CONTRACEPTION:  
Current Choices and Future Directions

April 6-8, 1989  Washington, D.C.

Course Director

David F. Archer, MD

Name: ____________________________
CONTRACEPTION
Current Choices and Future Directions
Course Faculty

GUEST FACULTY

Thomas B. Clarkson, DVM
Professor and Chairman, Department of Comparative Medicine
Director of Arteriosclerosis Research Center
Bowman-Gray School of Medicine

Duff G. Gillespie, PhD
Agency Director for Population
U.S. Agency for International Development

David Grimes, MD
Professor of Obstetrics and Gynecology
University of Southern California at Los Angeles

Herbert B. Peterson, MD
Chief, Epidemiologic Studies Branch, Division of Reproductive Health
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Malcolm Potts, MB, B. Chir, PhD
President
Family Health International

Irving Sivin, MA
Senior Associate
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Ronald J. Swerdloff, MD
Professor of Medicine
Chief, Division of Endocrinology
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Anibal A. Acosta, MD
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Director of Fellowships and Andrology – CONRAD

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Director of Applied Fundamental Research – CONRAD

Mason C. Andrews, MD
Professor and Chairman
Department of Obstetrics and Gynecology

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Research Professor, Department of Obstetrics and Gynecology
Director of Extramural Programs – CONRAD

Gary D. Hodgen, PhD
Research Professor, Department of Obstetrics and Gynecology
Program Director – CONRAD

REGISTRATION

Complete the course registration form and return it with your check made payable to EVMS-CME for the appropriate registration fee.
The fee includes participation in all sessions and the syllabus, as well as breakfast each morning, refreshment breaks, and lunch on Friday.

REFUND POLICY

A handling fee of $35.00 is deducted for cancellation. Refund request must be received three days prior to the course. No refund will be made thereafter.

COURSE REGISTRATION FORM (89-897G)

CONTRACEPTION: Current Choices and Future Directions
Washington, DC – April 6-8, 1989

NAME (as you wish it to appear on name badge)

SOCIAL SECURITY NUMBER (for attendance records only)

MAILING ADDRESS

CITY:STATE:ZIP

HOME PHONE (for emergency) OFFICE PHONE

REGISTRATION FEE

Complete this form and enclose your check made payable to EVMS-CME or provide credit card information and mail it to:

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Card Number

Expiration Date

Card Holder Signature
CONTRACEPTION:
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Thursday, April 6, 1989
12:15 pm REGISTRATION
1:00- 1:10 pm WELCOME
Mason C. Andrews, MD
ANNOUNCEMENTS
David F. Archer, MD

Moderator: Mason C. Andrews, MD
1:10- 2:00 pm GLOBAL NEED OF CURRENT AND FUTURE CONTRACEPTION
Malcolm Potts, MD, MPH
2:00- 2:45 pm SEXUAL TRANSMISSION OF HIV
Nancy J. Alexander, PhD
2:45- 3:00 pm REFRESHMENT BREAK
3:00- 3:50 pm SEXUALLY TRANSMITTED DISEASES AND CONTRACEPTIVES
David Grimes, MD
3:50- 4:40 pm CURRENT STATUS OF BARRIER CONTRACEPTION
Malcolm Potts, MD, MPH
4:40- 5:00 pm PANEL DISCUSSION OF AUDIENCE QUESTIONS
5:00 pm ADJOURN FOR THE DAY

Friday, April 7, 1989
7:30- 8:00 am CONTINENTAL BREAKFAST AND SIGN-IN
Moderator: Anibal A. Acosta, MD
8:00- 8:50 am IUDS — NEW DESIGNS/NEW AWARENESS
David Grimes, MD
8:50-9:40 am ANTI-PROGESTINS AND CONTRACEPTION
Gary D. Hodgen, PhD
9:40- 9:55 am REFRESHMENT BREAK
9:55-10:45 am IMMUNOLOGIC APPROACH TO CONTRACEPTION
Nancy J. Alexander, PhD
10:45-11:35 am MALE CONTRACEPTION — MEDICAL APPROACHES
Ronald Swerdloff, MD
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12:00- 1:30 pm LUNCH
Introduction of Speaker:
Gary D. Hodgen, PhD
Luncheon Address:
ROLE OF USAID IN WORLD POPULATION
Duff Gillespie, PhD

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1:30- 2:15 pm SURGICAL STERILIZATION: TECHNIQUES, RISKS, LONG-TERM RESULTS
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David F. Archer, MD
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3:15- 4:00 pm CARDIOVASCULAR RISK IN O/C USERS
Bert Peterson, MD, MPH
4:00- 4:40 pm ORAL CONTRACEPTIVES ANDATHEROGENESIS
Thomas Clarkson, DVM
4:40- 5:00 pm PANEL DISCUSSION OF AUDIENCE QUESTIONS
5:00 pm ADJOURN FOR THE DAY

