RECENT DEVELOPMENTS IN TECHNOLOGY
FOR THE CONTROL OF FEMALE FERTILITY

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Epidemiology of new fertility control methods

During the past two decades there have been rapid shifts in the pattern of usage of the various means of fertility control. The accelerating tempo of this change in recent years has resulted mainly from the confluence of two factors: the adaptation and development of new means of fertility control, and the rapid expansion of family planning programs, principally in developing countries.

The introduction of steroidal oral contraceptives in the sixties was of paramount importance, but the rediscovery and improvement of intrauterine contraception was also significant.

Lately, the greater reliance on surgical methods, particularly sterilization and abortion, to control fertility has been notable. As the means for performing outpatient female sterilization under local anesthesia became available the use of this modality increased markedly (1,2). (Estimated world usage of means of fertility control is shown in Table I.)

Female Sterilization

A number of circumstances have contributed to the increased use of sterilization—particularly female sterilization—as a means of fertility control around the world (1-4): recognition
that the demand for female sterilization is intense; some liberalization of policy constraints on availability of these services; increased efforts to provide female sterilization services; and important refinements in sterilization technology, making it practical in many settings where it had not previously been successful (5).

It appears that willingness to accept female sterilization far exceeds the ability of many countries to provide such services. Therefore, the principal objective of much recent research has been directed toward developing methods which serve to simplify and, consequently, increase their availability (6,7). In the past, the requirement restricting performance of the procedures to hospital-based skilled medical practitioners, including surgeons and anesthetists, has limited the use of this means of fertility control to a fraction of the target population in many countries.

**Laparotomy, Minilaparotomy, and Colpotomy**

The traditional techniques of laparotomy for surgical sterilization have been simplified, making them more acceptable, since they now require only a local anesthetic and a small suprapubic incision. Although there has been general agreement for some time on the use of local anesthesia for sterilization via laparotomy immediately postpartum, it was not until 1965 and 1969 that the
first descriptions approximating the current minilaparotomy appeared (8,9). Recent modifications, particularly those by Vitoon, are responsible for the current success of this procedure (10). Brenner and Dingfelder have delineated its key elements: the use of local anesthesia with short recovery time, low morbidity, and no overnight hospitalization (11). A combination of surgical techniques includes: the vaginal placement of an instrument to allow uterine elevation for facilitating access to the uterine tubes in the incision; visualization, manipulation, and occlusion of the tubes by means of suitable instruments (proctoscope, specula, etc.) to gain adequate exposure; and lifting and manipulating the uterine tube with instrumentation such as the tubal hook. While some surgeons prefer to use their finger to manipulate the tube before carrying out a sterilization procedure such as a modified Pomeroy, others employ a Falope ring or Hulka-Clemmens clip which may be applied without lifting the uterine tube into the incision (11).

Certain details of technique are worthy of particular emphasis: the patient's bladder must be emptied before surgery; the mobility of the uterus must be established; maximum safe doses of local anesthetic must not be exceeded; incision into or trauma to adjacent organs such as bladder, uterus, or bowel must be immediately diagnosed and repaired. If the patient's comfort
is to be assured, she should be given pre-operative sedation, and the practitioner must be careful to apply local anesthesia into every tissue plane and in the tube, and to carry out all manipulations with gentleness (11-13).

The study of a number of small series of operations suggests that complication rates and the nature of complications are of the same order of magnitude as alternative procedures (10-17). Pregnancy rates appear to be comparable to other sterilization techniques and one would expect them to be related to the type of occlusion rather than the approach to the tube.

The largest data set reflecting complication rates has resulted from the series of multi-center sterilization studies sponsored by the International Fertility Research Program (IFRP). Available information is based on pooled data from 2820 cases of minilaparotomy carried out in a variety of settings employing a number of variations of the technique (2). Minor surgical difficulties were encountered in approximately 10 percent of the procedures. No procedure was a complete failure and in just five cases was it possible to occlude only one tube. Surgical complications were reported for 1.6 percent of the cases, including eight cases (0.3%) of bowel/bladder injury and seven cases (0.2%) of uterine perforation. These rates are higher than the rates
reported for these complications in an earlier analysis of IFRP laparoscopy studies (18). The rate of bleeding of the tubes (0.9%) was similar to that among laparoscopy patients.

Thus, minilap is not without potentially serious complications. However, such complications are more likely to be recognized during minilap procedures than during laparoscopic procedures and can generally be repaired surgically through the minilap incision. Five percent of the patients experienced early postoperative complications, primarily fever and/or wound infection. These rates are higher than comparable rates (1.4%) among IFRP laparoscopy patients (18).

The limited experience available with minilaparotomy suggests that use of local anesthetic is not suitable for all patients, particularly obese women (14). Whether local or general anesthetics are used depends on the technique of tubal occlusion used, and on the preferences of individual surgeons. Future development of this rather new technique can be expected to result in further refinement of anesthetic techniques and surgical equipment to provide surgical exposure, uterine elevation, tubal manipulation, and tubal closure.

Interval sterilization by posterior colpotomy, when performed with spinal, epidural, or local anesthetics, is a relatively
simple technique for female sterilization (19,20). There is, however, evidence that rates of infection are higher (20,21) and, therefore, the need for medical after-care is greater. While often an easy operation in skilled hands, it may be technically difficult, depending on the obesity of the patient and the position of her uterus, especially if pelvic relaxation is not present. Although some improvements in surgical techniques and instrumentation seem possible, the expertise needed to carry out this procedure suggests it may eventually be superseded by other methods.

**Endoscopic Sterilization Techniques**

**Laparoscopy**

Although it requires complex and expensive equipment, laparoscopic sterilization offers important advantages: it can often be done on an outpatient basis with local anesthetic; it causes minimal abdominal scarring; and, compared to other endoscopic sterilization procedures, it seems relatively easy to learn.

Recent reviews have described its use mainly in sophisticated medical settings (22-25). Even so, current techniques have been associated with significant morbidity (23,26,27). Among the most serious complications are those relating to the use of general anesthetic and thermal damage to internal organs following
tubal electrocoagulation. Methods which eliminate the need for using general anesthesia and cautery have been developed. Considerable experience with the application of spring-loaded clips and tubal rings through single-puncture laparoscopes and using local anesthetic has demonstrated that tubal clips or rings are not effective unless continuing pressure allows them to adapt to tubal changes with resulting tissue necrosis (28-30).

A recent international study of 8500 cases of laparoscopic sterilization using clip, cautery and ring as the means of tubal closure revealed the following complications. In 0.4 percent of the cases the surgeon was unable to carry out the planned procedure. Laparotomy was required in five cases (0.1%) because of bleeding of the tube and/or mesosalpinx or because of bowel injury or suspected bowel injury. Bowel injuries occurred in five of the procedures (0.1% of electrocoagulation cases); in four of these surgical treatment was required. There was one death due to an explosion of the nitrous oxide gas used in insufflation. Bleeding of the tube and/or mesosalpinx was reported for a higher proportion of electrocoagulation (1.0%) and tubal ring (1.2%) patients than for spring-loaded clip (0.2%) patients. If treatment was required, the tube was generally re-cauterized in electrocoagulation cases, and in the tubal ring cases an additional tubal ring was applied (18).
The 12-month pregnancy rate (per 100 woman-years use) was 2.1 for clip patients, and 0.2 and 0.3 for cautery and ring patients (31). A recent follow-up of 902 patients using the tubal ring revealed an unexplained pregnancy rate of 0.3 and an additional 0.6 pregnancy rate from occluding only a single tube. This same study revealed a 2.5 percent rate of tubal transactions following ring application and a low incidence of other minor complications including postoperative pain (32). To minimize risks of tubal transection as the Fallopian tube is drawn into the inner cylinder of the tubal ring applicator, the instrument should be moved toward the mesosalpinx to minimize tension on the tube. In addition to using these mechanical means of occluding the tube, the hazards of sterilization by laparoscopic electro-agulation may be reduced through the use of bipolar electrocoagulation units to replace the present unipolar equipment (33). Results from studies of this approach are not yet available.

Perhaps the greatest drawback to the use of laparoscopic sterilization is that complex, delicate, and expensive equipment hinders extension of this method, particularly in developing countries (25).

Current research is focusing on further improvements of clip and ring blocking devices and is exploring the degree of reversibility of these devices. In initial studies, a needlescope
which would allow tubal cautery through two, minute puncture wounds seems promising and may eventually prove practical (34). Most urgently needed to extend the use of laparoscopic sterilization is simplified equipment which is low in cost, rugged, uncomplicated, and easy to repair and maintain.

Culdoscopy

Although it is probably more difficult technically than laparoscopy, culdoscopy usually requires only local anesthesia, eliminates the need for gas insufflation, and dispenses with tubal cautery (35-37). Tubal clips can be used to replace traditional ligation.

Transcervical Approaches to Female Sterilization

Recent advances in hysteroscopy techniques and instrumentation have renewed interest in the transcervical approach to the uterotubal junction and the Fallopian tubes. A review of the older literature describing this method in humans reveals a variable, but high, incidence of subsequent ectopic and intrauterine pregnancies (reflecting the excellent regenerative power of the uterotubal junction) and high complication rates, including intraperitoneal trauma, hemorrhage, and infection (38-41). In spite of the work of the past few years, utilizing controlled temperatures and time durations of cautery under direct vision,
there have not been significant improvements in hysteroscopic sterilization (42-43). Consequently, research interests in the transcervical approaches have shifted to work on chemical and mechanical blocking methods.

Although the possibility of nonsurgical sterilization, or at least methods that avoid the necessity to enter the peritoneum, is appealing, considerable advances are still needed if it is to become a useful method. Richart, et al. (44), infused scarifying and necrosing agents, such as zinc, chloride, phenol, silver nitrate, salicylic acid, strong acids and bases, atabrine, sodium morrhuate, and cyanoacrylate esters, by intubation of the Fallopian tubes. Of significance was the observation that the Fallopian tubes have a remarkable ability to regenerate, suggesting perhaps, that a sustained release of an epitheliotoxic substance might be required to produce permanent blockage and that such blockage is difficult to achieve (44-45). Even so, chemicals, such as silver nitrate and methyl-2-cyanoacrylate (MCA), have been identified which would probably cause reliable and permanent tubal fibrosis if they could be delivered to and confined to the tubes (46-49).

