or thermal coagulation, and those that occlude the tube mechanically, as with a silastic band or plastic/metal clip.

Electrocoagulation. Most endoscopic procedures are performed using laparoscopic electrocoagulation with either high frequency or bipolar current. Unipolar current deposits the electrical energy where the tube is

grasped by the forceps. The current travels through the patient's soft tissues and exits by way of a ground plate in contact with another part of the patient's body. The bipolar method differs from the unipolar system in that the operating forceps itself carries both the active electrode and the return. The current passes only through the tissue grasped between the prongs of the forceps. Although high-frequency current is used, it crosses only a small distance -- the thickness of the tube (1 mm to 2 mm). Statistics compiled by the American Association of Gynecological Laparoscopists (AAGL) indicate that the pregnancy rate following electrocoagulation and division of the tubes is 2/1000, while the FHI figure is 3/1000 procedures (Table 2). In addition to the complications associated with laparoscopy and electrosurgery, the principal anatomic disadvantage of electrocoagulation is that the amount of tissue destruction cannot be accurately quantitated or easily controlled.

Yuzpe and co-workers estimate that in their experience with a series of 2857 "burn only" laparoscopic tubal sterilizations using unipolar electrosurgical current, they destroyed approximately one-third of the oviduct. In many instances, when using electrosurgical techniques for tubal sterilization, even more of the oviduct is destroyed, since the tissue destruction may extend beyond the limits of the visible lesion.

Pregnancy rates are inversely proportional to the amount of tissue destroyed, hence where failure rates are low -- as is the case when sterilization is performed by experienced surgeons -- reanastomosis is difficult. Yuzpe and co-workers report a failure rate in their series of 0.35/1000. Frequently, only a few centimeters of infundibulum and ampulla remain, with the isthmus and the ampullary-isthmic junction totally destroyed.

Thermal coagulation. Low temperature thermal coagulation provides a laparoscopic approach with minimal tissue destruction. Valle has shown that with this procedure, using a battery source to heat the sterilization unit, an adequate end result could be achieved with destruction of only a 10-mm area of the oviduct. The chances for reversibility in this situation would undoubtedly be superior to those with electrocoagulation; however, due to the recent development of this technique, relatively few cases are available for analysis, and the opportunity for follow-up is limited. By 1980, Valle reported on 570 successful sterilizations with no failures or complications during a follow-up period of up to 4 and one-half years.

The Silastic band technique (Falope Ring). Silastic bands, applied to the ampulla or the ampullary-isthmic junction 2 to 3 cm from the cornual area of the uterus, destroy up to 3 cm of oviduct by aseptic necrosis. The end result is similar to a Madlener sterilization. The pregnancy rate for Falope ring sterilizations, according to the latest FHI figures, is 6/1000 (Table 2). The silastic band procedure was developed to provide a safe, simple, and effective mechanical approach to tubal sterilization; it should increase the possibility of reversal without compromising effective tubal occlusion. The equipment is relatively easy to use and maintain; thus the technique is extremely popular. Occasional problems have been reported, including transection of the tube on application and sloughing of the loop enclosed within the ring with subsequent

separation of the two ends.

In 1980, in a review of data from 23 countries, investigators at FHI compared the experiences with three methods of female sterilization: laparoscopy with occlusion by the tubal bands (7053 women), minilaparotomy with occlusion by the tubal bands (3033 women), and minilaparotomy with occlusion by the modified Pomeroy technique (5081 women). The 12-month failure rate was 6/1000 women for laparoscopy/bands and 3/1000 women for minilaparotomy/Pomeroy. The surgical complication rate for laparoscopy/bands (2.04%) was more than twice that for minilaparotomy/Pomeroy (0.79%). The technical failure rate of minilaparotomy/Pomeroy was twice that of laparoscopy/bands, but the complication and method-failure rates were much lower. Failure and complication rates with minilaparotomy/bands were intermediate.

Tubal clips. Mechanical tubal occlusive devices offer a promising new development in the field of female sterilization. The spring-loaded clip developed by Hulka is applied to the isthmic portion of the tube about 2 cm from the cornual area of the uterus. The device has two plastic jaws with interlocking teeth and is held closed by a gold-plated stainless steel spring. It damages less than 1 cm of the oviduct by pressure necrosis. Because of the minimal amount of tissue damage involved, clip sterilizations have proved relatively easy to reverse using microsurgical techniques. Published reports indicate a slightly higher pregnancy rate for patients having laparoscopic spring-loaded clip sterilizations than for other techniques. Recently, Hulka stated that with the instruments and clips currently available, there is no higher risk of pregnancy for clip sterilization than for electrocoagulation or Silastic band procedures.

In 1982, in a letter to the editor of Lancet, Hulka and several other leading investigators in this area reported the collective experience of attempts to reverse sterilizations done with the spring-loaded clip of the Hulka-Clemens design. There have been 85 attempts with 74 intrauterine pregnancies for a total success rate of 87%. These results suggest that the spring clip offers a high potential for reversal compared with other methods.

Sufficient information is as yet unavailable regarding plastic clips such as those developed by Bleier. This clip has the disadvantage of puncturing the mesosalpinx. One early preliminary report by Craft has pointed to problems with both clip design and application.

G. Marcus Filshie, in Great Britain, is doing extensive clinical trials on a metal clip that he has developed, made of titanium, with silicone rubber lining its inner surface. As the clip closes over the fallopian tube, both the tube and the silicone rubber are compressed. As the tube undergoes avascular necrosis and shrinks, the compressed rubber expands to take up the dead space, thus preventing recanalization. Human trials began in 1975, and clips of early and later design have been applied to more than 7000 women throughout the world, for a failure rate of 3/1000.

Newer models of the clip may reduce the failure rate by as much as one-third.

TUBAL PLUGS

Over the past ten years, several groups of investigators have been exploring the feasibility and effectiveness of mechanically blocking the fallopian tubes with various materials serving as plugs, with the goal of minimal tissue damage, reversibility, and simplicity of use.

Hosseinian's UTJD. One of the most successful occlusive devices has been developed by Hosseinian and associates, whereby uterotubal junction (UTJD) blocking devices are hysteroscopically placed into the tubal ostia and can subsequently be removed if reversal is desired.

Recent plugs are made of silicone rubber, varying from 7 mm to 9 mm in length. The metallic spines fix the plug in place in the tubal opening by penetrating the adjacent myometrium.

In animal studies, the efficacy of the device for contraception has been 100% in 21 baboons for a minimum of eight breedings. The reversibility potential has been tested; eight of 15 baboons became pregnant after hysteroscopic removal of the device, achieving a total of 12 pregnancies.

No side effects were noted in any of the animals, either after implantation of the devices or after their removal. The extent of tissue reaction around the plugs was minimal, with no difference between the polyethylene and silicone plugs. Conception after the removal of the devices progressed normally, and the offspring were physically normal in all aspects.

THE P-BLOCK PLUG

Brundin, in Sweden, has been working with a hydrogelic copolymerized device, designed to block the isthmic part of the oviduct. Called the Mark 7 P-block plug, the device is a 4-mm long and 1.2-mm wide hydrogen body fixed on a nylon skeleton. Two-mm wide nylon "wings" prevent expulsion from the tube before hydratization, which requires about 30 minutes.

The P-block, though not evaluated in animals, was tested in 35 women. In 15 of the 35 women, bilateral occlusion was achieved on the first attempt, and in 2 other women, a second procedure was necessary to produce successful occlusion of both tubes. One woman, who achieved satisfactory tubal occlusion, subsequently requested removal of the device due to bleeding. In another 15 women, the device could not be inserted owing to anatomical factors. Four women had uterine pregnancies -- in all cases, within 2 months after insertion.

Brundin feels that the Mark 7 P-block does not presently constitute an alternative to surgical sterilization, owing to the large number of cases in which the discrepancy between the size of the device and the uterotubal orifice or other anatomical factors precluded insertion of the device. In addition, the pregnancy rate after bilateral occlusion is high.

ERB AND REED'S SILASTIC PLUGS

Erb, Reed, and their associates have been investigating the possibility

of producing nondestructive, possibly reversible occlusion with silicone rubber (Silastic), instilled into the fallopian tubes as a viscous liquid through a specially designed dispenser that minimizes the danger of intraperitoneal spillage. The silicone rubber solidifies into a soft plug that conforms to the oviductal lumen, occluding the tube without distorting it or adhering to the tissue.

To date, the results have established good retention of the plugs, antifertility efficacy, retrievability, oviduct-polymer compatibility, and moderate reversibility. Serious complications other than pregnancy have been very few. In the 965 women treated, 13 pregnancies have occurred to date, all of which have been associated with failure to get proper bilateral plug formation. Of these, there has been only one ectopic pregnancy in a fallopian tube, on the side of an improper plug.

Overall results indicate that the method can be effectively taught and has adequate antifertility efficacy. It can be applied successfully to an estimated 90% of properly selected patients.

HAMOU'S NYLON INTRATUBAL DEVICE

Jacques Hamou has described studies with a nylon intratubal device. The device has an open loop at each extremity to prevent migration within the tube or uterine cavity. The midpiece is flexible and permits negotiation of the interstitial portion of the tube. The device is inserted without anesthesia and seems to be well tolerated by patient volunteers. It is presently undergoing clinical trials in France.