Saturday, April 8, 1989
7:30- 8:00 am CONTINENTAL BREAKFAST AND SIGN-IN

Moderator: Henry L. Gabelnick, PhD
8:00- 8:40 am HORMONAL CONTRACEPTIVES AND THE RISK OF CANCER
Bert Peterson, MD, MPH
8:40- 9:20 am FUTURE DIRECTIONS FOR RESEARCH IN MALE CONTRACEPTION
Ronald Swerdloff, MD
9:20-10:00 am NON-STEROIDAL GONADAL FACTORS IN CONTRACEPTION DEVELOPMENT
Gary D. Hodgen, PhD
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10:15-11:00 am DELIVERY SYSTEMS FOR CONTRACEPTIVES
Henry L. Gabelnick, PhD
11:00-11:30 am CLINICAL UTILITY OF SYSTEMIC LONG-ACTING CONTRACEPTIVES
David F. Archer, MD
11:30-12:10 pm NORPLANT CONTRACEPTIVE IMPLANTS: A NEW MODALITY
Irving Sivin, MA
12:10-12:30 pm PANEL DISCUSSION OF AUDIENCE QUESTIONS
12:30 pm ADJOURN
WHO SHOULD ATTEND ...?
If you see patients who are using contraceptives ...
If you see patients who have questions about contraceptives ...
If you want to update your knowledge of contraceptives ...
If you are interested in current contraceptive research ...

THIS COURSE IS FOR YOU!
This national course, sponsored by the leading contraception research program in the United States, has been designed to provide physicians and other health professionals with an in-depth review of current clinical issues related to the use of contraceptives as well as current research involving potentially new contraceptive agents. Distinguished faculty have been selected for their expertise in the topics included in the program.

COURSE OBJECTIVES
Upon completion of the course the participant will have a knowledge of:
- The current risks and benefits of the low estrogen dose oral contraceptives
- The role of various contraceptive agents (oral contraceptives, IUDs, barrier contraceptives) in the occurrence of sexually transmitted disease
- Current advances in immunology as they relate to contraception development
- The current status and future directions of male and female surgical sterilization procedures
- The cost effectiveness and side effects of systemic contraceptives
- The current status of non-steroidal gonadal factors and gonadotropin as analogues, as applicable to contraceptive development.

ACCREDITATION
Eastern Virginia Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians and certifies that this CME activity meets the criteria for 18 hours in Category 1 toward the Physician's Recognition Award of the American Medical Association.

This course has been approved for 18 cognates, Formal Learning, by The American College of Obstetricians and Gynecologists.

This program has been reviewed and is acceptable for 16.5 prescribed hours by the American Academy of Family Physicians.

THE LOCATION
The course will be held at the Loews L’Enfant Plaza Hotel located in one of the world’s most exciting and beautiful cities—Washington, D.C. The capital city was designed by Pierre Charles L’Enfant, selected by George Washington in 1791.

The largest Metro subway stop in Washington, D.C., is located directly beneath the hotel and connects you with theatre, shopping, business, and government centers.

1. U.S. Capitol
2. Jefferson Memorial
3. White House
4. National Gallery of Art
5. Lincoln Memorial
6. Washington Monument
7. Kennedy Center
8. National Archives
9. History & Technology
10. Smithsonian Castle
11. Air & Space Museum
12. Hirshhorn Museum of Art

Loews L’Enfant Plaza Hotel

ACCOMMODATIONS
A block of rooms has been reserved at Loews L’Enfant Plaza for course registrants. The room rate is $115 single or double occupancy. You may call L’Enfant Plaza toll free at 800/223-0888 to make your room reservation. To take advantage of the special group rate, specify that you are attending the Contraception course.

Please note that reservations made after March 16, 1989, will be on a space available basis only.

INFORMATION
If you have any questions or need additional information, please call Elaine Halverson, Program Administrator, at 804/446-6143.
Course Faculty

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Duff G. Gillespie, PhD
Agency Director for Population
U. S. Agency for International Development
Washington, DC

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Jaroslav F. Hulka, MD
Professor of Obstetrics and Gynecology
University of North Carolina, Chapel Hill

Robert H. Knopp, MD
Director, Northwest Lipid Research Clinic
Seattle, Washington

Malcolm Potts, MB,B.Chir, PhD
President, Family Health International
Research Triangle Park, NC

Ruby T. Senie, PhD
Epidemiologist
Centers for Disease Control
Atlanta, GA

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OVARIAN & BREAST CANCERS
Ruby T. Senie, PhD
4:00- 4:40 pm  SEX STEROID HORMONES & MGMT.
OF CARDIOVASCULAR DISEASE IN WOMEN - Robert H. Knopp, MD
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12:10-12:30 pm  PANEL DISCUSSION OF AUDIENCE QUESTIONS

ADJOURN
GLOBAL NEED OF CURRENT AND FUTURE CONTRACEPTION

Malcolm Potts, MD, MPH
Every four days and four hours the human race adds one million to its numbers.

The last decade of the millennium is likely to be one of the most challenging in human history. Whatever happens, human population will increase by a number greater than the total world population in 1800. Even more important, the changes of fertility that take place in the 1990s will largely determine whether the world our children inherit is peopled by 8 or 12 billion people.

Without exaggeration, it can be claimed that the next ten years are probably the last opportunity that the world has to control its numbers in a humane and voluntary way. Failure to exploit the opportunities of the 1990s will leave the world more overcrowded, polluted, overheated, politically unstable and with a high likelihood of setting in motion of number of irreversible and adverse changes in the biosphere.