With most drugs, preventing tubal spillage is essential since substances which produce tubal trauma of a degree likely to
cause sterilization may also cause problems in the peritoneum. Quinacrine is a possible exception, but multiple applications are necessary (47, 50-53).

In 1975, Zipper reported on studies involving transcervical instillation of quinacrine into the fallopian tubes of 800 women. Five different dosages or combinations of quinacrine with other pharmacological agents were studied. Considering all instillations, tubal occlusion was observed in 437 (68.4%) of the 638 women who had post-instillation insufflation to determine tubal potency. The most effective combination for occluding the tubes was quinacrine plus xylocaine with or without epinephrine instilled in two successive cycles of the menstrual cycle. This combination of chemicals yielded a 94 percent tubal obstruction rate after two instillations. In the entire series, two patients experienced excitation of the central nervous system and were treated with barbiturates given intravenously. Sixteen other women experienced minor complications (50).

Using a catheter filled with paraffin oil as a "push-transport medium," Lindemann and John injected 0.05 ml MCA monomer into 50 women via hysteroscopy. They suggested that carbon dioxide, rather than dextran, should be used as the uterine distention medium because contact with a liquid medium would result in polymerization of the MCA before it reached the tubes (31). The
investigators observed that MCA destroyed 3 to 4 cm of epithelium. It took 5 to 10 seconds to polymerize and no spilling occurred. Of the 16 patients followed up for four to six weeks, nine had bilateral occlusion at four weeks, while four additional patients showed bilateral occlusion at eight weeks. By 1976, Lindemann had instilled MCA into the tubes of 150 women. Bilateral tubal occlusion was achieved after 14 weeks in those cases where the solution was easily injected into the tubes without reflux into the uterus (31). Because tubal occlusion may take eight or more weeks to occur following treatment, patients must continue other contraceptives until occlusion is ascertained (48,54).

A promising blind transcervical delivery system for MCA has been developed by Richart in cooperation with Medical Concepts; it delivers a measured bolus of MCA at each uterotubal junction while most of the uterine cavity is occluded with a balloon. Then, further inflation of the balloon pumps the measured dose into the fallopian tube (55).

Animal experiments with gelatin-resorcinol-formaldehyde (GRF), a biodegradable tissue adhesive, reveal that it may prove effective in blocking the Fallopian tubes in humans. Resorcinol promotes adhesive strength and prevents immediate breakdown, while formaldehyde acts to solidify the gelatin-resorcinol solution and to promote adhesion between the glue and tissue.
Toxicity studies show that lesions form at the site of contact between GRF and various organs. Therefore, like MCA, it must be confined to the tubes to prevent injury to other structures (49).

Transcervically applied tubal plugs are unlikely to succeed unless connective tissue ingrowth and total blockage is achieved (56); the lengthy silicone rubber plugs (silastic) used by Erb may be an exception (57). Erb found a means of preventing intraperitoneal spillage by mixing one percent stannous octoate with 80 parts medical elastomer (S-382) and 20 parts 360 medical fluid. Stannous octoate, a catalyst, transforms the viscous silastic liquid to a rubbery solid in about four minutes. Tests in animals have shown that while the silastic plug conforms to the tubal lumen and resists deformation and expulsion, its high tensile strength permits removal by pulling it out of the tube (57-59). However, because the human Fallopian tube is more tortuous, removal may be more difficult if not impossible. To date, Erb has conducted only animal experiments.

One solid plug which has received clinical trials is a silastic device with a nylon thread core designed by Steptoe and intended for insertion into the ampulla of the tube via the fimbria. The plug is available in either 4 or 6 cm lengths, is 1 mm in diameter, and has 1.5 mm protuberances located at 1 cm...
intervals. Tantalum clips are applied between the protuberances to hold the device in place. Steptoe has described a quick, 15-minute laparoscopic approach for inserting the device. The major disadvantages of this approach are the need for a great deal of instrumentation (a special trocar and cannula to introduce the device and a special clip applicator with its own trocar and cannula) and for three punctures in the abdomen to insert these instruments. The silastic device has been placed in over 40 women. The longest period of observation has been three years. Tubal occlusion is potentially reversible by removal of the device from the tube with a grasping forceps. To date, no attempts have been made to reverse the procedure (60).

Sugimoto has developed a silastic intratubal device that he inserts hysteroscopically. The device is 1.2 mm in diameter, 10 mm in length, and is notched every 1.5 mm to prevent expulsion from the tubal ostium. To date insertions have been made only in patients who will undergo subsequent hysterectomy (61).

Experiments are just beginning on a polyethylene plug which is inserted into the tube at the uterotubal junction. The plug is 10 mm long and 1 mm in diameter. Projecting from its base are spines made of eligiloy (a bio-compatible metal) which penetrate the myometrium and fix the device in place. The plug is placed
in the tubal lumen with a stainless steel inserter with a 37° angled flexible tip that fits through the operating channel of a specially-designed hysteroscope. Hosseinian has tested the plug in baboons. Although reversibility has not been tested, investigators indicate that teeth on the end of the inserter can be used to grasp the base of the device and remove it from the tube (62).

Surgical or chemical ablation of the endometrium is a possible approach to sterilization by causing "end organ failure". Because the depth of tissue damage can be precisely controlled with freezing, cryosurgery is the most promising approach to endometrial ablation (63-65).

Drogemueller has recently modified this approach to freeze only the utero-tubal junction. Work in baboons using two rapid freeze cycles suggests that a highly effective tubal blockage is possible. Preliminary studies have been initiated in humans (66).

Systemic, Nonsurgical Female Sterilization

The most intriguing approach to female sterilization is the development of a pharmacologic and/or immunologic, permanent or semi-permanent method of sterilization. An easily administered
drug with specific toxicity to the germinal elements of the ovary would be desirable and could completely eliminate the need for surgical programs for female sterilization.

Immunologic approaches to sterilization are attractive because the woman could, theoretically, be immunized against a unique tissue antigen occurring only in embryonic or placental tissues, e.g., embryonin or trophoblast, or in semen, e.g., sperm cell antigens. Each pregnancy, or each intercourse in the case of anti-semen immunizations, could then act as a booster dose serving to keep antibody titers high (67-70). The success of such studies is hindered by the lack of a suitable adjuvant for use in humans to achieve high antibody titers and also by the difficulties in isolating both specific antigens and antigens that are unique to non-maternal tissues so that cross-reaction and difficulties with auto-immunity do not develop (69,71). Hulka has shown that local cervical secretion of anti-sperm antibodies can be induced. The initial bovine studies suggest that some decrease in fertility is possible with this approach (72).

Another theoretical approach being studied by a number of investigators involves immunization against hormones, preferably only those associated with pregnancy, such as human chorionic
gonadotropin (70,73-74). Talwar has described active immunization by injection of subunit fragments of HCG linked to tetanus toxoid causing antibody response to HCG and temporary sterility (75). Research on this approach would require determination of antibody specificity, tissue damage, immune complex disease, duration of response, reversibility, and individual variations in response (75-77).

**Reversible Techniques of Female Sterilization**

Garcia has reviewed the success of attempts to re-establish tubal patency and achieve pregnancy in women who had previously undergone tubectomy when no attempts were made to enhance reversibility at the time of the procedure (78). As might be expected, the removal or destruction of large segments of the oviduct and the presence of adhesions decrease the success of reversing operations. Although not fully proven, increasingly surgeons feel that microsurgical techniques improve the likelihood of success (79-80).

Numerous surgical techniques have been proposed for temporary female sterilization. Those which involve burying the tube or covering the tube with silastic caps have resulted in blurring of the delicate fimbrial anatomy and the frequent formation of adhesions. Burying the ovary beneath the peritoneum has not
proven successful because of adhesion formation and herniation of the ovary through the peritoneum. Covering the ovary with a silastic sheet, "ovariotexy", may enhance the success of this procedure (81-82).

Meeker has suggested ligation around a notched intratubal plug (83). Preliminary studies in baboons and rabbits are promising with respect to effectiveness and reversibility. The silicone rubber plugs developed by Erb are designed to allow their removal transcervically (58). There seem to be considerable species differences in tolerance of oviduct plugs; Hulka's experience with pigs was unsatisfactory since displacement, adhesions, and infection were frequent (28).

The relatively short segment of tissue necrosis resulting from some clips may enhance reversibility potential, but the minimal experience available suggests that more than a simple removal of the clips will be necessary. All of these procedures require extensive clinical evaluation, including assessment of the potential for ectopic pregnancies.
Termination of Pregnancy

Pregnancy Testing

Because of their inherent low sensitivity, standard immunologic pregnancy tests are of little assistance in establishing the diagnosis of pregnancy within two weeks of a missed menstrual period. For example, evaluation of the Pregnosticon Dri-Dot test, a commercially available rapid immunologic slide test designed to detect 1.5 IU hCG/ml, revealed a false negative rate over 80 percent at less than 35 days from the last menstrual period (LMP), which declined to less than 5 percent at 45 days or more from LMP (84). Such inaccuracy in the very earliest stages of pregnancy severely limits the usefulness of standard pregnancy tests with respect to selection of patients for menstrual regulation; when these tests are used, as many as 25 to 50 percent of women with delayed menses have subsequently been found not to have been pregnant on the basis of histologic examination of the aspirate (85).

Radioimmunoassays (RIAs) and radioreceptor assays (RRAs) are presently available which are both sensitive and specific enough to meet rigid diagnostic criteria. Unfortunately, these tests are not always available, and where they are, the tests are expensive and require 24 to 36 hours to complete. Kosasa et al.
(86) have described a two-hour version of the RIA specific for the beta subunit of human chorionic gonadotropin (hCG). Of interest was the fact that, among 51 women with positive tests at the time of a missed menses, all of whom simultaneously underwent MR, the endometrial aspirate showed no histologic evidence of pregnancy in four cases. On follow-up, however, each of these women was shown to be pregnant, including one who had an ectopic pregnancy.

Of more practical interest, Landesman and Saxena (87) have reported the results of a one-hour RRA in over 1000 subjects. In their hands, this test has been 100 percent accurate in detecting pregnancy at the time of a missed menstrual period. This test has just become available commercially in kit form from Wampole Laboratories under the tradename "Biocept G", Princeton, New Jersey.