PRESENT TECHNIQUES IN CLINICAL SETTINGS: ACCEPTABILITY AND EFFECTIVENESS

Table 3 indicates the percent distribution of estimated users of contraception worldwide. In 1982, almost one-third of couples used voluntary sterilization to limit their fertility -- a number approximately equal to the use of oral contraceptives and the IUD combined.

Table 4 details the frequency of various surgical approaches to female sterilization. Of the 49,625 female sterilizations reported to the FHI between April 1971 and June 1979, (including interval, postabortal and postpartum sterilizations), laparoscopic electrocoagulation and placement of tubal bands and clips accounted for 46.6%, with electrocoagulation representing almost half of the total. Next in frequency of use was laparotomy/minilaparotomy, with surgical or mechanical tubal ligation (interval as well as postpartum or postabortion) constituting 43.3% of the total. As anticipated, most postpartum sterilizations are performed abdominally by ligation through a minilaparotomy incision. These data were collected from 100 reporting centers in 27 countries, and therefore represent the approaches being used in a variety of international family planning services and research programs.

United States Experience. Nearly 14 million men and women in the United States have chosen vasectomy or female sterilization for permanent protection against unplanned pregnancies. An annual survey by the Association for Voluntary Sterilization in 1981 showed that 52% of the sterilizations had been accepted by women (464,000) and 48% (424,000) by men,

TABLE 3. Percent distribution of estimated contraceptive users worldwide, by method, selected years.

METHOD	1970	1977	1982
Voluntary sterilization	13	29	33
Oral contraceptives	20	19	16
Condom	17	13	12
IUD	10	16	18
Other methods	40	23	21
TOTAL	100	100	100

TABLE 4. Female sterilization procedures reported to the FHI between April 1971 and June 1979; figures from 100 centers in 27 countries.

Method	Interval sterilizations	Post-abortion	Post-partum	Total	%
Culdoscopy	2,394	212	77	2,683	5.4
Colpotomy	1,183	1,084	56	2,323	4.7
Laparoscopy	18,159	3,459	1,532	23,150	46.6
Laparotomy/ minilaparotomy	7,701	1,716	12,052	21,469	43.3
TOTAL	29,437	6,471	13,717	49,625	

for that year's total of 888,000. Some 14 out of every 1000 women in their reproductive years have undergone sterilization. About 60% of the women who request sterilization are between the ages of 25 and 34, 25% between 35 and 44, and about 15% are younger than 25. Most sterilizations are interval rather than postpartum procedures, and some 60% of interval sterilizations are laparoscopic procedures.

SUMMARY AND CONCLUSION

Voluntary sterilization plays a leading role in the regulation of human fertility, and the future of sterilization promises even more options for couples seeking family planning. Present methods, of which the Pomeroy is the most frequently applied, meet many of the criteria of an ideal method. Laparoscopic sterilization holds promise, and there are continuing improvements in thermal coagulation, the Silastic band technique, and the tubal clips, such as those being developed by Hulka and Filshie. Hysteroscopic and transcervical approaches also hold promise. There is considerable evidence that a large, unsatisfied demand for sterilization services remains. Good techniques for nonsurgical female sterilization have a number of potential major advantages over the current techniques, and therefore offer considerable potential to help meet the unsatisfied need. Since the role of any fertility regulation method results from a complex interplay of factors, the potential of a new technology cannot be accurately predicted. But improving the effectiveness, availability, and aceptability of all contraceptive services is likely to increase their use markedly.

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OPEN LAPAROSCOPY

Harrith M. Hasson

Numerous surgical procedures that previously required a large laparotomy incision can now be performed through small incisions with the use of laparoscopic technique. Laparoscopy has improved patient care by frequently eliminating the need for exploratory laparotomy and the pain, morbidity, recovery time and cosmetic results associated with such major surgery.

Although laparoscopy is considered to be a minor procedure, it is occasionally associated with major complications. Many of the complications result from the needles and sharp trocars used in conventional closed laparoscopy. It should be noted, however, that laparoscopy by definition does not mandate the use of these potentially dangerous instruments. Abdominal distention and the introduction of the laparoscope can be easily accomplished with the use of a mini-laparotomy technique. This variation is called open laparoscopy. The difference between open and closed laparoscopy relates exclusively to the method of abdominal entry, the sequence of entry-insufflation and the type of abdominal wall closure, as outlined in Table 1. All other apsects of laparoscopy remain unchanged.

INSTRUMENTATION

The tray of surgical instruments needed for open laparoscopy can be easily assembled in any surgical setting. The instruments include two Allis clamps, a knife handle with a small blade, a straight scissors, two

TABLE 1. Conceptual differences between open and closed laparoscopy.

Point of Difference	Open Laparoscopy	Closed Laparoscopy
Method of abdominal entry	Through mini-laparotomy incision, developed visually using standard surgical technique.	With insufflation needle, then with sharp trocar, utilizing a technique of blind puncture in both cases.
Instruments used	Standard surgical instruments and special laparoscopy cannula with blunt obturator.	Sharp needle and conventional laparoscopy cannula, bearing sharp trocar.
Sequence of abdominal entry/distention	Abdominal entry precedes distention with insufflated gas.	Abdominal entry follows distention with insufflated gas.
Type of abdominal wall closure	Layer closure	Skin closure only

Kocher clamps, two small hemostats, a dissecting tissue forceps with teeth, and a short needle holder. Additionally, "S" shaped retractors formed with curved and flat retracting ends were developed specifically to expose the small operative field.

Standard laparoscopic equipment is used, with the exception of the primary cannula and pneumoperitoneum needles. The open laparoscopy cannula is fitted with a cone-shaped sleeve that moves freely over the shaft of the cannula. The cone is locked into position along the shaft by means of a metal screw. A rubber cap seals the cone. V-shaped suture holders are mounted on the instrument. A blunt obturator replaces the conventional sharp trocar (Figure 1). Pneumoperitoneum needles are not used. It is important to utilize an instrument capable of affording adequate uterine elevation. The balloon uterine elevator cannula was developed for this purpose. The instrument provides fundal, rather than cervical mobilization, maintains self-sustained uterine elevation, seals the cervix, distributes the force of the uterine manipulation over a wide balloon surface and eliminates the need for cervical dilatation in most patients (Figure 2).

TECHNIQUE

The patient is prepped and draped for laparoscopy in the usual manner. Local, regional or general anesthesia is used, as is appropriate.

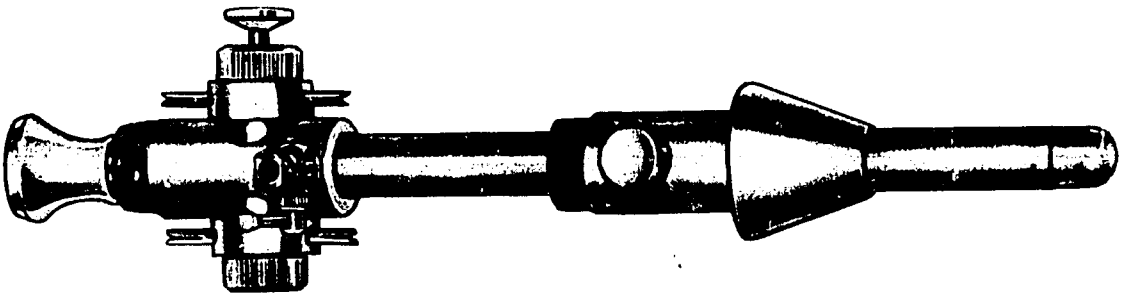

FIGURE 1. Open laparoscopy cannula.

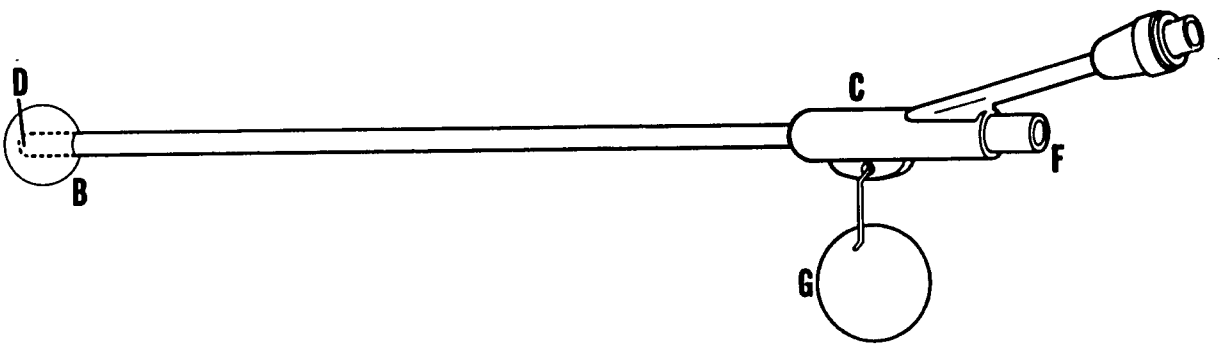

FIGURE 2. Balloon uterine elevator cannula.

Skin incision. The skin of the lower umbilical fold is held up by two Allis clamps applied on the lateral aspects of the fold. A longitudinal incision is made in the middle of the lower umbilical fold. The incision starts a short distance from a natural landmark of retracted skin within the umbilicus, which identifies the area where the skin is attached firmly to the underlying fascia. The incision proceeds inferiorly to the umbilical margin or beyond the margin, as necessary. The length of incision should be consistent with adequate exposure of the umbilical window, a natural cleavage plane where the skin is attached to the fascia, without any intervening subcutaneous adipose tissue. This will depend on the peculiar characteristics of the umbilicus and the degree of patient obesity, as well as the experience of the surgeon. A 2 cm incision is adequate for most patients. Markedly obese women require a slightly larger incision.