Fortunately, the unmet demand for family planning is very large, and sufficient know-how exists that if there is an appropriate allocation of resources and realistic decisions by those who plan services, then there can be rapid declines in human fertility.

In the 1970s, the rate-limiting factor in family planning service programs was often ideas; in the 1990s, it is certain to be money. The resources required to extend family planning in demographically
In meaningful ways, the vast majority of the world's population will be large relative to current budgets but still small in relation to other human activities.

The vision of family planning has been one of the most successful aspects of overseas aid. It has never taken more than 2% of the total resources available of foreign aid, yet has contributed to some spectacular successes in a number of countries in Asia and Latin America. If we compare the time it took in the U.S. for family size to fall from a mean of 6 children to 3.5, then the decline was twice as quick in Sri Lanka, 3.8 times as fast in Thailand and a supersonic 4.8 times in Colombia and South Korea.

Successful fertility regulation has a number of features which are common to most cultural and socioeconomic settings. It is essential that the community has access to a variety of reversible methods of contraception, as individuals will differ in their evaluation of various methods, and the same couple is likely to use different methods at different times during their fertile life. Voluntary sterilization has proved popular wherever it has been made available and has been a significant factor in fertility reduction in most countries with low birth rates. No country has achieved a low birth rate without recourse to abortion. The epidemiological evidence is that the legal status of abortion appears to make relatively little difference to the total numbers taking place, although it has a powerful effect on the health of women who subject themselves to abortion.

The methods that will be used in the 1990s are primarily those with which we are already familiar. Marked increases in contraceptive
silence in rapidly expanding populations will place a heavy strain on the logistics of delivering services. Only the most cost-effective methods will be appropriate for the scale of programs that are necessary. A large expansion of social marketing will be necessary, attention will have to be paid to costs to recovery and, in many countries, a much greater role will have to be played by private physicians.

The Indian subcontinent in Africa presents particular problems which are unlikely to be solved unless there are important changes of policy. In India, the traditional practitioners could play an important role in the distribution of reversible methods of contraception. In sub-Saharan Africa, little progress in fertility control will be made if services are tied to the government health infrastructure.

New, long-acting steroidal methods of contraception will become available in the 1990s, although the scale of use is likely to be limited by costs and medical outlets used for distribution. A nonsurgical method of female sterilization would be of great value and is an area where the needs of Third World countries have many important differences from those of the developed nations.

The one method of fertility regulation may be the antiprogestogens.
SEXUAL TRANSMISSION OF HIV

Nancy J. Alexander, PhD
HETEROSEXUAL HIV-1 TRANSMISSION

In 1981 AIDS emerged as a world-wide health problem. Since that time the number of cases has dramatically increased. The WHO estimates that 300,000 cases have occurred and that between 5 to 10 million are currently infected. Fifty to 100 million are expected to be infected by 1991. Concern over the spread has caused some countries to require proof that foreigners visiting are AIDS-free. Such countries include China, Equador, Bulgaria, Pakistan, and the Soviet Union. The United States estimates that 365,000 Americans will be suffering from AIDS by 1992. At the time of this writing (February 1, 1989) 83,000 cases have been reported in the United States and of these, more than one-half have died. In the United States 63% of the cases have been homosexual or bisexual men, 7% have been homosexual or bisexual men with a history of IV drug use, 19% have been heterosexual males or females who are IV drug users, 3% have been caused by blood transfusions, and 1% have been hemophiliacs (Figure 1).

Scientific American October 1988
There seem to be ethnic differences in the numbers of individuals affected within the United States. But these differences probably have nothing to do with immune response, but rather are more closely associated with socioeconomic situations. For example, blacks consist of 11% of the U.S. population, but 26% of the AIDS victims and 53% of the pediatric cases are black. Hispanics comprise 8% of the United States population, but 14% of the AIDS victims and 23% of the pediatric cases. Because there is such a high concentration of IV drug use in the Northeast, the risk of contracting AIDS is between 2 and 10 times greater for blacks and Hispanics living in that region.

To model a disease, epidemiologists need to know how long people remain infectious. An infection invades a susceptible population and causes an epidemic if each infectious person infects more than one individual. Population experts have suggested that AIDS is more infectious than smallpox and possibly, polio, but not as infectious as gonorrhea. For gonorrhea it is thought that male-to-female transmission is about 0.5 per sexual contact and for female-to-male transmission it is 0.2 to 0.3 per sexual contact.

In the United States, cases caused by heterosexual contact are small, but the proportion is a fast growing group. Investigators differ in their perceptions of whether AIDS will become a major epidemic in the heterosexual population. Factors that can affect development of a major epidemic include:

1. size of the pool of susceptible people
2. rate of contact among the subpopulation
3. risk of transmission
4. risk of infectivity over time
5. risk of co-factors and repeated exposures
HIV, being a retrovirus, is composed of RNA. When the virus enters the cells, viral reverse transcriptase uses RNA as a template to make DNA which travels to the cell nucleus and inserts itself among the host chromosomes. Investigators have suggested that the 3-dimensional structure of the virus resembles a soccer ball, composed of 12 pentagons and 20 hexagons in a sphere. Molecules of gp 120 appear as knobs at the corner of each hexagon and are attached to a gp 41 anchor. HLA, derived from the membrane of the human cells can be found on the surface of the virus.