A disadvantage of the pregnancy tests which have been available until very recently is the increasing complexity of the test corresponding to its increasing sensitivity. Recently, however, Lau and others have described a simple capillary tube pregnancy test having a sensitivity of 0.5 IU of hCG/ml. Since this test requires no refrigeration of test reagents, which is ordinarily required in most other test systems, it may prove to be applicable under field conditions in lesser developed areas of the
Cervical Dilatation

Although first trimester abortion by dilatation and evacuation (D&E) has relatively low immediate and delayed complication rates, some authors have suggested that mechanical dilatation may injure the cervix and predispose to subsequent incompetence.

Zwahr (91) performed hysterosalpingograms for 58 women undergoing vacuum extraction of their first pregnancy three to six months after cervical dilatation with Hegar dilators. Evidence of cervical damage was observed in 19 of the women. Hulka et al. (90) measured the force required to dilate the cervix at the time of first trimester abortion and showed that Hegar dilators required significantly more pressure than Pratt dilators. These authors also found that maximum resistance occurred at 9 mm and concluded that dilatation beyond 8 mm may represent tearing of the internal os rather than true dilation.

Various authors have recommended use of Karman cannulae, no larger than 6 mm, for pregnancy interruption of up to nine weeks to prevent cervical injury, and have reported satisfactory completion rates in comparison to standard techniques utilizing larger, rigid cannulae (91-92).
Liu and Hudson reported an incidence of cervical tears of 0.4 percent among 2045 Karman aspiration abortions as compared with 1.1 percent by standard curettage technique (93). A comparative study of flexible versus rigid metal cannulae suggests that these differences reflect variations in true cervical dilation rather than any effect resulting from the use of a flexible cannula per se (94). When equal degrees of cervical dilation were used, no significant differences in complication rates were associated with both types of cannulae.

Alternative methods of cervical dilation, using laminaria tents (95) or prostaglandin suppositories prior to mechanical dilatation (96) have been reported to be successful in reducing cervical resistance to mechanical dilation. However, side effects associated with laminaria (painful insertion) or prostaglandin suppositories (vomiting and diarrhea) were frequent. Pharmacologically induced dilatation of the cervix has also been reported following intracervical injections of 16,16 dimethyl PGE₂ P-benzaldehyde semicarbazone ester. When given three to four hours prior to vacuum aspiration in 120 patients in the 6th to 12th menstrual week of gestation, 75 percent of patients were able to undergo vacuum aspiration without requiring additional mechanical dilatation (97).
In cases where cervical dilation is difficult, such as primagravid women at seven weeks' duration or less, the use of "microdilators" of $\frac{1}{4}$, 1, $1\frac{1}{2}$, and 2 mm in diameter have been found to be particularly useful for initiating the process of dilatation (95). The Battelle Memorial Institute has recently developed a new mechanical dilation which is designed to prohibit overly forceful dilatation of the cervix, but there are as yet no published data regarding this instrument (98).

**Menstrual Regulation**

By definition, menstrual regulation (MR) is a procedure used to terminate a suspected pregnancy no later than 14 days after the expected onset of a menstrual period (99). It is also referred to as endometrial aspiration, menstrual extraction, menstrual induction, or miniabortion. The procedure can be performed either surgically or pharmacologically.

At present MR finds widest application in the evacuation of the uterine contents by vacuum aspiration through a 4 to 6 mm diameter cannula. The use of paracervical or intracervical anesthesia with 1% lidocaine has been shown to be particularly effective in reducing the degree of pain reported by nulliparous women (100). Little information has appeared in the literature of the past two years regarding improvements in the surgical
technique of MR. Miller, et al. have suggested a model to minimize unnecessary procedures on non-pregnant women (101).

On the other hand, pharmacologic methods of early pregnancy termination have received continued attention in the hope of improving upon initial trials which had indicated a relatively high degree of effectiveness, but also high rates of distressing side effects, notably pain (102). Intrauterine instillation of 5 mg PGF$\text{$_2$}_a$ is as effective in interruption of pregnancy as the vacuum aspiration method, but is accompanied by significantly higher rates of nausea, vomiting and diarrhea (30 vs. 9%) and prolonged bleeding (103). Another PGF$\text{$_2$}_a$ analogue, ICI81008, instilled into the uterus in doses of 100 to 400 µg is associated with unacceptably high failure rates and rates of incomplete procedures (104).

Early studies of the vaginal administration of PGF$\text{$_2$}_a$ have shown it to be less effective than vacuum aspiration and associated with higher failure rates. However, more recent investigations have focused on vaginal administration of 15(S)-15-methyl PGF$\text{$_2$}_a$ methyl ester contained in triglyceride or silicone rubber suppositories. This analogue has demonstrated an increased myometrial stimulating potency and lower gastrointestinal side effects when compared to vaginal administration of PGF$\text{$_2$}_a$ or
PGE$_2$ (105). A number of preliminary studies indicate that 15 methyl PGF$_{2a}$ ME, when administered in suppository form, has effectiveness rates varying from 66.5 to 100 percent, depending upon the amount of drug and the type of suppository (106-108).

Some practitioners have used hormonal injections in the hope of interrupting early pregnancy after nidation is established. However, evaluation of an intramuscular estrogen/progesterone combination was found to be ineffectual as a method of MR based on a controlled random allocation study (109).

**First Trimester Methods**

Vacuum aspiration remains the preferred method of abortion in the first trimester. Although vaginal or intrauterine administration of prostaglandin may be effective in inducing abortion at this early stage of pregnancy, the side effects are frequent and thus offer no advantage over the suction method at this time. For example, Ragab and Edelman (103) compared intrauterine administration of PGF$_{2a}$ with vacuum aspiration in 200 women in the fifth to eighth week of pregnancy. Although the efficacy and rates of incomplete abortion and intrauterine infection were not significantly different between the two groups, vacuum aspiration was superior in terms of time in the hospital, duration of bleeding and frequency of side effects.
Innovations in first trimester abortion techniques have addressed the need for analgesia in conjunction with vacuum aspiration. Shapiro and Cohen (110) studied a group of subjects all of whom received paracervical block prior to vacuum aspiration. The following supplemental treatments were then administered: 1) no further analgesia; 2) self-administered methoxyflurane; or 3) stereophonic music through headphones. They reported that the control and methoxyflurane patients appeared subjectively to experience the same incidence of painful procedures, whereas patients using the headphones had less than half the incidence of painful procedures of the other two groups.

The advantages and disadvantages of prophylactic antibiotics for first trimester abortion have frequently been debated. Hodgson et al. (111) evaluated the use of oral tetracycline hydrochloride 1.5 gm preceding vacuum extraction followed by 500 mg every six hours for four days among two groups of 1000 women compared to two similar non-treated groups undergoing vacuum extraction. Febrile complication rates for the antibiotic treated group combined were 3.2 versus 9.0 percent for the non-treated women. In addition, the antibiotic treated group experienced significantly fewer days of hospitalization in relation to major complications. Based on this study, the prophylactic use of a short course of oral tetracycline can be recommended.
Mid trimester Methods

In the 1970s the intraamniotic instillation of pharmacologic agents has become the most frequently used method of mid trimester abortion in the United States. Hypertonic saline had been the standard agent, but since PGF$_{2a}$ was approved for non-experimental use in 1973, this drug has been widely used. Currently, investigations of hypertonic urea/PGF$_{2a}$ have also been reported and it is the opinion of some that this will be the pharmacologic agent of choice in the future.

Intraamniotic instillation methods are often augmented by intravenous oxytocin and/or intracervical laminaria tents. While constant intravenous infusion of oxytocin beginning six hours after administration of hypertonic saline significantly reduces the abortion time, this combination therapy is associated with higher rates of consumptive coagulopathy and appears to inhibit expulsion of the placenta (112). If stimulation with oxytocin is prolonged, water intoxication may cause a troublesome complication. Use of intracervical laminaria tents for 12 to 16 hours prior to instillation of PGF$_{2a}$ shortens the induction-to-abortion time more than does placement of laminaria at the time of PGF$_{2a}$ administration (113). Although the use of laminaria probably decreases the incidence of uterine injury associated with mid trimester abortion by prostaglandin, cervico-vaginal fistulas have occurred with laminaria tents in place (114).
In situations where intraamniotic injection is not possible, such as small uterine size or rupture of membranes, intramuscular or intravaginal administration of prostaglandin has been found useful. However, intramuscular injection of the natural prostaglandins is unacceptably painful and the 15 methyl analogues require multiple injections to be effective, thus limiting their usefulness (114). Vaginal suppositories of PGE$_2$ or PGF$_{2a}$ methyl ester have also been found to be effective, but do require multiple administration (115). Experimental use of a silicone rubber disk impregnated with 15(S) 15 methyl PGF$_{2a}$ methyl ester is most promising in that only one insertion is necessary; the device and thus exposure to the drug can be removed in the case of complications or side effects (116).

Comparative studies between unaugmented intraamniotic instillation of PGF$_{2a}$ and hypertonic saline have been conducted by the IFRP, based on random allocation of subjects who receive 20 percent sodium chloride, a single 50 mg dose of PGF$_{2a}$, or a multiple injection 25 mg PGF$_{2a}$ regimen (117). The multiple dose prostaglandin schedule resulted in the shortest instillation-to-abortion time, while the saline injection group had the longest mean abortion time. Although the overall rates of major complications were not significantly different for the three groups, hemorrhaging, fever, and infections were more frequent with the
saline method, while cervico-uterine injuries were more frequent with the prostaglandin methods.