Exposure of the deep fascia. The Allis clamps, used to hold the skin prior to incision, are repositioned on the skin edges and used for retraction. The deep fascia (lines alba) is exposed by dissecting loose connective tissue fibers, connecting skin to fascia in the upper end of the incision, and by placing the "S" shaped retractors laterally within the wound. The amount of tension applied to the retractors should be equalized. Greater retention of one incision side may shift the operative field away from the midline onto the rectus muscle and lead to subsequent difficulties. Retraction should be applied along a more horizontal plane.

Incision of the fascia and placement of sutures. The exposed deep fascia is grasped with a Kocher clamp and raised. A second Kocher clamp is applied to the fascia above or below the first clamp. The fascia is held forcibly upward, by means of the Kocher clamps, in order to separate the abdominal wall from the bowel and omentum. The fascia is then incised transversely between the clamps, while maintaining fascial elevation. The incision need not exceed 0.5 cm. The small fascial gap is enlarged laterally by means of a hemostat using the Halsted spreading maneuver. A suture is passed through each fascial edge, tagged and held upward. The placement of fascial sutures requires the use of small strong needles attached to sutures of adequate tensile strength in order to prevent breakage and facilitate the procedure.

Entering the peritoneal cavity. The flat ends of the "S" shaped retractors are placed within the fascial incision for further exposure. Frequently, the surgeon discovers that the peritoneum has been entered during the previous step of the procedure. In this case, the surgeon simply repositions the retractors inside the peritoneal gap and lifts them up in order to discriminate omental from properitoneal fat. Otherwise, the surgeon uses a small hemostat to enter the peritoneum which is exposed and placed under tension by the retractors. The hemostat is opened inside the peritoneal cavity and the retractor's flat end is placed in the abdomen between the open jaws of the hemostat. The hemostat is removed, and a second retractor is applied on the other side. Another option may be utilized if it is difficult to enter the peritoneum with a hemostat as a result of increased tensile strength. In that case, the surgeon tents and exteriorizes the peritoneum with two small hemostats. The peritoneum is then incised between the hemostats and the

edges of the peritoneum are tagged. Care must be exercised during peritoneal incision to avoid injury to the small bowel. The surgeon must visualize the small bowel and/or omentum before proceeding further.

Insertion of the cannula. The cannula is prepared for insertion by adjusting the cone sleeve and locking it in an appropriate position on the shaft, so as to accommodate the individual thickness of the abdominal wall. The cannula is then gently introduced into the peritoneal cavity betwen retractors applied to both sides of the peritoneal gap. Insertion of the cannula must be guided by the retractors in order to avoid the possibility of placing the cannula improperly in the peritoneal space.

Fixation of the cannula. The cannula is stabilized by gentle inward pressure to prevent it from being dislodged into the preperitoneal space during subsequent manipulation. The retractors are removed and the tube carrying the insufflation gas is attached to the cannula. Gas flows through the cannula into the abdomen. The sutures that were previously placed into the facial edges are pulled tensely upward and threaded snugly into the suture holders. This maneuver pulls the fascia firmly against the cone of the cannula, providing an air-tight seal and anchoring the cannula to the abdominal wall. Withdrawal of the blunt obturator permits a more rapid flow of gas.

Performing the laparoscopic examination and manipulations. The lighted laparoscope is introduced through the cannula and the laparoscopic procedure is continued as planned.

Closing the abdominal incision. When the procedure is completed, the distended abdomen is deflated and the cannula is withdrawn. The surgical gap is closed in layers. To expedite closure, the fascial tag sutures are used to approximate the fascial edges; the sutures are positioned in parallel alignment thus presenting four ends. Two of the ends found on one side are connected by tying a square knot. The remaining two ends are pulled against the fascia and tied over the fascia. Additional sutures may be placed as indicated. Subcutaneous and/or skin sutures are then placed. Peritoneal closure is not essential.

TECHNICAL CONSIDERATIONS

Local anesthesia is particularly suitable for tubal sterilization procedures where the goal is limited to tubal interruption by mechanical devices or electric cautery. General anesthesia is preferred for diagnostic procedure and operative manipulations. Nitrous oxide or room air are the preferred gases for use with local anesthesia. CO_2 continues to be the insufflation medium of choice for operative laparoscopy, because of the potential use of electric cautery.

Although open laparoscopy is a relatively simple operation that can easily be learned by any physician trained in abdominal surgery the procedure does require a certain amount of expertise, due to the small size of the operative field and the need for establishing an air-tight seal. Other technical difficulties proceed from the presence of strong abdominal wall supports and/or previous peri-umbilical surgery. Those difficulties are minimized by adhering to the operative steps described above.

Given comparable degrees of expertise and experience, open laparoscopy does not require a greater amount of time to perform than closed laparoscopy. The cumulative time needed for satisfactory insertion of the pneumoperitoneum needle, establishment of an adequate pneumoperitoneum and successful introduction of the trocar is substantially equal to that needed for the open incisional technique. Obviously, if a surgeon uses one of the methods routinely and the other only occasionally, the more frequently used method will require less time to perform. Recovery time following open laparoscopy is identical to that noted with closed laparoscopy.

Other technical comparisons between open and closed laparoscopy relate to stability of the primary cannula and adequacy of the laparoscopic view. In closed laparoscopy, the size of the primary incision determines the degree of stability of the cannula. If the skin incision is made significantly larger than the diameter of the cannula, the cannula becomes unstable during laparoscopic manipulations. Upon introduction it slides completely into the abdomen, limiting the laparoscopic view; upon retraction it may be withdrawn completely from the abdomen. Since the open laparoscopy cannula is fixed to the abdominal wall, through attachment to the fascia, it remains stable during laparoscopic manipulation regardless of skin incision size. Additionally, adequate laparoscopic view is obtained in virtually all patients with the use of the open laparoscopy cannula; the degree of cannula protrusion into the abdomen is adjusted according to the thickness of the abdominal wall. The conventional cannula, lacking such an adjustment, may not completely traverse the abdominal wall of markedly obese patients. In this case the surgeon sees the cobweb appearance of the remaining layer(s) and may be forced to abandon the laparoscopic approach.

ADVANTAGES OF OPEN LAPAROSCOPY

When compared to closed laparoscopy, open laparoscopy offers several distinct advantages.

Elimination of needle and trocar injuries. Review of the literature reveals that most abdominal organs and structures have been punctured by pneumoperitoneum needles or sharp trocars. Insufflation of the cardiovascular system through needle puncture and laceration of major blood vessels by needles or trocars may result in fatal or near fatal complications. All of the injuries associated with the use of pneumoperitoneum needles of sharp trocars are effectively eliminated when open laparoscopy is performed, since this procedure does not utilize such potentially dangerous instruments.

Fewer and less serious complications. Wound infection and small bowel injury are two recognized complications of open laparoscopy. The risk of bowel injury is reduced when the abdomen is opened under direct vision. Should injury to the bowel occur under such circumstances, the problem is expected to be readily recognized and corrected. Wound infection associated with open laparoscopy is minimized by avoiding excessive dissection and bacterial contamination. Existing data indicates that there is no difference between open and closed laparoscopy, with regard to intraoperative infection.

Fewer contraindications. Unlike closed laparoscopy, the presence of marked obesity, large abdominal masses or scars and/or history of previous abdominal surgery does not contraindicate the use of open laparoscopy.

Easier to learn. Our data indicate that surgeons become proficient in open laparoscopy following a brief learning phase which is not associated with noticeable increases in complication rates. This phenomenon may be explained by the fact that open laparoscopy utilizes standard and familiar surgical techniques. On the other hand, closed laparoscopy, which utilizes less familiar skills, generally requires a greater amount of learning time to achieve competence.

Greater probability of success. The procedure of closed laparoscopy is occasionally discontinued before successful visualization of the peritoneal cavity is achieved because of one or more problems: 1) inappropriate placement of the needle and subsequent insufflation of gas in subcutaneous tissues, fascial compartments or the omentum, causing significant emphysema; 2) marked obesity; 3) abdominal adhesions or metastatic masses forming compartments in the peritoneal cavity. Such failed attempts are less likely to occur with open laparoscopy, since the abdomen is entered under visual control through a naturally occurring anatomical window and gas is insufflated only after successful entry has been confirmed.

Smaller probability of post-operative herniation. In closed laparoscopy, the fascial tear induced by the sharp trocar is not accessible and therefore not repaired. Post-operative incisional hernias could thus develop through the unapproximated fascial gap. Such a complication has been reported numerous times in literature. On the other hand, the fascial incision in open laparoscopy is clearly accessible and easily approximated. Routine closure of the fascia should minimize the possibility of postoperative herniation.

Alleviation of physician stress. The act of thrusting needles or sharp trocars blindly into a closed abdomen is associated with a certain amount of uncertainty or anxiety. Teachers supervising trainees performing closed laparoscopy frequently find the experience to be even more stressful. Open laparoscopy relieves the surgeon from such unnecessary stress since the procedure involves a more familiar and more predictable surgical technique.