The virus enters T4 lymphocytes. The CD4 molecule is part of the HIV specific receptor. Studies have shown that monoclonal antibodies to different epitopes of the CD4 molecule can prevent HIV infection of CD4 lymphocytes. Co-precipitation of the viral envelope and CD4 molecules suggest a close association. After entry of the virus, it can remain latent until the lymphocyte is stimulated by a secondary infection. The virus can also combine with other lymphocytes in order to form syncia. These syncia can break open, releasing free virus and killing the cells. Viral protein can also be found free in the blood of infected patients. It can attach to the surface by means of the CD4 receptor and, subsequently, the natural killing mechanisms of the host (killer cells or cytotoxic T cells) can result in the demise of normal uninfected cells. The patient's immune system is crucial for controlling the immune response (Figure 2).
The virus can perturb the immune system, directly as a consequence of viral replication. Disordered immune regulation results. Indirectly infection of lymphocytes in macrophages can result in the release of lymphokines and
monokines. These soluble factors may affect other uninfected cells. Thus, the marked amplification can occur although an infection of only a small number of cells occurs.

Heterosexual AIDS Risk

In the United States the number of men affected compared to women is 17 to 1. However, in other countries such as African countries, the male-to-female ratio is about 1:1. In Africa the disease is often seen as continued diarrhea and weight loss and, thus has been referred to as "slim disease". In Africa there is strong evidence that AIDS is sexually transmitted in a manner similar to other STDS. For one thing the age that women acquire the disease is around 30 years, compared to 40 years for men. The percentage of seropositive women of female prostitutes has risen markedly. It was 4% in 1980, 51% in 1983, 59% in 1986, and 86% in 1988. Seropositivity is strongly correlated with the presence of genital ulcers. The WHO has recently stated that reduction in genital ulcer disease in Africa could be a strong factor in reducing heterosexual spread of AIDS (Figure 3, 4).

Factors implicated in heterosexual transmission of HIV

- Chancroid
- Syphilis
- Herpes Simplex 2
- Gonorrhea
- Chlamydia
Factors influencing probability of heterosexual transmission

- Clinical Status of index case
- Presence of concurrent STDs
- Anal intercourse
- Circumcision

HIV is transmitted vertically to the fetus. The virus has been found in the placenta as early as 12 weeks of pregnancy and it thought to be passed in the prenatal as well as the perinatal period. Whether breast milk can be infective in seropositive women is not totally clear. Transfusion and IV drug use of new mothers indicates that babies who are seronegative at birth can convert if exposed to infected mother. However, such mothers would be in the viremic stage of the disease rather than the antibody positive stages of the disease, so it is not yet clear as to the role breast milk in transmission.

The risk of heterosexual transmission is not totally understood. Only 4% of all adults diagnosed with AIDS in the United States report acquiring the disease through heterosexual contact. But this mode of contact accounts for 30% of all the AIDS cases in women. STDs certainly are a co-factor in transmission. These include syphilis, gonorrhea, and even chlamydia. Studies of heterosexual transmission have been clouded by the study group, either prostitutes or IV drug users. Some studies conducted on spouses of patients who received the virus via a blood transfusion have provided information concerning transmission. One infected female became seropositive after only one act of coitus, whereas others
in cases of spouses of hemophiliacs.

The mechanism of transmission is not clear. Investigators have found virus in about half the patients whose saliva was evaluated. However, saliva may inhibit HIV from infecting cells. When HIV and white blood cells are mixed with saliva, no infection occurs in culture.

In semen lymphocytes and macrophages may be an important reservoir. These potential host cells are present in every semen sample that has been evaluated. It is estimated that about 1 million viable leukocytes are present in the ejaculates of normal men. Immunosuppressive factors in seminal plasma may inhibit antiviral defense mechanisms in sexual recipients. Semen itself contains many immunosuppressive factors which may incapacitate the recipient’s immediate immune response (Figure 5, 6, 7).

![Graph](image)  
Fig. 7. Blood plasma PGE-II concentrations from six adult monkeys at 0, 20, and 120 min after infusion per rectum of human seminal plasma.
There is not a clear understanding of how the virus enters the female body. Can the virus enter via intact mucus membranes in the vulva, vagina, cervix, endocervix, or endometrium? Some investigators suggest that virus attaches to the sperm surface where it can be carried into the uterus, other investigators suggest that free virus within the seminal plasma, or virus within white blood cells is important for transmission from males to females.

Virus has been detected in cervical secretions. There is no strong evidence that menstrual blood is associated with transmission. A review of studies of sexual transmission is shown in (Figure 8, 9).
Contraceptives and HIV Transmission

Little information is available as to the role of contraceptives and HIV transmission. There are suggestions that contraceptives could alter receptivity to the virus. For example, hormonal contraceptives that abolish the midcycle estrogen surge could result in a dry vagina. Oral contraceptives are associated with colonization with Candida and anaerobes. IUDs increase the colonization of chlamydia, anaerobes and mycoplasma. Diaphragms could cause rubbing and

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**Sexual Transmission of HIV $\Phi \rightarrow \Phi$**