Recent reports from the Center for Disease Control comparing PGF$_{2a}$ and saline (with oxytocin augmentation in an unknown percentage of cases) have pointed to higher total complication rates, major complication rates, operative intervention rates and hospital readmission rates with the intraamniotic PGF$_{2a}$ method (118). In addition, review of six deaths associated with the use of PGF$_{2a}$ reported to the Center for Disease Control between 1972 and 1975 led Cates, et al., to conclude that the relative safety of intraamniotic PGF$_{2a}$ as a midtrimester abortifacient, compared to saline, remains to be established (119). Additional, as yet unpublished, reports from the Center for Disease Control suggest that dilatation and evacuation of up to 20 weeks' gestation is associated with lower rates of major or total complications, hemorrhage, suspected infection, retained products and minor operative intervention for completing the abortion than the hypertonic saline method at comparable lengths of gestation (118). At present, however, fewer clinicians are intentionally attempting abortion by D&E after 16 weeks' gestation, and even though this preliminary report may find confirmation in the hands of other workers, it is questionable whether this practice will become widespread since it involves morcellation of a recognizable fetus.
Long-term Effects (Sequelae of Legal Abortion)

The protective effects of legal abortion on maternal mortality, and the incidence of early medical postabortal complications have been well documented and reviewed (120-121). Of current concern is the possible adverse long-term effect on future reproductive functions, including increased risk of premature midtrimester abortion, prematurity (by birthweight), and neonatal mortality (121). These concerns are not universally accepted. Some investigators (122-123) have questioned the validity of results based on retrospective reporting of prior induced abortions because of the phenomenon of selective recall, i.e., the increased tendency for a woman to admit to a previous abortion if she has subsequently experienced an abnormal pregnancy than if she has had a normal birth after an abortion. A number of multi-center prospective studies currently being carried out are designed to provide more reliable information on this question.
Steroidal Contraception

Steroidal contraceptives are the only widespread means of fertility control based on systemic administration of drugs. Because the regimen is simple and not directly related to sexual activity, oral contraception has proven extremely popular in all societies where it is available. Fears of side effects appear to have slightly diminished usage in the United States. However, in developing countries an increasing number of women are relying on this method. With an estimated 55 million now taking these drugs, oral contraception has become the most important single means of reversible fertility control (124). Recent advances in steroidal contraception relate to new formulations, means of administration, and increased knowledge of physiological effects. Of greatest significance has been the reduction in dosage in both the estrogen and the progestogen.

Mackay et al. estimate that a preparation containing 30 micrograms of Ethinyl estradiol and 150 micrograms of D-Norgestrel or its equivalent, represents the lowest practical dosage, and that if this is further reduced, malabsorption or irregular ingestion of tablets may result in lower contraceptive effectiveness (125). Some data also suggest that the low dose
preparations are associated with an increased incidence of breakthrough bleeding. Additional data on the effects of the various progestins and estrogens contained in all contraceptives and on the differences among oral contraceptive preparations are now available. Some studies have shown equivalence between mestranol and ethinyl estradiol with respect to endometrial action, ovulation inhibition, suppression of plasma gonadotropins and synthesis of cortisone binding globulin by the liver in humans (126). Various progestins have been demonstrated to have differential specificity in terms of binding to progesterone receptors (125).

A recent study comparing symptoms associated with the use of three oral contraceptives using double blind crossover methodology has revealed significant differences among the three preparations (127). Ovral (Norgestrel 0.5 mg and Ethinyl Estradiol 0.05 mg), Norinyl (Norethindrone 1 mg and Mestranol 0.05 mg), and Norlestrin (Norethindrone Acetate 1 mg and Ethinyl Estradiol 0.05 mg). The study revealed decreased breakthrough bleeding for Ovral, compared to the other two preparations, a higher incidence of nausea among Ovral users and a higher incidence of breast discomfort among Norinyl users. Switching from Ovral to Norinyl or Norlestrin resulted in increased intermenstrual breakthrough bleeding. Various side effects of all contraceptives have been attributed to estrogen excess or deficiencies
and progestin excess or deficiencies (128-129). Data collected in the double blind crossover study suggested that it will be difficult to correlate contraceptive side effects with current knowledge of the relative potencies of their chemical components (127-130).

It is now recognized that steroidal contraceptives result in a wide range of metabolic changes (131); however, the clinical significance of many of these changes is uncertain. The best established of the serious complications is thromboembolism. Vessey has lately reviewed the risk of venous thromboembolism and stroke attributed to use of steroidal contraceptives (132). Both retrospective case control studies and prospective studies have revealed the relative risk of thromboembolic disease among users compared to nonusers to be slightly less than two to one up to eleven to one (132-140). He estimates the risk of suffering clinically significant venous thromboembolism to be 100/100,000 per annum and of suffering stroke around 25/100 000 per annum for women using contraceptives containing 50 micrograms of estrogen. The corresponding risk of suffering a fatal episode of either disease, he judges to be perhaps only 1/50th as great, or two per 100,000 and 0.5 per 100,000, respectively (132).

There is some evidence that lower doses of estrogen are associated with a lower incidence of thromboembolic disease (140-
141), but none that are not apparently responsible for some increase in venous thrombosis, pulmonary embolism and other thromboembolic events, ordinarily rare in young women who do not take oral contraceptives.

In a study of non-fatal myocardial infarction, Mann found that the relative risk for women who had been using oral contraceptives in the previous month compared with the risk to women who have never used them was 3.1 to 1, after standardization for possible confounding variables (142). The study revealed a very strong association between smoking and increased risk of myocardial infarction. The relative risk increased from 1.9 to 1 in women smoking fewer than 15 cigarettes a day to 4.4 to 1 in women smoking 15 to 24 cigarettes a day, and 11.9 to 1 in women smoking more than 25 cigarettes a day.

Risk relating to other predisposing factors to thromboembolic disease was synergistic. Risk of myocardial infarction increased from 4 to 1 in women of one factor to 20 to 1 in women with two factors and in 128 to 1 in women with three or more factors. Mann, Ory, and Jain have made estimates of annual incidence of fatal myocardial infarction, after standardizing for the confounding variables such as hyperlipoproteinemia, cigarette smoking, hypertension, etc. Their estimate of annual risk to
women of different ages among women with and without predisposing factors is presented in Table II (142-144). These data suggest that the greater the number of underlying risk factors for coronary disease, the higher the risk of developing the disease regardless of whether the patient was an oral contraceptive user. Smoking was the greatest additional risk factor. Oral contraceptives, in combination with other risk factors, appear to provide an additional risk. Among young women, and in the absence of other risk factors, oral contraceptive users may have little significantly increased risk of myocardial infarction. Ory estimates 70 percent of premenopausal women are free of conditions which predispose to myocardial infarction (144).

Analysis of any association between neoplasia and oral contraceptive use has shown a reduced occurrence of benign breast tumors, and several relatively short term studies have shown no increase in the incidence of breast cancer (145-150). Some reports support the conclusion that risk of genital cancer and abnormal cervical cytology among women taking oral contraceptives is not greater than among users of other non-barrier methods (150-152). In Western Europe and Scandinavia oral contraceptives containing progestone magestrol acetate have been withdrawn because they cause breast cancer in beagles after a long term of high dosage. These preparations have never been available in the
United States. The relevance of these studies to humans is unknown. Among animals, primates receiving compounds used in steroidal contraceptives seem resistant to developing breast cancers.

A study of endometrial cancer occurring among women who happened to be taking oral contraceptives shows a preponderance of users of sequential oral contraceptive preparations among them (153). The methodology of this study is such that no causal relationship between the sequential oral contraceptives and the cancers was demonstrated. In February 1976 the United States Food and Drug Administration (FDA) banned sequential oral contraceptives from sale in this country. Other factors in the FDA decision were higher potential risks for thromboembolic disease, since the sequentials contain more estrogen than other oral contraceptives, and a higher failure rate. Sequential oral contraceptives made up only about 10 percent of the United States market at the time of their removal.

Over the last several years there have been a number of reports linking the pill with an increase in benign hepatomas. The role of oral contraceptives remains unproven in this regard, but the relationship seems increasingly evident. Both prolonged use and possibly type of estrogen (Mestranol more than Ethinyl Estradiol) may be related factors. There is no substantial
evidence to link the few malignant cases reported to oral contraception (154-158).

Many aspects of the relationship between the oral contraceptives and nutrition are under investigation (159-160). The clinical significance of most of the many physiological changes resulting remains obscure; perhaps the most important of these are a decreased incidence of iron deficiency anemia, because of decrease in total menstrual blood loss, and a possible relationship between Vitamin B-6 deficiency and symptoms of depression (161-164).

There is also evidence of more hypertension (165-169), surgical gall bladder disease (137), and a decrease in glucose tolerance (169), as well as the suggestive finding of greater susceptibility to infections. In one study, an increase in the incidence of significant bacteriuria was found among oral contraceptive users, (2.4% of users versus 1.6% of non-users) (125). Recent studies indicate that if there is any relationship between fetal malformation and ingestion of oral contraceptive steroids during or immediately preceding pregnancy, it is of an extremely low order (170-172). Initial concern raised by the Oxford Family Planning Association Study that a higher proportion of nulliparous pill users may experience infertility than users of other
means of fertility control appears to be laid to rest—at 42 months discontinuation, fertility rates were identical (173-174). For a few women post pill amenorrhea, sometimes associated with galactorrhea, may be a problem (175).

Although considerable concern about the risks of oral contraceptives remains, studies by Tietze et al. (176) and Potts et al. (131, 177) reveal a satisfactory risk ratio compared to other means of fertility control, in the absence of conditions predisposing to increased risk of thromboembolic disease. When these conditions are present, women over the age of 35 should consider other means of fertility control, and all women on oral contraceptives ought to be advised to give up smoking.

Considerable work is going forward seeking other long-acting pharmacologic agents to control fertility. Perhaps the most advanced of these involve new ways of delivering contraceptive steroids (178). Other approaches, such as anti-gonadotropins, inhibition of releasing factors, are still in the early stages of research (179-180). Mishell has recently reviewed the large body of research on a long acting steroidal agent or delivery system for the regulation of fertility (178).

A number of long-acting injectable formulations are presently used in many countries. The progestins—depomedroxyprogesterone
acetate (DMPA) 150 mg and norethindrone enanthate (NET-ENT) 200 mg are given at three-month intervals. DMPA may also be given in a dosage of 300 mg at six-month intervals. The efficacy of Depo Medroxyprogesterone acetate (DMPA, Depo provera) is well established (181). Clinical trials using 200 mgs of NET-ENT injected every three months showed the unacceptably high pregnancy rate of over three pregnancies per 100 woman-years of use, compared to 0.7 for DMPA. It appears that giving NET-ENT at a two-month interval may be necessary.