Other techniques for open laparoscopy. Several investigators have proposed operations based on the same concept of abdominal entry, but without the use of specific open laparoscopy cannula. Hale describes a drop-in technique through the umbilicus. Grimes uses a purse string suture placed around a standard laparoscopic cannula in the subcutaneous tissues to prevent escape of the gas. Grundsell and Larsson prefer to carry out finger dissection following incision with a knife. Treat uses towel clips placed in the skin and subcutaneous tissues surrounding a standard cannula to create a nearly air-tight seal. These procedures resemble those undertaken by the author during the initial stages of development of the technique. They were abandoned for specific reasons: infection, technique difficulties, gas leakage and insufficient safety margin. One

should not expect to perform open laparoscopy successfully without using the instruments and techniques developed specifically for this operation. Acquiring proper instruments, adequate instructions and a certain amount of training is almost as essential for open laparoscopy as it is for conventional closed laparoscopy.

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LONG-TERM SEQUELAE OF FEMALE STERILIZATION

Samir El Sahwi,
Mohamed Rocca

The immediate problems following surgical sterilization are well documented in the literature but later complications and sequelae are less clearly defined and are still the subject of great controversy.

In 1951, Williams et al indicated that tubal ligation may be followed by late sequelae mainly in the form of heavy periods and pelvic pain. Since then, reports have emerged from all over the world emphasizing that the mortality rate following tubal ligation is almost morbidity, and that the operation is not infrequently followed by a group of symptoms collectively called "The post ligation syndrome".

Today, and after the passage of over thirty years, this syndrome is still an enigma that is not clearly defined. Thus while some researchers identify the "Post tubal sterilization syndrome" as a definite and important sequela of sterilization, others still question whether such a syndrome really exists.

Several confounding and methodological points render the study of such problems difficult. The effect of discontinuing the use of oral contraceptives or intrauterine devices and the changes attributable to abortion or delivery have to be considered. The normal changes that occur with the passage of time, and the difficulty in finding suitable control groups should also be accounted for.

Many of the symptoms included in the syndrome were assessed subjectively and in most of the reports the data were collected retrospectively. As the interval between sterilization and the onset of complaints increases, it becomes increasingly difficult to implicate the sterilization procedure. Instead, many gynecological illnesses are more likely to reflect the advancing age of the woman.

The following symptoms constitute the post ligation syndrome:

Menstrual disorders

The occurrence of menstrual disorders following tubal ligation was documented by many workers. They are considered the most common sequelae of sterilization. However, the incidence of this symptom varied from one report to another. Thus while it was denied completely in some recent reports, a high incidence of above 50% was mentioned previously.

The most common menstrual disorder encountered following sterilization is menometrorrhagia. Figures of 25-51% were mentioned that seemed to be much higher than what is expected in the general female population. When it occurs, it usually starts six months after the operation.

The importance of this disturbance lies in the fact that most reports indicated that surgical treatment in the form of dilatation and curretage or even hysterectomy is needed in a great number of patients.

Other forms of menstrual disorders were also reported, e.g. dysmenorrhea, amenorrhea and oligomenorrhea, but these are rare.

The cause of menstrual disturbances following tubal ligation is not clearly defined and several theories have been put forward, however, none of them gained universal acceptance.

Scott thought that this symptom is due to psychogenic instability after the operation. He stated that "The threshold of symptomatic tolerance to menstrual dysfunction becomes lower in post ligation patients because the menstrual period is a constant reminder of the presence of a functionless organ." Accordingly, a valid judgment regarding a relationship between tubal sterilization and menstrual disorders cannot be reached by the subjective data in respect to flow, duration, and interval of menstrual cycle.

This view was supported by different studies which objectively measured the menstrual blood loss before and after sterilization and could not detect any significant difference between the two measurements.

The finding of significant differences in the incidence of menstrual disorders following different techniques of tubal interruption led Letchworth and Noble to doubt the validity of the psychogenic theory. Also, this theory cannot explain the occurrence of amenorrhea and oligomenorrhea encountered in some patients.

Another view is that the post sterilization menorrhagia is due to pelvic adhesions or the development of hydrosalpinx or pelvic varicosities after

the procedure. Stock, however, found no relation between pelvic varicosities and the incidence of post-sterilization syndrome. In addition, hydrosalpinx and pelvic adhesions were rarely seen in cases who had hysterectomies for the treatment of post sterilization menorrhagia.

Lu and Chan postulated that post sterilization menstrual disorders are due to interruption of the terminal branch of the uterine artery to the ovary, resulting in cystic degeneration and ovarian dysfunction. However, no gross alterations, or microscopic changes in the ovaries could be detected after tubal ligation (14). Also, selective ateriograms in vivo and in vitro to sterilized patients failed to detect significant changes in ovarian perfusion.

In sheep, removal of a uterine horn prolongs the corpus luteum function of the ipsilateral ovary but does not affect the contralateral side. This prolongation was thought to be due to the absence of a luteolytic substance that normally perfuses from the uterine horn to the ovary of the same side. In humans, a such substance could not be detected, and no change in ovarian function had been recorded after hysterectomy. However, infusion of prostaglandin F_2 gives rise to a transien luteolytic effect. A lack of this substance may lead to a disturbance in ovarian steroidogenesis resulting in menstrual disturbances.

Ringrose indicated that the interruption of vascular connection between the ovary and uterus prevents direct diffusion of estrogen and progesterone from the ovary to the uterus. The systemic journey necessitated attenuates the action of the hormones chiefly because the antagonistic effect of the liver on steroid hormones. Coupled with the fragile transient nature of progesterone the uterus rarely experiences an adequate effect from this hormone. The subsequent shedding of the endometrium is frequently prolonged and heavy.

Studies of the hormonal profile of women after tubal ligation are also controversial. Hyperestrinism was found by some authors. Khanna et al found that in cases of post sterilization menstrual disorders there was either normal or increased ovarian activity when compared to the control group. They indicated that this increased activity may be either psychological in origin or due to a low grade inflammation.

Several cytological studies however, failed to show this persistent estrogenic effect. To add to the controversy, Hefnawi et al found low levels of estradiol 17B or hypoestrinism in all the women who had menstrual disturbances following tubal ligation.

Most of the recent studies on post sterilization hormonal profile indicated that there is a low progesterone level in the midluteal phase of the cycle.

Doyle el al showed that cyclic ovarian function persisted in patients after hysterectomy, but that the progesterone levels were often below 10 ng/ml. In such cases, the utero-ovarian blood flow has been completely severed. More recent works indicated that the mean plasma progesterone levels in sterilized women were significantly lower than a control group.

Donnez et al compared the midluteal progesterone levels in patients sterilized by laparoscopic coagulation, by Hulka clips and a control group. They found the same previous results in the coagulation group but failed to detect any diminution in the Hulka clip group as compared to the control group.

To explain these findings, it has been mentioned that the ovary is invested with arterial effluents derived from both the ovarian artery and the uterine artery. The integrity of this system is probably very important since it has been shown in sheep that the blood flow to the ovaries was 5-6 times higher during the luteal phase. Since the arterial branches to the ovaries that course along the mesosalpinx are vulnerable to disruption at the time of tubal ligation, the ovarian blood flow might be affected. Naturally the extent of vascular disruption will depend on the method of tubal interruption. The Pomeroy technique or tubal coagulation are expected to cause the maximum disruption, while the new mechanical devices as the Yoon ring and the Hulka-Clemens clip produce minimal damage.

Alvarez-Sanchez et al found that the preovulatory LH and 17B estradiol peaks, as well as the midluteal LH and 17B estradiol levels were significantly lower in tubal ligation cases compared to the control group thus indicating that tubal ligation may also affect the pituitary ovarian axis.

The modern view concerning the occurrence of menstrual disorders following tubal sterilization can be represented by the recent results of a multicenter, multinational randomized study that was sponsored by FHI. The investigation compared the effects of electrocoagulation and ring application on menstrual pattern changes. It was found that the majority of women do not experience a change in menstrual patterns following sterilization. Among women who do, about one-third to one-half of the changes can be attributed to the discontinuation of the pill or IUD. The remaining women experienced changes about equally in both directions (increase or decrease in menses). The data suggests that if a large group of women is studied, the menstrual patterns are in a constant state of flux, with the proportion of women experiencing change in one direction approximately equalling the proportion of women experiencing change in the opposite direction. Furthermore, there was no significant difference between the two methods of tubal interruption in terms of the proportion of women who reported changes in any of their menstrual parameters. These results do not support the theory that states that the greater the degree of destruction of the utero-ovarian vascular anastomosis (as with electrocoagulation), the greater the amount of subsequent menstrual pattern disturbance.

The importance of studying the problem of alteration of ovarian function following tubal ligation is twofold. First, it can be the cause of intractable menstrual disorders that may necessitate surgical intervention. Second, ovarian dysfunction is now thought to be partly responsible for the low pregnancy rates after successful sterilization reversal operations. Disturbance of ovarian function may lead to abnormal ovulation in these cases and can be a reason for the persistent infertility even after perfect restoration of tubal patency.

Pelvic pain

Pelvic pain has been reported as one symptom of post sterilization syndrome. Again, the incidence of pelvic pain varied greatly in different reports.