<table>
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<tr>
<th>Risk Factor of Index case</th>
<th># of partners studied</th>
<th>% partners seropositive</th>
<th>reference</th>
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<td>mixed</td>
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<td>transfusion</td>
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<td>IV drugs</td>
<td>13</td>
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<td>Johnson et '88</td>
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<td>50% African heterosexuals</td>
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<td>13</td>
<td>Laga et '88</td>
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<td>IV drugs (AIDS/ARC)</td>
<td>14</td>
<td>50</td>
<td>Steigbigel et '88</td>
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<tbody>
<tr>
<td>hemophilia</td>
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<td>hemophiilia</td>
<td>164</td>
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<td>Kamradt et '88</td>
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<td>Goedert et '88</td>
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<td>transfusion</td>
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<tr>
<td>African heterosexuals</td>
<td>62</td>
<td>53</td>
<td>Laga et '88</td>
</tr>
</tbody>
</table>
unpredictable spotting, thus exposing the partner to blood. Sex steroids affect the immune response. They down-regulate the immune system. Hormonal effects are not totally understood, but could lead to the hypothesis that the use of steroids could alter an immune response to HIV exposure.

Animal Model for Sexual Transmission

A retrovirus in monkeys is associated with an acquired immune deficiency syndrome. This retrovirus, SIV, seems more closely related to HIV-2 rather than HIV-1. Animals exposed to this virus develop lymphadenopathy and other signs including splenomegaly, neutropenia, lymphopenia, weight loss, anemia, abnormal peripheral blood monocytes, bone marrow hyperplasia, necrotic gingivitis, persistent diarrhea, chronic opportunistic infections, fibrosacomas, and retroperitoneal fibromatosis. In our recent work we have shown that clinical symptoms of AIDS can be reproduced in rhesus monkeys by applying SIV to the genital mucosa of both male and female macaques. The disease symptoms are identical to those produced by intravenous inoculations. The females were infected after six to twelve exposures given throughout the menstrual cycle. Males were infected with as little as to 2 to 3 inoculations. Primary studies suggest that ten times the dose required for intravenous inoculation was needed. Our data indicate that SIV, similar to HIV, can be sexually transmitted. The use of the rhesus monkey as a model will allow definition of pharmacological and biologic co-factors important in disease spread (Table 1).
Table: Macocal Transmission of SIV to Rhesus Macaques

<table>
<thead>
<tr>
<th>Sex</th>
<th>Exposure Route</th>
<th>SIV Isolation &amp; of Inoculation prior to SIV Isolation</th>
<th>to SIV</th>
<th>Clinical Signs and Symptoms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous</td>
<td>7</td>
<td>1</td>
<td>Weak</td>
<td>Died with SIDS - Severe weight loss - Diarrhea - Adenoviral gastritis</td>
</tr>
<tr>
<td>F</td>
<td>#22654</td>
<td>14</td>
<td>1</td>
<td>Strong</td>
<td>Died with SIDS - Thrombosis right ventricle - DIC, thrombocytopenia - Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>#22659</td>
<td>14</td>
<td>5</td>
<td>Strong</td>
<td>Enhance</td>
</tr>
<tr>
<td></td>
<td>Vaginal</td>
<td>#21311</td>
<td>37</td>
<td>10</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>#21293</td>
<td>37</td>
<td>10</td>
<td>Strong</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>#8063</td>
<td>negative</td>
<td>no infection</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>M</td>
<td>Intravenous</td>
<td>7</td>
<td>1</td>
<td>Weak</td>
<td>Enhance</td>
</tr>
<tr>
<td></td>
<td>#23235</td>
<td>7</td>
<td>1</td>
<td>Strong</td>
<td>Enhance with SIDS - Interstitial Pneumonia</td>
</tr>
<tr>
<td></td>
<td>#21851</td>
<td>7</td>
<td>1</td>
<td>Strong</td>
<td>Enhance</td>
</tr>
<tr>
<td></td>
<td>#218191</td>
<td>7</td>
<td>1</td>
<td>Weak</td>
<td>Enhance with SIDS - Interstitial Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Rectal, Mucosa</td>
<td>#21875</td>
<td>16</td>
<td>2</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>#21943</td>
<td>31</td>
<td>3</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

SIDS: Acquired Immune Deficiency Syndrome
DIC: Disseminated Intravascular Coagulation
HIV: Human Immunodeficiency Virus
SIV: Simian Immunodeficiency Virus
Nancy J. Alexander, Ph.D.
SEXUALLY TRANSMITTED DISEASES
AND CONTRACEPTIVES

David Grimes, MD
The Preventive Role of Contraceptives in STDs

DAVID A. GRIMES, MD

As noted by U.S. Surgeon General Koop, in this era of viral STDs, primary prevention of infection assumes critical importance. Contraceptive methods are an important component of contemporary prevention strategies. This article will summarize what is known about the relationship between contraceptive methods and STDs.

The relationship between contraceptive methods and sexually transmitted diseases (STDs) has suddenly become front-page news. For many decades, strategies to control STDs relied on containment rather than on primary prevention. However, the growing epidemic of viral STDs in the United States has rendered the containment strategy largely obsolete: the assurance of rapid cures of STDs has vanished. We are now reliving the pre-antibiotic era of American medicine, in which physicians must confront infections for which there is no cure.