Other methods of long-term administration of steroids under investigation include the insertion of one or more polysiloxane capsules containing steroids just beneath the skin and the use of polysiloxane intravaginal rings containing various progestins (178).
Locally Active Methods

In the past few years there has been renewed interest in barrier and spermicide means of fertility control (182-183). The circumstances leading to this increased utilization include: product improvement (more attractive and handier dispensers for vaginal foams); growing provision of non-clinical family planning services through retail outlets, community and household delivery systems, vending machines, etc.; concern over the safety of other medical methods, particularly steroidal contraceptives and IUDs; side effects caused by some other methods of fertility control; need for a method appropriate for those with infrequent sexual exposure; need for a method to increase reliability of other means, such as IUD or condom; easy availability without physical examination, medical procedures or prescriptions; complete safety of the method with respect to side effects; and possible protection against venereal diseases.

Vaginal Foams, Creams, and Jellies

Most modern vaginal chemical contraceptives, sometimes called local contraceptives or spermicides, are made from two components: a relatively inert base material which will physically block sperm, plus active spermicidal agents. The active component of most modern spermicides is based on surface active
agents, which act by disrupting the sperm cell walls, thereby killing sperm cells by producing an osmotic imbalance.

The principal drawback of vaginal spermicides is their relatively high failure rate. Although in most studies the theoretical effectiveness of this method is reasonably good, i.e., below five per 100 woman-years of use, its use effectiveness may be as poor as 35 pregnancies per 100 woman-years of use. There are a number of studies of theoretical effectiveness which give figures of less than two or less than one pregnancy per 100 woman-years of use (182). It would appear that the requirement for use immediately before intercourse on a regular basis has limited the use effectiveness of this method. The National Fertility Survey carried out in the United States in 1970 showed that 31 percent of foam users experienced an unplanned pregnancy during the first 12 months of use, compared to 6 percent of pill users and 8 percent of IUD users (184).

Although the subject of relatively little research activity, there have been some fairly recent changes in these methods. At one time the spermicidal agents in such preparations were possibly hazardous compounds containing mercury and hydroquinines. There was concern that they might be irritating, absorbed systemically, harmful to the fetus, or possibly affect the genetic
material of the sperm cell agents. Accordingly, agents presumed to be safer, based on the surface active principal or surfactants, have been substituted. Other recent advances in these techniques are in methods of application and packaging, particularly the development of single dose tampon-shaped prefilled disposable applicators, and of small foaming tablets by the Eisai Company, called Neosampoon loops, based on a new surface active agent p-methanylphenyl polyoxyethylene (182).

Another delivery technique is the use of a water soluble contraceptive film called the C-Film, with a water-soluble plastic polyvinyl alcohol base and the spermicide Nonoxynol-9. The USV Pharmaceutical Corporation now holds the patent on this product. Some clinical studies with C-Film have resulted in very high pregnancy rates, suggesting that this method will not prove successful in its current form.

Vaginal preparations are evidently useful for venereal disease prophylaxis. In vitro tests show that most of them are active against T-Palidum and N. gonorrhoea. The results of a small-scale clinical trial suggest that women who used a foam vaginal contraceptive preparation (Ortho) had about one fourth the reinfection rate of women using other methods of fertility control during the first six months. Dropout rates and numbers
of patients in this study were such that conclusive results are not available (185).

The Diaphragm and Other Intravaginal Barriers

Wortman has recently provided a comprehensive review of the current status of the diaphragm (183). Until very recently there has been little change in this particular technique. Many studies in the literature show good use-effectiveness rates, although some of the older literature describes failure rates approaching 20 per 100 woman-years of exposure. Two recent analyses by Vessey et al. in 1974 (186) and Lane et al. in 1976 (187) revealed failure rates of fewer than three per 100 woman-years of use. Vessey and Kiggens found a failure rate of 2.4 per 100 woman-years of use.

In recent years flexible plastic caps have been produced. Presumably, this material would not deteriorate in hot climates, nor react with acidic vaginal fluid, and would not be destroyed by oil-based spermicides. The cervical cap appears to be as effective as a diaphragm; however, there is so little data that one can only guess at these results. Sein reports there has been no failure among 300 British and Indian women who were fitted with his flexible plastic cervical cap between 1965 and 1975 (183).
One of the most interesting recent developments in this field is the use of a resilient and liquid absorbent collagen sponge as a vaginal diaphragm (188-189). This sponge can be self-applied into the upper vault of the vagina where it is retained for several days. The high fluid binding capacity of the collagen contributes to the trapping and immobilization of sperm within the sponge. In initial trials, various shapes of cylindrical cups, about 6 cms wide and 2.5 cms thick, have been evaluated for a period of three months in 27 volunteers. Average retention time was seven to nine days. Among the most sexually active the collagen sponge contraceptives were removed every three or four days, rinsed in tap water and then reinserted. Odor was noticed by 4 percent of the users. No cases of irritation, itching, or discharge were reported. Contraceptive efficacy of this method remains to be determined. The research on collagen sponges carried out by Chvapil and his colleagues have been supported by Medicoll, Inc., and The Program for Applied Research in Fertility Regulation, (Agency for International Development).

Other work in this field relates to steroid-loaded intra-vaginal rings. Clinical trials are under way, testing devices which release 1200 micrograms per day of progesterone, 250 micrograms per day of norethisterone, and 20 micrograms per day of D-
norgestrel. These dose levels have been selected in the hope that the progestins will alter cervical mucous to prevent sperm penetration without inhibiting ovulation. The devices release progestins at a reasonably constant rate from a central reservoir covered with a silastic membrane. It is planned to use the same delivery system to deliver spermicides. Release of 15 mg per day of non-oxynol-9, 30 mg per day of urea, and 100 mg per day of quinine are the current target doses (190).

Yet another approach to locally active means of fertility control relates to intracervical devices (190). At this time, the program is focused on perfection of a device which would be retained without side effects in the cervix. Initial studies with a prototype branched cylinder revealed an unacceptably high rate of expulsions and increased bleeding. This mechanism could also be used for release of progestins and spermicides. Work on intra-cervical designs and vaginal rings has been supported by the Expanded Program of Research Development and Research Training in Human Reproduction of the World Health Organization.
**Intrauterine Device (IUD)**

From the first account by Graefenberg (191) in 1930 of the contraceptive effectiveness of his intrauterine contraceptive device (IUD) until Oppenheimer's report in 1959 (192), standard texts in obstetrics and gynecology warned against the use of IUDs. Only after Oppenheimer's reassessment did IUD research again flourish. In 1962 Lippes (193) presented data on the Lippes loop to the first international conference on IUDs, convened by The Population Council. The next year Tietze organized the Cooperative Statistical Program (CSP) for the evaluation of IUDs and by 1970 could provide a final progress report (194) on 10 devices totaling 23,917 first insertions and 469,217 woman-months of use.

In the late sixties, Zipper (195) demonstrated the effectiveness of copper used with IUDs. His work indicates that both the amount and placement of copper on different parts of the T or 7 device can influence both pregnancy and expulsion rates (196).

The copper T and copper 7 show no deterioration in effectiveness through 36 months of use (197) and they have recently been approved by the Food and Drug Administration (FDA) for this period of use. This effectiveness is in spite of decreasing release rates of copper over this time (198). Actually, the
yearly pregnancy rate of these copper devices is almost uniform over the first 36 months of use, whereas pregnancy rates of inert devices tend to decrease over time (199). For this reason, the performance of the Lippes loop is generally superior to these copper devices at the end of two years of use (200). Newer designs of the copper T that have copper cylinders on the horizontal arms of the T show lower pregnancy rates than the Lippes loop, and these rates also decline over time (201).

Scommegna (202) first demonstrated the efficacy of intrauterine release of progesterone. The presently marketed progesterone T device releases 65 µg of progesterone per day for at least one year. Results of trials indicate this device is associated with less total menstrual blood loss, but longer menstrual periods and somewhat increased intermenstrual bleeding. There is evidence that there is less dysmenorrhea with this device, and further studies to confirm this are in progress (203).

The possibility of teratogenic effects of exposure to progesterone in pregnancy failures has been considered and thought to be low or non-existent (204). This matter will have to be reconsidered, however, for other steroids considered for intrauterine release (205-207).
The IUD has become an important method of contraception world-wide in the past decade, but use of this highly effective contraceptive method has lagged behind that of sterilization, oral contraceptives and condoms (208). Compared to the risk of death associated with childbirth, the risk of an IUD use-related death is low and if one considers births averted by use of contraception, the risk benefit ratio of IUD-related deaths to births averted is lower than the corresponding ratios for oral contraceptives or condoms/diaphragms (209). Though the benefits appear high, recent reports of an increased risk of pregnancy-related complications (210-214), a higher risk of pelvic infection (215-217) and a possibly accelerated rate of ectopic pregnancies with extended duration of use among IUD users (218-219) have stimulated reappraisal of the proper role of IUDs.

**Mechanism of Action**

The basic mechanism of action by which IUDs prevent pregnancy is unknown. It is clear from animal studies that it is related to an alteration in uterine secretions, since a fistula between two horns of the rat uterus in which only one horn has an IUD will protect the other horn from pregnancy (220). The many developments in endometrial histology and uterine fluid chemistry have been reviewed elsewhere (221). It has been suggested that an IUD causes the uterine fluid to become metabolically inert and
unfavorable for growth and survival of the preimplantation
blastocyst (222). These uterine fluid changes are not thought to
be related to an effect of the IUD on ovarian function (223).
The principle endometrial changes include a sterile, foreign body
reaction of cellular infiltrates, edema near the IUD, and erosion
and increased permeability of small blood vessels in contact with
it. The cellular response is exaggerated by the presence of
copper (224).

Research on uterine motility, chemical activity and voltage
gradients within the uterus is expected to open new avenues for
IUD improvement. Current studies of electrochemical effects
within the uterus have been undertaken in regard to their influ­
ence on pregnancy and expulsion, particularly as they pertain to
IUDs made totally or in part of metal (225).

The intrauterine potential as measured with either metal or
non-polarizable salt electrodes is positive at the fundal with
respect to the cervical end of the uterus. Placement of dis­
similar metal electrodes within the uterus will induce voltage
gradients that are roughly predictable from their cell potential
in blood as an electrolite. When copper and zinc electrodes are
placed at opposite ends of the uterus, they induce voltage gra­
dients that are typically greater than 100 mv per cm. External
copper and zinc wires connected at one end and with the other
ends in contact with various positions on the skin of rats were found to influence potential gradients within the uterus.