Different types of pain were described after tubal ligation. It may be pelvic or lower abdominal, persistent or intermittent, localized or diffuse, and mild or severe. In general, all types of pain tend gradually to decrease or disappear with time. A 6.2% rate of dysmenorrhea was reported following sterilization, after correction for former complaints about pain and for pill use. Also 8.7% of women complained of continuous vague abdominal pain since sterilization.

Several explanations have been put forward to account for post-sterilization pain. Strangulation of a segment of the fallopian tube with ischemia, post-operative pelvic congestion and adhesions, tubal irration secondary to ring application, crushing of a nerve by the clip, hydrosalpinx, and avascular necrosis of the distal loop of the tube, have all been mentioned. Pain might also be a manifestation of the psychological effect of the operation.

In Lu and Chun study, secondary dysmenorrhea occurring after sterilization was experienced by 16.8% of women. The pain was either premenstrual or intramenstrual. Abdominal pain was also experienced by 20.5% of women but in most cases the pain was mild, amounting only to vague abdominal discomfort without any positive pelvic findings.

One interesting type of post sterilization pain is the intermittent pelvic pain that occurs in episodes and is invariably related to activity. This pain was explained to be due to intermittent torsion of the remaining fimbriated end of the tube after ligation. The infundibulo-pelvic ligament, the utero-ovarian ligament and their accompanying vessels and nerves seem to be disturbed by the operation, and this favors an increased incidence of torsion in the adjacent ovary or tubal fimbria. Deshmukh et al described three cases presenting symptoms of acute abdomen and all had twisted hydrosalpinx at emergency laparotomy. All three patients previously had abdominal Madlener's tubal ligation.

Adenomyosis and endometriosis were also seen in some cases of post sterilization abdominal pain but most probably these were not related to the operation.

One interesting observation, however, is the occurrence of endometriotic patches at the tip of the proximal stump of the interrupted tube. These patches might constitute an initial nidus for the propagation of pelvic endometriosis later on, resulting in pelvic pains.

Several disturbing reports indicate that some of the patients that develop complications of tubal ligation (mostly menometrorrhagia) may not respond to simple regimens of treatment and consequently may need surgery in the form of dilatation and curettage, or even hysterectomy. Again however, there are variations in the prevalence rate of surgical interventions following ligation. Old figures were high amounting to

a 19% or even 25% rate of post sterilization hysterectomy.

More recently, Meyer indicated that 6.5% of women who have undergone laparoscopic ring tubal sterilization needed subsequent dilatation and curettage for dysfunctional uterine bleeding. Histologic findings in all these cases showed no significant pathology. Also 5% of his patients had hysterectomies since the operation. But he recognized that two-thirds of all the patients that needed surgery had had seedling fibroids or endometriosis at the time of the original operation.

In another study, 6.5% of the women had undergone a gynecological procedure after sterilization. More than one half of them had a curettage because of menometrorrhagia while one quarter had a hysterectomy for the same reason. In dealing with this problem it has to be recognized that a number of these bleeding changes are surely related to the higher incidence of metropathia hemorrhagica during the menopausal years. Also, hysterectomy may be resorted to for the retreatment of new pathologies, e.g. fibroids, ovarian tumors or prolapse that did not exist at the time of sterilization.

Though most of the reports indicate that the incidence of menstrual disorders and pelvic pain is almost the same after different methods of tubal interruption, it appears that fimbriectomy may be associated with the lowest incidence of post ligation pain and menorrhagia. Also, the transcervical techniques of tubal obliteration utilizing chemical substances appear to avoid the sequelae of pain and menorrhagia.

Failure

A rather unexpected complication of female sterilization is the occurrence of pregnancy which after tubal sterilization is more likely to be ectopic. This adds much to the gravity of the problem.

Pregnancy rates varying from 0% to as high as 16% were reported. Currently, however, with the modern techniques of sterilization the acceptable figure should not exceed 0.5%.

The possible explanations of pregnancy following sterilization are the following:

1. Faulty technique of the operation, e.g. occlusion of the round ligament instead of the tube, or partial occlusion of the tube leaving a segment of its lumen patent.
2. Improper timing of the operation. If the operation is done in the second half of the menstrual cycle, the patient might be already pregnant and therefore the pregnancy continues after the operation. This is referred to as "Luteal phase pregnancy".
3. Recanalization of the tube after its complete occlusion.
4. Development of tubo-peritoneal fistula.
5. Bad quality of the mechanical device ring or clip used for tubal occlusion.

Post sterilization pregnancy rates are usually high at the inception of programs, during training, or when there is a shift from one procedure of

tubal interruption to another. At these times the experience of the operating staff is limited and as they gain more command of the operation the pregnancy rate goes down to negligible levels.

Ectopic pregnancy occurs due to partial obstruction of the fallopian tube as a result of the tubal occluding procedure so that the narrowed lumen can allow the passage of the tiny spermatozoa but it is too narrow for the passage of the rather larger fertilized ovum. Therefore, the latter remains in the fallopian tube and implants there, resulting in ectopic pregnancy.

The overall risk of ectopic pregnancy is reduced following sterilization. The expected lifetime rate with one ectopic pregnancy is 15.6 per thousand women if they were utilizing other methods of contraception versus 2.1 per thousand women after tubal sterilization.

The risk of pregnancy being ectopic among women who had tubal sterilization however, is higher than it is among women using no contraceptives who become pregnant. Some 5% or more of all pregnancies in women who have been sterilized can be expected to be ectopic. This compares to less than one percent among non-contraceptive users.

Sense of regret

The true prevalence of regret after sterilization is not known as there is marked disagreement among various authors. The regret rate in different reports ranges between 0.6% to 20%.

With the increased publicity of sterilization and adverse reports of oral contraceptives, younger women with small families are seeking tubal ligation. It is particularly important that sterilization counselling for such women be adequate so that the risk of subsequent regret is minimized.

Some patients show transient mood disturbances shortly after sterilization but this represents a bereavement reaction in a certain personality type. Patients who become dissatisfied only after some time, do so because of such changes in circumstances as divorce, remarriage, or death of a child. Other reasons are change of mind, lack of complete knowledge about the operation or the development of complications.

Rubinstein et al analysed the feelings of sterilized women and found that 90% of them were satisfied, 3% were unhappy and 7% were ambivalent. Feelings of regret were not related to the post operative complications but appeared to be related to the reasons of sterilization. Those who regretted the procedure chose sterilization either for financial reasons or because they desired to discontinue their present methods of contraception. It appears that reaching an ideal family size is the motivation for sterilization associated with the highest incidence of satisfaction and lowest incidence of regret or ambivalence. This explains the very low incidence of feelings of regret in our sterilized patients as the motivation for sterilization in our community is almost always completed family size. The same results are borne out by the study of Buytaert and Viaene where the regret rate was very low (only 2 out of 322 patients). They attributed this low regret rate to various factors

that included the following: most of the women were not under 35 years, lack of marital problems at the time of sterilization, and finally, that sterilization was mainly performed for contraceptive reasons, and never during or immediately after an abortion or delivery, thus avoiding a time of extreme emotional instability. Post partum or post abortal sterilizations are followed by higher regret rates than interval sterilization. Again it was found that 75% of women asking for reversal of sterilization chose this method of contraception because of bad marital relations.

A recent questionnaire survey of sterilized patients has indicated that about 80% were satisfied with the operation while 20% expressed regrets. Strangely however, about 60% of those who regretted the operation said they would have chosen the operation again in the same circumstances, presumably accepting sterilization as their only available solution despite reservations and regrets. It is interesting to note that in this study the regret rate was 14% in women who were 30 years or over, compared with 39% in women who were sterilized under 30 years of age.

The regret rate in any service should be used as a guideline to improve future management. Proper counselling of women, explaining the nature of the operation, the risks, effectiveness, advantages and disadvantages as well as a comprehensive introduction to all of the alternative contraceptive modalities that can be used should be clearly mentioned. Also the fact that it is a permanent procedure has to be stressed. Other factors that can minimize the regret rate are the lack of early complications, low incidence of failure, and naturally minimal late sequelae.

Though some indicate that in-depth psychiatric or personality assessment of women before sterilization might avoid operations in high risk unstable women, this is no guarantee or eventual satisfaction, and is probably impossible logistically.

Psychiatric and psychological disturbances

There are some lay beliefs deeply ingrained among people that sterilization affects the temper, causes deterioration of memory and renders the woman less fit to work. Reviewing the literature, controversy also exists, but in general most of the studies did not indicate that there is rationale behind the belief that sterilization can cause psychiatric or psychosexual disturbances.

In modern life, psychiatric upsets are very common and people tend to link their suffering to special events in their lives. For women, sterilization, whether they are satisfied or dissatisfied with it, is a memoral event that stands as a milestone for several changes in life.

Lu and Chun found that there were undeniably some psychological effects of the operation, as some patients subconsciously felt that the permanent loss of their reproductive function would necessarily decrease their womanhood or femininity. The same study, however, indicated that about one-third of the women had an improvement in sex and family life after sterilization. Also, most of the patients felt that their temper, memory and fitness were the same before and after sterilization.

Cooper et al indicated that although post-operatively a small number of patients were psychologically disturbed, dissatisfied with their sexual relationships or regretted having the sterilization, these women had been psychiatrically disturbed before the operation, and there is no reason to assume they would have been less disturbed if they had not had the operation.

Also a large prospective study has indicated that sterilization is a safe and effective method of birth control with little or no evidence of long-term sequelae. In an analysis comparing women who had undergone tubal sterilization with those whose husbands had undergone vasectomy, the authors found little evidence to suggest an excess in gynecologic or psychiatric disorders in the former group.