Three infections illustrate this point. Herpes simplex virus infections can be recurrent and socially debilitating, and acyclovir offers only palliation for selected patients. Urked with cervical neoplasia, human papilloma virus infections; topical treatments are often ineffective, since viral particles may have infected adjacent, normal-appearing skin. The impact of the human immunodeficiency virus epidemic is just beginning to be felt; as many as 1.5 million men and women in the United States may already be infected. This tragic story will continue to unfold in the years ahead.

Barrier contraceptives, e.g., condoms or diaphragms, protect against transmission of STDs. If used consistently and correctly, condoms provide highly effective protection against a range of STDs. Numerous studies among soldiers and naval personnel have documented a protective effect. In laboratory studies, condoms have been found to be impermeable to Chlamydia trachomatis, cytomegalovirus, herpes simplex virus and human immunodeficiency virus. Diaphragms also protect against transmission of STDs, although no studies have investigated diaphragm use without use of a spermicide. In clinical studies, both cervical gonorrhea and pelvic inflammatory disease (PID) were reduced among women who used a diaphragm plus spermicide.

While condoms and diaphragms pose a mechanical barrier to sexually transmitted pathogens, spermicides constitute a "chemical" barrier. Spermicides are detergents that destroy cell walls—not only cell walls of spermatozoa but also those of a broad range of sexually transmitted organisms. In laboratory studies, spermicides have been shown to kill or inactivate the gonococcus, Treponema pallidum, Trichomonas vaginalis, herpes simplex virus, Ureaplasma organisms and human immunodeficiency virus. In vivo studies have demonstrated protection against cerebral gonorrhea and PID.

The impact of the human immunodeficiency virus epidemic is just beginning to be felt; as many as 1.5 million men and women in the United States may already be infected.

On the negative side, use of a diaphragm increases a woman's risk of developing a urinary tract infection by about 2- to 2.5-fold. Barrier contraceptives used in conjunction with spermicides have a complementary effect. Hence, for persons who have intercourse outside of mutually monogamous relationships, use of a barrier contraceptive plus spermicide should be encouraged, regardless of what method of contraception is being used. For example, I have a number of young patients who are simultaneously using oral contraceptives plus condoms and foam—each for different reasons.

Oral contraceptives (OCs) are the most popular and effective method of reversible contraception in the United States. Used by more than 11 million women, combination estrogen-progestin pills confer protection against being hospitalized with PID. More than ten studies have found the reduction in risk to be about 50 percent. One study has suggested that this protection applies to chlamydial salpingitis as well as to gonococcal salpingitis, although protection against the latter was stronger.

OCs and PID

How this protective effect is mediated is unknown. One hypothesis is that the progestin in OCs makes cervical mucus relatively impermeable to sperm—and pathogens. Alternatively, changes in the endometrial histology, decreased menstrual blood flow, decreased retrograde menstruation or some combination of these may be responsible. When pill users do develop PID, the course of the disease appears modified by pill use: pill users have less severe inflammation of the fallopian tubes, as judged by laparoscopy. Moreover, use of OCs also appears to protect against the Fitz-Hugh-Curtis syndrome. As perihepatitis caused by either the gonococcus or C. trachomatis, this syndrome is an important cause of right upper quadrant pain in young women.

All the news concerning OCs and STDs is not good, however. Over a dozen studies have found that women who use OCs have about a two-fold increased risk of cervical infection with C. trachomatis. This may be mediated through cervical ectropion, which tends to increase in size in pill users. Since C. trachomatis preferentially infects columnar epithelium, a woman's cervix may be more susceptible to this organism.[13]

[13] Dr. David A. Grimes is a professor in the Department of Obstetrics and Gynecology at the University of Southern California School of Medicine, Women's Hospital, Los Angeles, CA.
In laboratory studies, spermicides have been shown to kill or inactivate the gonococcus, Treponema pallidum, Trichomonas vaginalis (shown above), herpes simplex virus, Ureaplasma organisms and human immunodeficiency virus.

The potential relationship between IUDs and PID led to the downfall of IUDs in the United States. Regrettably, much of this concern was unwarranted, as revealed by recent, more sophisticated epidemiologic studies. The risk of PID among IUD users has been exaggerated for several reasons. First, most studies prior to 1980 compared the risk of PID in IUD users with that in women using other contraceptives. As discussed above, since other contraceptives lower the risk of PID, these comparisons made the risk associated with IUD users seem spuriously high. The appropriate comparison group for such studies is sexually active women not using contraception. In studies with this comparison group, the risk of PID associated with IUD use is much lower than in most early reports.

Second, ascertainment bias has inflated the apparent risk. Physicians are probably more likely to diagnose PID in an IUD user than in another woman with the same complaints and findings but without an IUD in place, because the physicians are aware of the putative association between IUD use and PID. This relative overdiagnosis of PID among IUD users would artificially increase the risk of PID among IUD users. In studies using more objective outcome measures (such as laparoscopy or diagnosis), the increase in PID risk has been small for IUD users, ranging from 1.5 to 2.6 times higher than for women not using IUDs.

Third, women who use IUDs are probably different from women who use other contraceptives—or none. These differences, such as numbers of sexual partners, frequency of coitus and personal hygiene, may be important risk factors of PID, though very difficult to quantify. This type of bias may account for much of the reported increase in the risk of PID among IUD users.