When a length of zinc wire was wound around the upper portion of the stem of a small Cu-7 200 IUD, it took about one year from insertion for the zinc to disappear. When the zinc wire was wound around the lower portion of the stem, it disappeared in one month. The zinc reduced intrauterine corrosion of the copper and it was more effective at reducing copper corrosion when in the lower stem position.

Zinc in the upper stem position decreased pregnancy rates significantly relative to the small Cu-7. When placed in this lower position, a pregnancy rate lower but not significantly lower than the small Cu-7 was noted. The results relative to expulsion were somewhat anomalous. It appears that the presence of zinc may in some way depotentiate the copper inhibition of uterine motility and thus compromise one of the retention mechanisms of this device. This theory is supported by the experience with the small Cu-7-200 in which zinc was placed in the inferior position. In this position, the zinc disappeared by corrosion within month and therefore had little effect on expulsion rates (226).
As with the mechanism of action in preventing pregnancy, the mechanism of action of the IUD relative to bleeding is not clear. It has recently been shown that both inert and copper bearing IUDs are associated with an increase in local fibrinolytic activity (227–229) and that oral administration of agents that inhibit plasminogen activator, such as AMCA and EACA, can reduce menstrual blood loss in women with menorrhagia (230–233). Besides this relationship to increased bleeding among IUD wearers, it has been suggested that this very local fibrinolytic activity may be a factor in the contraceptive action of IUDs by preventing adhesion and implantation of the zygote (233). The effectiveness of postcoital insertion of the copper T may support this explanation of the mechanism of actions of IUDs (234). Other medications, including corticosteroids (235) and prostaglandin antagonists (236) have been suspected of interfering with the mechanism of action of IUDs by decreasing the inflammatory response.

Current IUD Design Research

An overview of results from studies of medicated and non-medicated devices is given in Tables III and IV. Efforts to rationally improve design of inert IUDs or carriers of bioactive IUDs based on past IUD performance patterns have been frustrated by the poor quality of data for large series of many different IUD designs previously tested (237). It is possible to find
specific designs that are exceptional in performance of one criteria, but they are generally poor in another (238). An example is the inverse relationship with pregnancy and direct relationship to removals for pain and bleeding by increasing surface area of IUDs as shown in Figure 1. Metals used with IUDs have provided alternatives to increasing the surface area in order to decrease pregnancy rates. The addition of 200 sq mm of copper to the horizontal arms of the loop has resulted in a near-zero pregnancy rate but a moderate increase in removals for pain and bleeding (239). It should be noted that both the Spring Coil Device (240) (Figure 2) and the Intrauterine Membrane (IUM) (241) (Figure 3) show that surface area per se is important in IUD effectiveness and not merely surface area in contact with the endometrium. The IUM is found to be almost pain-free, but its pregnancy rate is not better than the Lippes loop, although it almost completely covers the endometrium. It also causes more bleeding than the loop in interval cases but, for unknown reasons, not in postabortion cases (242). The lead from animal studies (243) that hydron coating of an IUD may reduce bleeding was disappointing when applied clinically. No improvement in rates of removal for bleeding occurred when the Spring Coil Device (244) and the IUM (245) were hydron coated. The hydron also took up calcium, making these devices hard and even brittle over time.
Other design efforts are in the direction of modifications of standard devices such as the Lippes loop or T shaped devices to reduce their side effects as well as improve their efficacy. The addition of copper (246) and progesterone (247) to the Tatum-T is a past example. Several modifications of the Lippes loop are presently being tested. They include minor variations of the basic geometry of the Lippes loop D. In one study the variation consisted of a 20% decrease in thickness at the cervical end (248) and an increase in the limb height or thickness of the loop at the fundal end. The fundal end was altered because contraception has been positively correlated with IUD thickness and this position is where implantation usually occurs (237); the cervical end of the loop was modified because flexibility may reduce the initiation of IUD-induced contractions.

Bleeding, both menorrhagia and intermenstrual bleeding, remains the main challenge of improved IUD design. Analytically, it has been found that the criterion of removal of an IUD for bleeding is too variable to be useful, except in large comparative trials with random allocation of devices to subjects. The development of a few centers that can perform quantitative blood loss studies will be increasingly important in screening the many possible medicaments that can be added to IUDs to reduce excessive bleeding (249-250). Also, the use of bleeding calendars and
the measurement of abnormal bleeding episodes, as subjectively reported by IUD wearers, is an improvement over rates of removals, especially in small, early studies of new devices (238).

IUD development has undergone the transition from the recognition of excessive menstrual bleeding and spotting side effects as a major deterrent to IUD use to the development of hemostatic additives for IUDs to reduce or eliminate these bleeding side effects. Current research is aimed at developing a new generation of systems for sustained release of medication from IUDs. Where heretofore silastic has been a universal choice of material, there now exists a variety of semipermeable polymers and biodegradable materials for use in sustained drug release systems. A modified Lippes loop (248) has been developed that can receive sleeves impregnated with drugs that are released over several months to reduce bleeding. Devices with sleeves containing AMCA (251) and sleeves containing EACA (252) are in trial. A previous trial of AMCA in the experimental U-coil device has shown marked reduction in bleeding caused by this high surface area device (253). In another trial, Norgestrel was released by use of a biodegradable film wrapped around a T vector (254). A reduction in menstrual bleeding was also noted in this study.
The better performance of several IUDs when inserted after abortion than when inserted in the interval period (255) has led to a study now in progress of removing the endometrium by vacuum aspiration before insertion of the Lippes loop (256). The safety of IUD insertions after incomplete abortions is also well documented (257).

Modifications of the Lippes loop and Copper T have been designed for postpartum insertion of these devices (258). The superior arm of the loop (Figure 4) has a series of biodegradable tines that embed in the postpartum endometrium, but disappear by six weeks postpartum leaving a standard loop. The T device (Figure 5) has biodegradable extensions to accommodate the larger postpartum uterine cavity. The extensions disappear in six weeks.

Several suggestions have been made for anchoring IUDs in the myometrium (258). The largest clinical trial involves the Monterrey Device which has an arrow-head-like projection into the uterine fundus (259).

**Epidemiological Research**

Epidemiological research in IUD performance has been focused primarily on IUD associated infections, ectopic pregnancies,
spontaneous and septic abortions, and perforations. Retrospective case control studies have indicated a more than three-fold risk of pelvic infections in IUD cases among patients treated in outpatient clinics (260-262). Hospitalization for infections related to IUD use in early 1973 in the United States are estimated to be 5 per 1,000 woman-years of use (210). Increased incidence of both gonococcal and nongonococcal pelvic infections is associated with IUD use (263).

The recent increase in female sterilization procedures in the U.S. and abroad has provided an opportunity to examine pelvic organs and in some cases to biopsy the fallopian tubes in women with and without a history of recent IUD use. These studies again indicate a higher risk of pelvic infection among IUD wearers (264). The risk appears to apply to both inert and copper devices. Copper does not appear to offer protection against gonorrheal infections (265).

A specific infection related to IUD use that has recently been identified is due to Actinomycosis Israeli (266). The exact incidence of infection by this common saprophite of the vagina (267) is unknown. The clinical infection is frequently found as a tubal abscess in an IUD wearer (268). Such infections are probably not common, but can lead to sterility. There does
appear to be an increasing risk of actinomycosis infection with length of wearing of the IUD (269). Another anaerobe, Bacteroides fragilis, has been cultured from the surface of an asymptomatic perforated copper loop removed laparoscopically (270).

Spontaneous abortion was also found to be more likely to occur in women who conceived with an IUD in situ. One case-control study in England has delineated a three-fold difference between women wearing IUDs and those using other methods (219). In an American study, 49% of the 46 women who became pregnant with an IUD in situ experienced spontaneous abortion (271), as compared to a general spontaneous abortion rate of about 15% (272).

The association detected between septic abortion and one type of IUD, the Dalkon shield, illustrates the important contribution of epidemiologic research to IUD programs. In a nationwide survey (273-274) on morbidity and mortality associated with IUD use in the United States, a significant relative excess of Dalkon shield IUDs was observed among hospitalized women carrying the diagnosis of "complicated pregnancy". Categorization by patient's age, race and geographic region showed a comparable excess for each group. This relative excess was postulated as either due to an elevated rate of pregnancy with this device, or
an elevated incidence of complications once the pregnancy was established, or both. Its multifilament tail may have acted as a wick for ascending infection from the vagina, giving the third possibility of the abortion having been induced by sepsis (275). It is subsequently withdrawn from the market. The high incidence of abortion and the possibility that some of these will be septic has led to recommendations that IUDs be removed if there is a pregnancy failure (276).

The recent evidence of increased risk of infection associated with IUD use differs from previous reports of experience in the 1960s (277). The possibility that recent IUD-related infections are part of the present pandemic of gonorrheal infections must be considered (278).

The incidence of perforations varies in different studies from 1 in 120 to 1 in 2000 insertions. The Birnberg bow (279), and Dalkon Shield (280), have been found to have high perforation rates in some studies. It is generally agreed that copper devices should be removed because of an inflammatory response and possible subsequent adhesions and bowel obstruction. Closed devices are not recommended because of the high incidence of bowel obstruction associated with perforation (277). Disagreement exists concerning the management of perforated inert devices
(281). More of the inert ones are now being removed laparoscopically in a few centers with experience in this procedure.