A study from Pakistan, on the other hand, indicated that although some sterilized women did suffer psychological setbacks, no significant differences were found between test and control groups in frequency of intercourse or self-ratings of happiness, ability to work, or general health. Thus it is clear that sterilization has a minor impact on the psychological set up of women. Naturally, the adverse psychological effects of sterilization can be lessened if clinicians and other medical support staff take more time to explain the procedure and expected side effects to women before the operation.

Weight gain

There is a belief that sterilization can lead to adiposity but this is not a constant phenomenon, and change in weight in the form of increase or decrease can occur.

In the Lu and Chun study, 83.3% of patients showed minor deviations in weight that can be expected in the space of some years in any group of parous women.

Bhatt et al found that considerably more women had weight gain than weight loss after sterilization. He thinks that for developing countries where malnutrition is a major problem especially among high parity women, this becomes an added benefit of the procedure.

CONCLUSION

In recent years, the acceptability of sterilization has markedly increased. The large majority of women subjected to the operation are satisfied in many respects, and regard the procedure as an ideal contraceptive modality. The increased publicity of tubal ligation calls for a critical appraisal of the operation in an effort to assure its total safety. The immediate post operative complications are well documented but the prevalence of late sequelae and complications is less clearly defined.

Since time immemorial there are lay beliefs that link femininity and the ability to bear children. Lay people concede that tubal ligation affects the menstrual flow, upsets the psyche and mood, changes the shape of the body, diminishes the sexual desire, and ultimately leads to early senility.

Unfortunately, most of the old studies have substantiated these beliefs. These studies were mostly retrospective, uncontrolled, and subjective questionnaires, that did not take into consideration the previous use of contraceptives, the effect of recent pregnancy prior to the operation or the presence of pelvic pathology before or at the time of surgery.

Recent controlled studies, however, that have corrected their results according to the previously mentioned factors and that assessed objectively the parameters studied, have indicated that tubal ligation is quite an innocuous operation with minimal or no late sequelae.

Such knowledge is definitely needed worldwide in order for sterilization to continue its dominant role in solving the population problem. Moreover, the complete safety of the operation, and the fact that it does not lead to major changes in the human body should help to abolish the arbitrary eligibility criteria imposed by many governments in the developing world that keep surgical sterilization from those who want and need it most.

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FEMALE STERILIZATION USING CHEMICAL AGENTS

Ralph M. Richart

Sterilization is a highly effective means of fertility regulation and ranks as the most popular method worldwide.

Female sterilization using conventional techniques is always a surgical procedure requiring invasion of the peritoneal cavity. Whether ligation or electrocoagulation of the fallopian tubes is performed by means of a postpartum incision, a laparoscopic puncture, or a minilaparotomy, the peritoneal cavity is exposed to potentially fatal invaders that inhabit the nonperitoneal world, and the surgical manipulation and treatment may cause major injuries to the abdominal viscera and blood vessels. Morbidity is difficult to avoid, especially in large series of patients, and deaths, though rare, do occur.

Conventional female sterilization techniques cannot be offered on a broad scale, because most procedures require the considerable training usually possessed by a gynecologist or general surgeon.

Many family planning specialists and policy makers believe that voluntary sterilization, because of its high effectiveness and acceptability, must

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become the mainstay of family planning programs. But conventional surgical approaches for female sterilization cannot be used in many areas of the world. Thus, a procedure is needed that can be performed without surgical entry of the woman's abdominal cavity, and is safe, effective, inexpensive, simple in design, and easy to learn.

The most promising nonsurgical female sterilization approach presently being evaluated is the transcervical introduction into the fallopian tubes of a pharmacologically active agent to produce tubal closure. Such a system has been sought for more than a century, and during the past two decades, many chemical agents have been tested, some in clinical trials.

AGENTS FOR TUBAL CLOSURE

Chemical agents that have been tested for tubal blockage are numerous and fall into several major categories: Caustic, sclerosing, granuloma-producing, and cytotoxic agents, acids and bases, tissue adhesives, and agents that are not pharmacologically active.

Strong caustic agents

In 1849, Froriep reported the use of a nitric acid-coated probe, passed transcervically on the tip of a cannula, to engage the tubal ostia and to cauterize the tubal lumen. Over the next hundred years, a number of caustic agents, such as silver nitrate, zinc chloride, copper sulfate, and formalin, used alone or in combination with ethanol, were tested for their ability to produce tubal closure in a number of animal species and in humans.

Silver nitrate, zinc chloride, and copper sulfate all produced similar reactions, regardless of the species tested: Immediate, extensive necrosis, inflammation, and edema. The extent of injury was dose-related and with higher doses of the agents, the entire wall of the fallopian tube became necrotic and the animals died, presumably of chemical peritonitis. Despite the massive injury, however, tubal closure was rarely achieved with these agents, and epithelial regeneration and re-establishment of the tubal lumen were common. The tubes were usually damaged severely, and complex intratubal adhesions simulating the follicular salpingitis found in humans were frequent following a healing phase.

Attempts to increase the closure rates using gelfoam, sponges, gauze strips, and surgical mesh repair materials were unsuccessful, as was the use of granuloma-producing chemicals and other agents to potentiate the action of these acute necrosis-producing agents.

Chronicity of exposure was important, and when silver nitrate was placed in a slow-release vehicle, it proved to be a technically satisfactory tube-closing agent. In human clinical trials, however, this combination proved unsatisfactory, because it was as caustic to the peritoneal cavity as to the fallopian tube and produced a chemical peritonitis.

Formalin, alone or with ethanol, is a potent tube-closing agent and produces sclerosis of the endometrial cavity in small animals, but in clinical trials, the closure rate after multiple applications was insufficient

to warrant continuing efforts.

Strong acids and bases

A variety of strong acids and bases have been used to treat the fallopian tubes of animals and humans. Sulfuric acid, salicylic acid, carbolic acid (phenol), and sodium hydroxide were all studied in the rabbit by Richart and co-workers. Phenol was used in combination with tincture of iodine in humans by Brazilian midwives, and in combination with a mucilago compound by investigators in the People's Republic of China.

These agents had an immediate effect on the epithelium of the fallopian tube and endometrial cavity, producing tissue destruction and both acute and chronic inflammation. As with the strong caustic agents, the effects were dose-related, and complete tubal necrosis could be produced with a sufficiently high concentration of these highly active chemicals. When delivered without a slow-release carrier, they were difficult to control and not infrequently spilled into the peritoneal cavity, where they produced acute chemical peritonitis and necrosis of pelvic structures. Phenol is the only agent in this group that has been used in humans, but it is effective only in a compound that limits its accessibility to the peritoneal cavity and apparently limits its release rate as well. When the agent is used alone and produces acute effects, tubal damage is the rule, but tubal closure is the exception.

Sclerosing agents

Sclerosing agents, commonly used by vascular surgeons for the obliteration of vessels, have also been applied to the endometrial cavity and fallopian tube in an effort to produce closure. Sodium morrhuate, sotradecol, and sodium lauryl sulfate have all been studied in animals, and sodium morrhuate has been used in humans as an adjunct to tubal ligation. Sclerosing agents have not been useful in producing tubal blockade and appear not to be effective in producing epithelial necrosis or fibroblastic ingrowth.

Granuloma-producing agents

A large list of granuloma-producing agents, among them talc, asbestos, cellobiose, silica, diatomaceous earth, beryllium nitrate, quartz, and plant cells, have been studied in rabbits and monkeys and talc granules were used by Ringrose in an attempt to potentiate the action of silver nitrate in humans. These agents do produce granulomata in the wall of the uterus or fallopian tube, but the granulomata never reach sufficient size to produce tubal blockade, and the agents have no effect on the epithelial lining. If they reach the peritoneal cavity, they also produce adhesions and granulomata on peritoneal surfaces and the pelvic viscera, a serious drawback to their use as potentiating agents in combination with more effective compounds.

Cytotoxic agents

ThioTEPA and quinacrine have been studied in animals and quinacrine has been studied extensively in humans. The mechanism of action of quina-

crine in producing fallopian tube blockade is not known, but it appears to be species-specific and highly dose-related. Quinacrine binds to DNA, apparently intercalating between the coils of double-stranded nucleotides at the A-T base pairs. When the quinacrine is bound to DNA, the bound portions of the molecule are less likely to be replicated, and synthesis of DNA, RNA, and protein decreases. Histologically, in humans quinacrine appears to exert its effects only in the interstitial portions of the fallopian tube, where it produces subepithelial hyalinization and scarring, and destruction of the tubal lining epithelium. The effect appears to be highly localized and variable, and the precise mechanism is not known.

Cadmium, colchicine, and podophyllin have also been investigated but appear to be ineffective.

Tissue adhesives

Tissue adhesives from the cyanoacrylate series of compounds have been studied in a number of animals and in humans and the methyl derivative has been found to be effective in closing the fallopian tubes. Both ethyl and isobutyl cyanoacrylate cause less local toxicity than the methyl compound, and although both function as effective tissue adhesives, the failure to produce local necrosis makes them ineffective in closing the fallopian tubes. Gelatin resorcinal formalin (GRF) has been studied in experimental animals and, although it produced functional sterility in the rabbit, at histologic examination the majority of the tubes were patent, and GRF was not explored further.