Several studies suggest that the risk of PID is inversely related to duration of use of the IUD. In the largest of these studies, Lee and her colleagues at the Centers for Disease Control found that in the first month after insertion, the risk of PID was increased about four-fold over that for non-contraceptors. In months 2 through 4, the risk fell to 1.7-fold, just barely statistically significant. By five months and beyond, the risk was not.

Condoms have been found to be impermeable to Chlamydia trachomatis (as seen above in an iodine stain), cytomegalovirus, herpes simplex virus and human immunodeficiency virus.

Physicians are more likely to diagnose PID in an IUD user than in another woman with the same complaints and findings but without an IUD in place, because the physicians are aware of the putative association between IUD use and PID.

This observation supports the hypothesis that most PID related to IUD use stems from bacterial contamination of the endometrium at the time of insertion. That contamination routinely occurs during this instrumentation has been known for more than 20 years. Further evidence for this hypothesis comes from a randomized clinical trial recently conducted in Nairobi, Kenya. Women given a single oral dose of 200 mg of doxycycline at the time of IUD insertion had a one-third lower risk of PID in the first month of use than did women given a placebo at insertion. In general, PID that develops more than four months after insertion appears due to acquisition of an STD rather than to the insertion of the IUD.

Contraceptives Reviewed

In summary, barrier methods of contraception confer significant protection against a number of STDs, especially when used in conjunction with spermicides. OCs lower a woman's risk of being hospitalized with PID, although the risk of chlamydial cervicitis appears to be doubled. Finally, the risk of PID among IUD users has been exaggerated as the result of methodologic problems with published studies. IUD use does appear temporally related to PID, which can be attributed to contamination of endometrial cavity at the time of insertion. If supported by other studies now in progress, use of prophylactic antibiotics at IUD insertion may make IUDs even safer in the years ahead.
CURRENT STATUS
OF BARRIER CONTRACEPTION

Malcolm Potts, MD, MPH
The 1980s have seen a reversal of previous declines in the relative importance of barrier methods of contraception. The rapid spread of a number of STDs and the dramatic appearance of AIDS, along with the appropriateness of barrier methods for social marketing in Third World countries is leading a renaissance of interest and increase in overall use at a global level.

Condoms are still the only reversible male method of contraception, and they provide the most effective protection against STDs and AIDS that is known. Condoms have proved popular in countries where there is a division of sexual roles within marriage and they have been the most popular single method in the quite successful social marketing of contraceptives for birth control that has been carried out in a number of countries.

The limitations of condoms are that they are relatively high in cost, they have a poor shelf-life, and uneven acceptability. The 1990s may see condoms made from plastics enter widespread use.

Spermicidally lubricated condoms have been used since the 1970s, and have a number of theoretical advantages in birth control and in retarding STDs, although it remains exceptionally difficult to prove these advantages in clinical use.

New female barrier methods of contraception continue to be invented.
Today Sponge, the C-Film, the "female condom" have either entered the marketplace or are under intensive investigation. The cervical cap, which has been available in Europe for 150 years, has just reached the American market. While new female barrier methods can be studied prior to introduction, it is difficult to obtain objective information on the effectiveness of over-the-counter methods of contraception once they are in widespread use.

Biologically, spermicides are a logical and potentially safe and simple way to interrupt human fertility. To date, the failure rates of spermicides have been higher than that for systemic or mechanical methods. If new spermicides, cocktails of spermicides, or innovations in delivery systems could be devised with substantially lower failure rates than those now in use, spermicides would be likely to become exceedingly important -- both as methods of birth control and as a way of slowing the spread of STDs and AIDS.
IUDs—NEW DESIGNS/NEW AWARENESS

David Grimes, MD
CONTRACEPTION

INTRAUTERINE DEVICES AND PELVIC INFLAMMATORY DISEASE: RECENT DEVELOPMENTS

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Department of Obstetrics and Gynecology
University of Southern California School of Medicine
Los Angeles, California 90033

The potential relationship between use of intrauterine devices and pelvic inflammatory disease is one of the most important issues in contraception today. A number of large, sophisticated studies published since mid-1980 have clarified this association. All have consistently revealed an increased risk of pelvic inflammatory disease among intrauterine device users, but the most objective of these studies indicate a relative risk compared to women using no method (1.5 - 2.6) lower than previous estimates. For most intrauterine device wearers, the increased risk of pelvic inflammatory disease persists for only a few months after insertion. The Dalkon Shield appears associated with a higher risk of pelvic inflammatory disease than the Lippes Loop, Saf-T-Coil, or copper devices. Careful selection of candidates for intrauterine devices may further reduce the risk of intrauterine device-associated pelvic inflammatory disease.

INTRODUCTION

The potential association between use of intrauterine devices (IUDs) and the development of pelvic inflammatory disease (PID) is one of the most important issues in contraception today. Pelvic inflammatory disease is the most frequent serious infection women encounter during their lifetimes. For example, in the United States, an estimated 1 million cases occur each year, and 1 in 7 women in the United States report having had PID in the past (1). In Sweden, the annual incidence of PID among women 15-34 years of age is estimated to be 1% (2). PID has been linked with increasing rates of ectopic pregnancy and infertility (2,3). In addition, over 150 women die from PID each year in the United States alone (4). Because of the high incidence of PID and the seriousness of its sequelae, if IUD use were to increase a woman's risk of PID, then the public health impact of such an association could be large.