**Prescription IUDs**

A composite of much of the basic work on reproductive biology and applied IUD research is now being directed toward prescription of the best available IUD for a particular woman. Previous studies have identified various characteristics of the woman that seem most important. Among them are:

1. Age and parity (194, 279)
2. Socio-economic status (282)
3. Number of previous abortions (283)
4. Internal os to fundus length (282)
5. Motivation for contraception (limiting or spacing of children) and period of desired contraception (282)
6. Accessibility to removal and reinsertion of IUDs and availability of other contraceptives (282)

Efforts to prescribe devices to individual women based on uterine measurements have been hampered by lack of instrumentation. The Hasson Sound (284) has provided a simple method of
making internal os to fundus measurements. Previous animal research has shown that lateral measurements also affect performance of the IUD (285). Hysterographic studies have suggested that bleeding is increased with an IUD inserted in a too narrow uterus (286). Instrumentation to determine lateral measurements as well as longitudinal measurements has been developed by (287) Battelle-Northwest and is currently in trial. As more associations with IUD performance of particular devices and characteristics of users become known, it is anticipated that a more accurate prescription of the best IUD for a particular woman will be possible (288).
PERIODIC ABSTINENCE

Variously called the rhythm method, natural family planning, or periodic abstinence, this method is based on two premises: that fertility is confined to an identifiable period each month; and that abstinence will be practiced during this period. Theoretically, then, this method would not necessitate any ingestion or use of chemicals, hormones or the use of unreliable mechanical devices, leaving no risk of side effects or mechanical failure. However, two major shortcomings of this hypothesis are the feasibility of accurately defining fertile period and the practice of abstinence.

The accurate identification of the fertile period is not yet possible. It is dependent on the time within the month that each ovulation occurs and its predictability, the number of days of fertility of the ova, the number of days of fertility of the spermatozoa, and the variations of each within the population practicing the method. Each of these variables is the subject of current research. The practice of abstinence, on the other hand, requires behavior which is not needed to use other contraceptive methods. Abstinence, when successfully practiced, reflects a high degree of cooperation on the part of the sexual partners, an ideal the proponents of this method feel is attainable.
Since certain religious groups consider periodic abstinence to be the only acceptable method of family planning, continuing research on this method is appropriate. However, the requirement of periodic abstinence remains an imposed difficulty. Research concerned with identifying time of ovulation or efficacy of the method is being conducted by a number of organizations with support from the World Health Organization (WHO) and the National Institutes of Health (NIH).

As late as 1854 Bischoff promoted the concept that the fertile period was during menses (315). Recognition of the mammalian ovum occurred only 150 years ago and the time of ovulation was not guessed until 20 years thereafter (316). However the modern concept of midcycle ovulation-fertility was not developed until the 1930s when Ogino and Knaus separately identified the existence of this period, marking the beginning of the development of more reliable abstinence methods.

In spite of considerable recent research, the prediction of the time of ovulation remains a problem. The principle methods practiced today, which are effective to a degree, are those based on study of cyclic thermal patterns and changes in cervical mucous. Certain other methods rely on exogenous hormonal stimulation of ovulation. These may be practiced in conjunction with
self-determination of "Mittelschmertz" or other individual symp­
toms of ovulation. The older "calendar" method promoted by Ogino
and Knaus for which a w­men plotted out her average-length monthly
cycle and avoided intercourse for three days before and after the
assumed date of ovulation is generally considered inadequate
today (317).

The thermal, or temperature, method is related to the monthly
rise in basal body temperature (BBT) which occurs at or about the
time of ovulation (318). The woman intending to practice this
method must have a thermometer, preferably one suited to regis­
tering small changes between 96 and 100° F. She then records
daily temperatures in the early morning before eating to assure
close to basal readings. The change in temperature is in the
range of 0.5 to 1° F and may be abrupt or take several days to
manifest itself. By keeping a careful record, she can tell the
approximate day of ovulation.

The obvious drawback of this method is that she is not able
to predict in any way the occurrence of this change, so that, in
order to avoid fertilization, intercourse must be restricted to
the 10 to 12 days starting 3 to 4 days after the temperature rise
and ending with menses, when she is again preovulatory. A
second problem is that this change in temperature may not corres­
pond exactly to the time of ovulation or may not be picked up
until nearly 24 hours after the change has actually occurred (319). A third difficulty is that ovulation may occur without this temperature change (320). Fourthly, each woman must study several of her own cycles before this method becomes efficacious. Temperatures normal for one woman are not applicable to the next. A fifth and significant problem is that approximately 10 percent of all BBT curves are uninterpretable secondary to temperature aberrations of subclinical illness, emotional or environmental changes (318).

The cervical mucous or ovulation method relies on collection and examination of this substance and judgment as to quality and quantity. Initially promoted as an adjunct to the calendar or thermal methods, Drs. Evelyn and John Billings began to advocate its practice as a separate method in the early 1960s. When changes in the mucous were correlated with time of ovulation as determined by daily urinary output of estrinol, estrone, estradiol and pregnandial they were found to be indicative (321).

Postmenses, cervical mucous is found to be cloudy and slightly sticky, becoming progressively clearer and more slippery. At the time of the LH surge, just prior to ovulation, the mucorrhea has an egg-white-like consistency and increased volume. During this time, the vagina provides a more alkaline environment
and the cervical mucous has a stringy quality, both conducive to sperm transport. After ovulation, the quantity of mucous decreases, becoming cloudy, thick and more acidic, probably in response to increased progesterone (322). The "safe" period for intercourse, then, would be when mucous quantity is small, and of non-lubricative, non-stringy quality.

In this method again, the natural differences among women necessitate careful study of her own patterns by the individual practitioner. Faulty self analysis may occur when there is a superimposed infection or irritation, when there is early ovulation, and in the occasional woman where this patterning does not occur. Another difficulty may lie in the fact that the women who experience the most clear-cut changes in mucous lubrication and normal vulval sensation may find the practice of abstinence more difficult at this time.

The Groden Method is based on the original hypothesis by Matthews, later promoted by Groden, that date of ovulation within the cycle could be regulated by administering a progestin during the second half of the menstrual cycle (323-324). This would supposedly cause ovulation to occur at a set time in the following month during which abstinence could be practiced. The regimen as currently promoted in the Philippines, consists of 14
iron pills started on the first day of menses to be followed by 11 days of Norinyl 1+50 (norethindrone 1 mg. and Mestranol 0.05 mg) (325). Abstinence is promoted on days 11 through 18.

Two studies have been performed to evaluate this method using Ovulen (ethynodiol diacetate 1 mg and 0.1 mg Mestranol), a slightly stronger pill. Lorenzo and Sturgis administered medication to 20 women for a total of 88 cycles. Judging date of ovulation by LH peak and thermal change, they found that ovulation may occur up to three days after onset of pill use (326). Ovulation occurred in the treatment group as late as day 19. Since abstinence should begin about day 10, such a method necessitates at least 10 days of abstinence, not 7 as promoted in the Groden Method (324).

Boutsellis, Dickey, and Vorys studied a similar method for 348 menstrual cycles. They found from 22 to 33 percent to be anovulatory. Ovulation occurred in the remainder from day 12 through day 19 (323). Taking into account sperm survival and ova viability, this would necessitate at least an 11-day period of abstinence. Many Catholic groups do not accept this as a means of natural family planning since it sometimes suppresses ovulation.
Other methods of ascertaining fertile periods are beset with the same basic problem: they cannot accurately predict ovulation far enough in advance to allow for avoidance of intercourse two to three days before ovulation. Methods promoted have been as diverse as astrological projections and nonlinear serendipity based on light cycles (327-329). Although some credence has been given the latter, more scientifically tested methods include detection of electro-energy changes, amount of various components in saliva, or crystallization of saliva (330-333). Bioassay of hormone levels is not practical as an ongoing method. Instrumentation is being developed for use at home. One method showing promise is the Viscometer or "Ovutimer™" being developed by Kosasky at Harvard. This method has the potential to predict when the woman is three to eight days pre-ovulatory. The instrument is used to measure viscosity of cervical mucous which changes as much as 1000% during the course of the menstrual cycle (334-338). It is being developed in two forms—a sterilizable piece of equipment for physician use and a tampon-sized disposable version for home use. A probe is applied against the external os to collect the necessary few milligrams of mucous. It is then replaced in the instrument which will indicate the degree of fluidity only, not registering when the mucous is thick, or "safe". Kosasky feels that the instrument is most useful in indicating the maximum fluidity, the period preceding ovulation by 12-18 hours.
Instruments have been developed to measure the electro-potential shift, the components of saliva and cervical mucous glucose levels (333, 339). Smith is exploring the potential for measuring the minute changes that occur in breast temperature during the normal menstrual cycle. This is being carried out with computer-linked electrodes worn by the subject (340). None of these methods is practicable at this time for home use.

With the identification and characterization of LH releasing hormones it was hoped that natural LHRH or an analog could be used to induce ovulation at a known time. Schally et al. and others tried this approach but it soon became apparent that a very precise estrogen-progesterone milieu is required in humans for LH to work (341). The efficacy of LHRH to induce ovulation is thus limited to the period that ovulation would probably occur naturally.

The area of research most vital for natural family planning to become a more useful contraceptive method is improvement and confirmation of efficacy. There are couples who choose natural family planning for religious reasons, but there are also couples who, for medical reasons, desire a safe, effective method of birth spacing without steroids, chemicals, or surgery. Natural family planning, if efficacious, could meet the needs of some
highly motivated couples. Variations in menstrual cycles are lowest in the "middle life" zone, the twenties to early thirties, which may lend additional efficacy to the practice of rhythm in this highly fertile age group (342).

Studies in the past have been fraught with three major problems. Method descriptions may vary slightly as well as method of education for the couples; hence comparison of failure rates may not be accurate. Most studies allow self selection of a natural family planning method, potentially causing a severe bias. Some studies choose to ignore those cases where abstinence was not practiced correctly giving falsely low failure rates for rhythm as a practiced method. However, use-effectiveness, as opposed to theoretical effectiveness, is the true measure of efficacy of a method.

Although failure rates of former studies vary from 0.3 to 47.0 per 100 woman-years (315, 343-344), recent studies have attempted to better control the initially stated variables (method and motivation) and to present their findings in terms of use-effectiveness. Ball reports a failure rate of 15.5 per 100 woman-years use in a prospective field trial of the ovulation, or cervical mucous, method with a theoretical effectiveness of 2.9 in 1629 woman-months (345). Marshall, using a combined BBT and
mucous method, found a rate of 22 per 100 woman-years use which is in line with of mucous alone carried out in Tonga (346). In both these studies, the subjects were women who were motivated to use a rhythm method for medical or personal reasons. These results are comparable to the earlier rates reported by Tietze and Vennings of 14.4 and 24, respectively (347-348).