Other agents

Although not pharmacologically active, silicone rubber and hot water have also been used to close the fallopian tubes, and both are potentially amenable to outpatient sterilization procedures. Silicone rubber was first studied by Hefnawi and co-workers in rabbits and subsequently reexamined using different formulations by Erb and co-workers and Davis and co-workers in rabbits and monkeys. The Erb formulation has also been applied in humans, using a special mixing device and a specially-designed hysteroscope for its administration. Rakshit reported human trials with blindly delivered silicone rubber techniques. Moulding and associates have reported the use of hot water to obliterate the tubal epithelium, but this approach has not been used clinically. Droegemueller has described an apparatus for producing necrosis cryotherapeutically at the uterotubal junction of the baboon; this apparatus has also been used in a limited clinical trial.

DELIVERY SYSTEMS

An important factor in developing a practical transcervical method of sterilization is to find a system whereby a toxic chemical can be delivered to the site where it is to produce the desired destruction without damaging surrounding tissues. Most of the agents mentioned above are toxic not only to the tubal epithelium, but to the peritoneum and pelvic viscera as well. Possible exceptions are quinacrine and methylcyanoacrylate (MCA), which seem not to be toxic in the peritoneal cavity unless

introduced in very large amounts. Agents that produce immediate acute necrosis with widespread tissue damage and acute inflammation appear not to be satisfactory for tubal closure, since their flow cannot be controlled. They have consistently leaked from the fallopian tube into the peritoneal cavity, producing local or generalized peritonitis, depending on the volume reaching the peritoneal surfaces.

Attempts to control the flow of these cauterizing agents, by combining them with inert carriers or polymeric systems, have usually been unsuccessful, since the agents are chemically so active that there are very few systems with which they can be utilized. No satisfactory slow-release system for delivering highly caustic agents has yet been devised that produces tubal closure without undesirable or dangerous side effects. Some of these agents would probably produce effective tubal closure, if it were possible to combine them in a slow-release delivery system, but efforts to develop such a system have not succeeded, and no new approaches are currently being studied. The problem is further compounded by the fact that most potentially useful carriers, such as thixotropic gels or carboxymethylcellulose, have a high viscosity that inhibits their easy flow through the interstitial portion of the tube.

Viscosity is an important variable in considering a method for delivering tube-closing agents, in the selection of the agents themselves, and in the development of active agents and carriers. The uterotubal junction is small and leads to a several-centimeter long, narrow, interstitial tubal segment which, in turn, is contiguous with the slightly wider isthmic tube and the increasingly wide ampulla and fimbrial sections. Since the tube is, for practical purposes, a fluid-filled potential space, and since the tubal orifice can be dilated to only 1 to 2 mm mechanically, considerable hydrostatic pressure is required to force a fluid into the tube for any significant distance.

Delivery is much easier with a substance of low viscosity, and becomes increasingly difficult as viscosity increases. Substances such as GRF and the silver acetate/alginate mixture are difficult to work with and to deliver using a catheter, a cannula, or other delivery technique. The hand-held cannula described by Corfman and Taylor, the balloon-tipped cannula systems described by Moulding and co-workers and the tube-finding cannula developed by Battelle Laboratories, which has extendable arms designed to form a triangle, all were unable to pump viscous materials without being forced away from the cornua. The only systems that have delivered tube-closing agents successfully in a reproducible fashion have been those in which the tubal orifice is cannulated directly, or blindly, or those in which the uterus and fallopian tubes become a closed system and medication is forced into the tubes under pressure.

Erb and his colleagues have used a specially-designed hysteroscope to deliver silicone rubber to the fallopian tubes, but have reported that approximately 11% of patients cannot be treated with this system because the geometric configuration of the uterus precludes adequate tubal cannulation. If the catheter is not precisely placed in the uterotubal orifice, the high pressure required to drive the silicone rubber into the fallopian tube also causes leaking around the seal and inadequate application of the material.

Other agents, such as MCA and quinacrine, have also been delivered using hysteroscopy, and the investigators reporting on these attempts have noted similar difficulties in tubal cannulation. Although the hysteroscope is useful in a variety of clinical applications, it is a difficult instrument to use, service, and maintain; considerable training and experience are required before an operator becomes skilled in its use, and a delivery system based on hysteroscopy will probably be too complicated for use either in the developing world or in most of the developed world.

The FEMCEPT device being studied by Richart and associates uses a highly expandable balloon as a piston to drive the MCA into the fallopian tubes, and is capable of delivering a precisely measured volume of the material to the tubes without the danger of peritoneal spill or the need to leave large volumes of the chemical, which must eventually be expelled, behind in the uterus.

The delivery systems used for quinacrine initially comprised a blind system in which a catheter was passed transcervically to the fundus and the quinacrine solution was gently introduced using a lavage technique. Some investigators used a closed system with a cervical olive, attempting to determine whether failures occurred because the quinacrine did not reach the fallopian tubes, or because it was inactive as a tube-blocking agent. Subsequent studies indicated that multiple exposures to quinacrine were more efficacious than a single acute insult and that chronic exposure was the most effective.

On the basis of these findings, quinacrine pellets have been devised that can be placed in the uterus with an IUD inserter and left in place to diffuse into the fallopian tubes. Whether this approach will significantly increase the quinacrine closure rates is not yet known, but clinical investigation is underway.

In the most recently developed delivery system, the quinacrine is compressed onto the tips of a T-shaped or V-shaped IUD-like vector. The vector is inserted into the uterine cavity, and the tips, which lie in close proximity to the tubal ostia, theoretically enable the quinacrine to diffuse slowly into the tubes, thereby producing more complete closure.

Another method of delivery being considered is the incorporation of quinacrine into slow-release polymers, again, to extend the diffusion time and produce a higher rate of closure.

CLINICAL TRIALS

The only tube-closing agents that have been tested clinically in a significant number of patients are silver-based compounds, ethanol-formaldehyde, quinacrine, and methylcyanoacrylate. Some of the more interesting clinical trials are described in the following sections.

Silver-based compounds

Clinical trials, using silver nitrate compounded in a water-based cream, were undertaken in 14 patients by Richart and co-workers. In these

patients, the fallopian tubes were brought into the vagina through a posterior colpotomy incision; a cannula was passed through the fimbriated end of the tube, and the silver nitrate cream was injected under direct vision. The tubes were then replaced in the abdomen and the vagina was closed.

The response of the patients was carefully studied. Although all the fallopian tubes in this series were closed, many of the patients experienced fever, leukocytosis, and significant pelvic pain ascribed to a chemical peritonitis. All these symptoms disappeared under treatment, and no long-term sequelae occurred.

Ringrose, in a separate study, used a blind cannula system to deliver various concentrations of a silver nitrate-based compound (10%, 15%, and 20%) to the fallopian tubes of 260 patients. The closure rates were approximately 50% with the 10% silver nitrate compound, and 70% with the 15% compound; the rate was not stated with the 20% compound. There was apparently a significant degree of intraperitoneal spill with all three concentrations, presumably due to the uncontrolled blind delivery system. The clinical sequelae increased with increasing concentration of silver nitrate: a number of patients suffered severe peritoneal signs, two had paralytic ileus, many required hospitalization, and some suffered additional complications not reported in the original publication.

In our recent attempts to incorporate the silver ion into a polymeric system that might be useful clinically, we found that even with a complicated alginate-based mixture, migration of the silver ion into the peritoneal cavity could not be prevented. In a recent series using baboons and Cebus monkeys, significant peritoneal damage and extensive necrosis occurred, and several animals died. It would appear that silver-based tube-closing compounds are potentially highly toxic, that further studies using these materials as a base should be undertaken with great care, and that thorough testing should be done before these compounds are used in clinical trials.

Ethanol-formaldehyde

In 1972, Zipper and co-workers, in a series of 93 women, used 2 ml of a 2% solution of formaldehyde in ethanol to lavage the uterus through a biopsy cannula. They determined tubal closure by insufflation or hysterosalpingography. Overall, non-patency was obtained in only 54 of the 97 women (58%), and the rate of closure increased steadily with serial injections. A number of women dropped out before completing the study, but those who had six instillations had a high rate of obstruction. The optimal number of treatments reqired to produce clinically satisfactory results was not shown conclusively with this study. At the two-year follow-up, 8.7% of the patients with supposed tubal closure had become pregnant.

Mucilago phenol

A group of investigators from the People's Republic of China have reported their findings with the largest series, involving 3,940 women whose fallopian tubes were treated with pharmacologically-active agents. They

began their studies in 1970 with a phenol-based compound and modified the administered agent through a series of trials extending through 1977. The rate of bilateral occlusion ranged from 77.6% in the initial series to 93.5% in the most recent series. The compound was administered using a hand-held plastic catheter inserted through a metal tube placed at the uterine tubal ostium. Normal saline was injected through the plastic catheter, and if there was no back-flow, 1 ml of air was injected, followed by 0.1 to 0.15 ml of mucilago phenol. Although the mucilago phenol was compounded differently in each of the separate trials, the details of the compounding are not given in the text, nor are the closure rates of the individual trials presented. The compound used most recently consisted of 35 ml liquid phenol, 5 g mucilago of tragacanth, 20 ml glycerin, and 100 ml or less of distilled water. Tubal patency was determined by hydrotubation.