The World Health Organization has funded at least five clinical field trials since October 1975 (349). NIH is presently funding an extensive prospective study at the Cedars-Sinai Medical Center of Los Angeles and other hospitals in the area to compare and evaluate the effectiveness of the Ovulation Method and the Sympto-thermal Method. Development of the protocol for this was funded by the Human Life Foundation in an attempt to ascertain accurate efficacy figures for the United States with comparative data for improvement of future programs (350-351).

One area of concern requiring additional study is the higher rate of abnormality in pregnancies and offspring that occurs unplanned in rhythm method users (1). This has been attributed to "aging" sperm or ova since intercourse at the time of ovulation, and these findings seem to increase at the temporal extremes of the possible fertile period (352-354). A possible explanation for this phenomenon is that the ovum or sperm which could survive these extremes is innately abnormal or would be fertilized abnormally and therefore would tend to produce abnormal pregnancies.
Table I

ESTIMATED WORLD USE OF MEANS OF CONTROLLING FERTILITY, NUMBER OF COUPLES BY YEAR AND METHOD (PREVALENCE IN MILLIONS)

<table>
<thead>
<tr>
<th>Method</th>
<th>1970</th>
<th>1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilization</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>Condoms</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Intrauterine Devices</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Other Methods*</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Abortion**</td>
<td>30</td>
<td>35</td>
</tr>
</tbody>
</table>

*Diaphragm, Spermicides, rhythm, withdrawal, etc.

**Annual incidence

Source: Modified from reference 2.
### TABLE II

**Estimated Excess Annual Incidence of Fatal Myocardial Infarction Attributed to Oral Contraceptives Per 100,000 Users by Age and Presence or Absence of Predisposing Conditions†**

<table>
<thead>
<tr>
<th>Age and Author</th>
<th>Women Without Predisposing Conditions</th>
<th>Women With Predisposing Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39 Jain (143)</td>
<td>0.6</td>
<td>9.0*</td>
</tr>
<tr>
<td>Mann (142)</td>
<td>0.7</td>
<td>24.0</td>
</tr>
<tr>
<td>Ory (144)</td>
<td>1.5</td>
<td>25.7</td>
</tr>
<tr>
<td>40-44 Jain (143)</td>
<td>3.3</td>
<td>54.6*</td>
</tr>
<tr>
<td>Mann (142)</td>
<td>3.9</td>
<td>124.0</td>
</tr>
<tr>
<td>Ory (144)</td>
<td>5.1</td>
<td>86.2</td>
</tr>
</tbody>
</table>

†Predisposing conditions include type II hyperlipoproteinemia, smoking, diabetes, hypertension and preeclamptic toxemia.

*Smoking only predisposing condition present.
<table>
<thead>
<tr>
<th>Device</th>
<th>Reference</th>
<th>No. of Insertions</th>
<th>Woman-Months of Use</th>
<th>Pregnancy</th>
<th>Expulsion</th>
<th>Bleeding/Pain Removal</th>
</tr>
</thead>
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<td>Loop</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Tietze (194)</td>
<td>3489</td>
<td>31,032</td>
<td>3.0</td>
<td>19.1</td>
<td>11.0</td>
</tr>
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<td>D</td>
<td>Tietze (194)</td>
<td>7553</td>
<td>72,046</td>
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<td>9.5</td>
<td>11.7</td>
</tr>
<tr>
<td>D</td>
<td>Kessel (289)</td>
<td>2079</td>
<td>14,310</td>
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<td>5.9</td>
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<tr>
<td>Saf-T-Coil</td>
<td>Tietze (194)</td>
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<td>17,636</td>
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<td></td>
<td>Laufer et al (290)</td>
<td>290</td>
<td>2,848</td>
<td>1.1</td>
<td>8.8</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Hayes (291)</td>
<td>327</td>
<td>2,910</td>
<td>0.4</td>
<td>7.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Antigon-F</td>
<td>Fuchs (292)</td>
<td>1480</td>
<td>8,093</td>
<td>1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16.9</td>
<td>19.6&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Somboonsuk et al (293)</td>
<td>821</td>
<td>7,022</td>
<td>0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.5</td>
<td>12.9</td>
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<td></td>
<td>Lauersen et al (294)</td>
<td>884</td>
<td>14,436</td>
<td>0.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.1</td>
<td>7.9</td>
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<tr>
<td></td>
<td>Kessel (289)</td>
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<td>922</td>
<td>1.6</td>
<td>10.5</td>
<td>13.0</td>
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<tr>
<td>Ypsilon</td>
<td>Lauersen et al (294)</td>
<td>910</td>
<td>14,348</td>
<td>1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Cook (295)</td>
<td>3527</td>
<td>na</td>
<td>2.9</td>
<td>3.9</td>
<td>4.6</td>
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<tr>
<td></td>
<td>Rodrigues and Nogueira (296)</td>
<td>2180</td>
<td>na</td>
<td>3.6</td>
<td>4.9</td>
<td>2.9</td>
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<td>Dalkon Shield</td>
<td>Ma et al (297)</td>
<td>2007</td>
<td>23,598</td>
<td>1.7</td>
<td>1.9</td>
<td>5.4</td>
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<td></td>
<td>Marshall et al (298)</td>
<td>296</td>
<td>1,826</td>
<td>5.6</td>
<td>1.3</td>
<td>34.8&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Reyners (299)</td>
<td>1044</td>
<td>5,041</td>
<td>3.6</td>
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<td></td>
<td>Madrigal et al (300)</td>
<td>2848</td>
<td>27,573</td>
<td>2.1</td>
<td>2.5</td>
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<td></td>
<td>Snowden (301)</td>
<td>1031</td>
<td>6,669</td>
<td>3.8</td>
<td>3.9</td>
<td>4.6</td>
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<tr>
<td>Pleated Membrane</td>
<td>Kessel (289)</td>
<td>349</td>
<td>3,748</td>
<td>1.5</td>
<td>1.7</td>
<td>9.0</td>
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<tr>
<td>Spring Coil</td>
<td>Randic (302)</td>
<td>309</td>
<td>3,116</td>
<td>0.0</td>
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<td>Lampe (240)</td>
<td>811</td>
<td>4,298</td>
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<td>18.5</td>
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<td>Ragab (302)</td>
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<tr>
<td>Tecna (Fluid Filled)</td>
<td>Andolsek (303)</td>
<td>290</td>
<td>2,592</td>
<td>4.6</td>
<td>23.1</td>
<td>8.0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>Margolis (304)</td>
<td>307</td>
<td>na</td>
<td>1.5</td>
<td>10.5</td>
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</tr>
</tbody>
</table>

<sup>a</sup> Calculated as Pearl Index.

<sup>b</sup> Includes removals for all reasons except pregnancy.
### Table IV
MEDICATED IUDS: ONE YEAR NET RATES OF EVENTS PER 100 WOMEN

<table>
<thead>
<tr>
<th>Device</th>
<th>Reference</th>
<th>No. of Insertions</th>
<th>Woman-Months of Use</th>
<th>Pregnancy</th>
<th>Expulsion</th>
<th>Bleeding/Pain Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-T(TCu-200)</td>
<td>Jain (197)</td>
<td>16,345</td>
<td>116,155</td>
<td>2.6</td>
<td>7.3</td>
<td>8.7</td>
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<td></td>
<td>Tejuja et al (305)</td>
<td>4,357</td>
<td>37,429</td>
<td>0.9</td>
<td>7.4</td>
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<tr>
<td></td>
<td>Timonca et al (306)</td>
<td>2,689</td>
<td>29,143</td>
<td>1.6</td>
<td>2.2</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Kessel (289)</td>
<td>3,422</td>
<td>31,210</td>
<td>1.8</td>
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<td></td>
<td>Zipper et al (199)</td>
<td>833</td>
<td>8,854</td>
<td>2.3</td>
<td>3.4</td>
<td>3.1</td>
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<td>Copper-T(TCu-300)</td>
<td>Tatum (307)</td>
<td>2,394</td>
<td>16,700</td>
<td>1.1</td>
<td>5.7</td>
<td>11.8</td>
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<td>Copper-T(TCu-380A)</td>
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<td>15,834</td>
<td>0.6</td>
<td>6.7</td>
<td>8.9</td>
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<td>Copper-T(TCu-220C)</td>
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<td>12,890</td>
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<td>14.4</td>
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<td>Copper 7(Gravigard)</td>
<td>Jain (197)</td>
<td>1,831</td>
<td>12,289</td>
<td>2.8</td>
<td>15.5</td>
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<td>8,065</td>
<td>83,676</td>
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<td>Tejuja et al (309)</td>
<td>854</td>
<td>5,177</td>
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<td>516</td>
<td>5,553</td>
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<td>Kessel (289)</td>
<td>1,322</td>
<td>13,685</td>
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<td>Copper-7(Small)</td>
<td>Medel et al (226)</td>
<td>468</td>
<td>2,929</td>
<td>3.6</td>
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<td>Medel et al (226)</td>
<td>496</td>
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<td>1.2</td>
<td>4.0</td>
<td>1.9</td>
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<td>Scommegna et al (311)</td>
<td>249</td>
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<td>Zador et al (313)</td>
<td>150</td>
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<td>2.0</td>
<td>9.5</td>
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<td>Sadovsky (314)</td>
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<td>3.8</td>
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<td></td>
<td>-essel (289)</td>
<td>463</td>
<td>5,294</td>
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<td>8.3</td>
<td>6.9</td>
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<tr>
<td>U-Coil with AMCA</td>
<td>Ragab et al (253)</td>
<td>200</td>
<td>1,146</td>
<td>0.0</td>
<td>1.1</td>
<td>1.1</td>
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<td>Ragab et al (253)</td>
<td>250</td>
<td>1,333</td>
<td>0.0</td>
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<td>9.9</td>
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a Includes early postpartum insertions.
Figure 1. Two-Year Pregnancy and Bleeding/Pain Removal Rates of Some Barium Polyethylene IUDs as a Function of Their Surface Area. (Data from Cooperative Statistical Program of the Population Council and the International Fertility Research Program.)
Figure 2. Spring Coil IUD (Manufactured for the International Fertility Research Program by Ekder Plastic Works, Hong Kong).
Figure 3: The Pleated Membrane IUD.
Figure 4. Modified Lippes Loop with biodegradable tines.
Figure 5. Modified T device with biodegradable extensions.
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