The investigators also treated lactating women with the agent. The rate of successful location of both cornua was 92.8% in these women, as opposed to 82.5% in non-lactating women, but the rate of bilateral closure was 91% in 156 lactating women, as opposed to 94.9% in 275 non-lactating women.

A number of side effects occurred following the application of the phenol compound. Forty percent of the women had mild lower abdominal pain and back pain for 2 to 3 days and 1.2% were febrile. Thirty-five patients suffered acute pelvic inflammatory disease. The minor side effects disappeared spontaneously, the acute pelvic inflammatory disease was treated symptomatically, and all patients recovered without further problems. In three lactating women, the uterus was perforated. Nirety-six women underwent laparotomy after tubal occlusion for reasons not related to the sterilization procedure. Six patients developed adhesions between the tubes and the pelvic side wall or ovary, but five of these six patients had suffered acute inflammatory disease immediately after the operation.

The investigators followed 2,487 women for two to seven years after bilateral tubal occlusion was achieved using the hydrotubation technique. Of these women, 64 became pregnant (a pregnancy rate of 2.6%). In 909 women, hydrotubation or hysterosalpingography was performed two to seven years after a diagnosis of bilateral tubal obstruction. Of these patients, 15 were found to have one or both tubes patent (a patency incidence of 1.65%). Menstruation was unaffected.

The Chinese investigators also studied the relationship between the length of fallopian tube that was filled with the mucilago phenol compound and the rate of tubal closure, as determined by hysterosalpingogram. When more than 1 cm of tube was filled, 97% of the tubes were occluded. In contrast, if the agent was placed in the cornu alone, only 16% of the tubes were occluded.

At the time of the report, ten pregnancies had occurred, including one ectopic pregnancy, and two women were found to have patent fallopian tubes on hysterosalpingography. The total clinical failure rate was 0.7% after 7 years. An additional five procedures failed during years 7 to 9, making a total failure rate of 1%. There was a direct relationship between the length of fallopian tube filled and the pregnancy rate. If

a 1 to 2 cm portion of tube was filled, the pregnancy rate was 7.1%. If 2 to 4 cm were filled, the rate decreased to 3.3%, and when the tube was filled to the ampullae, the rate decreased to 0.1%. There were no pregnancies if the entire fallopian tube was filled.

Quinacrine

Quinacrine hydrochloride has been widely studied by a number of investigators. In Zipper's initial study, the quinacrine was administered as a solution of 250 mg/2 ml, using a polyethylene catheter that was passed transcervically and placed at the fundus. In subsequent studies, the quantities of quinacrine were increased, and in some studies, attempts were made to use a cervical olive to ensure that the quinacrine came in contact with the fallopian tubes. The closure rates using quinacrine lavage varied widely from study to study after a single application and, with the exception of Davidson's small series, seldom exceeded 70% unless multiple lavages were performed.

In the most recent studies, Zipper and his colleagues have compressed the quinacrine into pellets and introduced a number of them, totaling 250 mg, into the uterine fundus using an IUD inserter. In the initial studies, this process was repeated three times, and a bilateral closure rate in excess of 95% was achieved.

Laufe and associates, in addition to inserting compressed pellets into the uterus, have fashioned V-shaped and T-shaped IUD vectors that carry a compressed bolus of quinacrine in the tips of their arms. These arms are thought to deploy the quinacrine in the vicinity of the tubal ostia when the IUD is inserted into the uterus, ensuring that the quinacrine will be diffused in the region of the fallopian tube and produce the desired effect. Although only a few cases have been studied, the preliminary results are encouraging.

Quinacrine has been used widely to treat malaria and neoplastic effusions. Its mechanism of action in producing tubal closure is not known, but is thought to be related to its ability to intercalate with DNA, and to inhibit DNA, RNA, and protein synthesis. A puzzling aspect of the quinacrine studies has been the variability of the tubal lesions produced by the drug. Even in patients in whom the quinacrine was applied directly to the fallopian tubes, lesions might involve a wide area or be focal, and some tubes were undamaged. The drug is thought not to produce local complications in the peritoneal cavity, but has been associated with a variety of other side effects, the most serious of which is central nervous system excitation. The fact that the few patients treated with quinacrine pellets have not experienced CNS excitation suggests that the pellets may be a more satisfactory mode of administration.

MCA

A number of investigators have studied the effects of MCA in the fallopian tubes (Table 1). MCA is an epitheliotoxic agent that releases acetocyanic acid and formaldehyde upon degradation, and produces necrosis of the tubal lining epithelium adjacent to the MCA. As the agent is gradually degraded over a period of six weeks, an inflammatory infiltrate

replaces the tubal epithelium and it, in turn, is replaced by young fibroblasts, which are gradually converted into dense scar tissue.

TABLE 1. Results of clinical trials with MCA.

STUDY/ REFERENCE	YEAR	NO. PATIENTS	BILATERAL CLOSURE(%)	COMMENTS
Stevenson, Taylor	1972	12	--	Prehysterectomy application
Stevenson	1976	34	66	HSG at 8 weeks
		11	90	Reapplication of MCA
Neuwirth, et al	1980	131	72	Closure rates of 54% to 78% in 3 series with various volumes of MCA (0.4-0.65)
		19	74	Reapplication of MCA
Richart, Neuwirth	1981	180	80	0.6 ml MCA; modified FEMCEPT device
		19	98	Reapplication of MCA following patency detected by HSG
Richart, et al.	1983	821	78	Single application
			87	Two applicating 1 month apart
			87	Single application radio-opaque MCA
			90	Application after HSG failure

The largest series of MCA-treated patients studied to date has been reported by a group of collaborators using the FEMCEPT device.

Approximately 850 patients have been treated by the FEMCEPT/MCA system to date using a variety of protocols and a series of MCAs. With a single injection of MCA, the overall bilateral tubal closure rate was 78%. In patients who received two applications one month apart, the bilateral clousure rate was 87%. In patients who were retreated after having been found to have unilateral or bilateral patency by HSG four months after MCA application, the bilateral closure rate was 90%. Thus, in patients retreated after an HSG confirmed failure, the theoretical bilateral closure rate was 98% (80% + 90% of 20%). A prospective series designed to

confirm this calculation is presently underway.

It has also been possible recently to compound a radio-opaque MCA which is more "spreadable" than prior formulations and which has other properties which are expected to enhance its tube-closing abilities. In preliminary studies of this radio-opaque formulation, there was an 87% bilateral closure rate on a single application. Until a larger number of patients have been studied, it will not be clear whether this formulation is superior to the previously studied ones.

DISCUSSION

Certain principles have evolved from the studies of pharmacologically active agents applied to the fallopian tubes; these principles may be applicable to the design of future delivery techniques and tube-closing pharmacologically-active formulations. It is evident, because of the efficient regenerative capacity of the tubal lining epithelium, that acute injuries, even when they are massive, routinely fail to destroy all the epithelial cells, which may rapidly regenerate and reconstitute tubal patency during the period of healing and reconstruction. Those agents that are most effective in producing tubal closure are associated with a chronic long-term effect, because of their slow degradation rates (for example, MCA), or are released over a prolonged period of time (for example, mucilago phenol). It is also apparent that in the absence of chronicity, multiple applications are more effective than single applications and enhance the cumulative rate of tubal injury and closure (for example, quinacrine in solution or ethanol-formaldehyde). Most of the authors studying this problem at length have commented upon the necessity of meeting these requirements in order to produce a high rate of tubal closure.

It has been documented in the mucilago phenol studies from the People's Republic of China, and it was apparent in the studies of MCA done by our group on Rhesus monkeys, that another major determinant of tubal closure rates is the length of the fallopian tube exposed to the pharmacologically active agent. This is consistent with observational data from laparoscopic electrocoagulation studies, in which the early attempts at closure using coagulation alone had a high failure rate, due to the small segment of tubal damage. As the length of injured segment was increased, tubal closure rates increased substantially, and it is generally thought that a 3 cm injury is optimal. It is apparent that the fallopian tube is more easily reached during the immediate postmenstrual and early proliferative phases of the cycle, when the thickness of the endometrium has only begun its cylic growth, and it is probable that applications performed late in the cycle, or when the tubes are in spasm, will result in failure. It is also clear that there will be unavoidable failures in women with anomalous uteri or with intrauterine disease, such as uterine synechiae or submucous leiomyomata, which cannot readily be detected even by a carefully taken history and a pelvic examination.

The side effects of the agents that have been used to close the fallopian tubes relate principally to the ease with which their transit through the tube to the peritoneal cavity can be controlled, and to their local toxicity. It is difficult to control strong acids and bases or strong

oxidizing and reducing agents, regardless of the manner in which formulation is attempted. Even when release rates are slow, the action of these generally highly corrosive ions is so intense that their spill into the peritoneal cavity produces serious sequelae.

The only two chemical agents for tubal closure that have been tested clinically and that appear to have minimal side effects are quinacrine and MCA. Both have been applied in a variety of settings, both produce roughly comparable closure rates, and both appear to be candidates, with modifications in the delivery system or the ability to monitor tubal penetration, for a clinically useful outpatient-based sterilization technique for women. The delivery systems appear to be relatively simple and easy to use. The efficacy must be increased in order to have the greatest utility without requiring multiple applications, and a substantial number of women must be followed for a significant period of time to determine that there are no long-term sequelae with these systems. If these goals can be met, it is probable that tubal blockade can be accomplished using a safe, rapid, and relatively inexpensive outpatient procedure.

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