As of mid-1980, 16 studies (5-20) had addressed the IUD-PID question. Three comprehensive review articles (21,22,23) concurred that the available literature supported the hypothesis that IUD users were at a 2- to 9-fold increased risk of developing PID compared with other women. The consistency of the findings in these 16 studies suggested a causal association between IUD use and PID.
CONTRACEPTION

On the other hand, these studies had a number of methodologic limitations, one of the most serious being inclusion of women using barrier methods or oral contraceptives as the comparison group. By 1980, the protective effect of these methods of contraception on the development of PID had been recognized (22,23). When only women not using any contraceptive method comprised the comparison group, the relative risks of PID among IUD users generally decreased, in some studies to non-significant levels. However, in all of the studies where this correction was possible, the relative risk for IUD users remained greater than 1.0, indicating an increased risk (23).

Since mid-1980, a number of large, sophisticated studies have clarified the relationship between IUDs and PID. This article will summarize and critique those dealing with PID and its sequelae of tubal infertility. Recent pathomorphologic studies (24) of fallopian tubes excised in the course of tubal sterilization will not be discussed; the inflammatory response seen in fallopian tubes of IUD users represents a sterile salpingitis, and its relationship to infectious salpingitis, if any, has not been established (25).

REVIEW OF RECENT LITERATURE

Case-Control Studies

In 1980, Pauvonen and Vesterinen (26) published a prospective case-control study from Helsinki, Finland (Table I). Cases were women hospitalized with acute PID; controls were asymptomatic sexual partners of men with non-gonococcal urethritis. Compared with women using "other methods (of contraception) or none", IUD users had a two-fold increased risk of PID, a statistically significant difference.

The next case-control study which was published (27) remains the largest study of this question to date. In the Women's Health Study, 16 hospitals in the United States included as cases women admitted with acute PID; controls were women admitted for medical and surgical illnesses. Compared with women using no contraception, IUD users had a relative risk of PID of 1.6, a statistically significant difference. Using a logistic model, the authors were able to rank the independent contribution of numerous risk factors for PID: more than one sexual partner, 2.6; coitus more than 5 times per week, 1.9; age less than 25 years, 1.9; race black, 1.8; current IUD use, 1.6; and parity 1 or more, 1.2. Other potential risk factors were not statistically significant.

Two case-control studies published in 1983 examined the association between PID and IUDs in general and between PID and specific types of IUDs. In one, Kaufman and associates (28) in the Boston University Drug Epidemiology Unit used as cases women admitted to collaborating hospitals with first episodes of acute PID; controls were women admitted with other conditions. Compared with women using other contraceptives (but never an IUD), IUD users had a relative risk of 8.6, a statistically significant difference.
Table I

Summary of recent case-control studies concerning intrauterine devices and pelvic inflammatory disease

<table>
<thead>
<tr>
<th>Authors (Ref. No.)</th>
<th>Location</th>
<th>No. of Cases</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paavonen and Vesterinen (26)</td>
<td>Helsinki, Finland</td>
<td>144</td>
<td>2.1</td>
<td>1.2 - 3.5</td>
<td>Standardized for effect of parity. Referent group: women not using IUDs or OCs</td>
</tr>
<tr>
<td>Burkman et al. (27)</td>
<td>16 U.S. hospitals</td>
<td>1,447</td>
<td>1.6</td>
<td>1.2 - 2.0</td>
<td>Adjusted for the effect of age, race, parity, no. of partners, frequency of coitus. Referent group: women not using contraception</td>
</tr>
<tr>
<td>Kaufman et al. (28)</td>
<td>U.S. and Canadian hospitals</td>
<td>155</td>
<td>8.6</td>
<td>5.3 - 13.8</td>
<td>Standardized for effect of age. Referent group: women using contraception but never an IUD</td>
</tr>
<tr>
<td>Lee et al. (29)</td>
<td>16 U.S. hospitals</td>
<td>657</td>
<td>1.9</td>
<td>1.5 - 2.4</td>
<td>Adjusted for effect of education. Referent group: women not using contraception</td>
</tr>
<tr>
<td>Witoonpanich et al. (30)</td>
<td>12 centers worldwide</td>
<td>608</td>
<td>11.5</td>
<td>3.6 - 36.2</td>
<td>Nulliparous women in developed country; Referent group: women not using contraception, no prior IUD use</td>
</tr>
<tr>
<td>Cramer et al. (31)</td>
<td>7 U.S. and Canadian centers</td>
<td>283</td>
<td>2.0</td>
<td>1.5 - 2.6</td>
<td>Primary tubal infertility as outcome, adjusted for multiple factors. Referent group: women not using contraception</td>
</tr>
<tr>
<td>Daling et al. (32)</td>
<td>King County, Washington</td>
<td>159</td>
<td>2.6</td>
<td>1.3 - 5.2</td>
<td>Primary tubal infertility as outcome, adjusted or matched for multiple factors. Referent group: women with no prior IUD use</td>
</tr>
</tbody>
</table>
CONTRACEPTION

Lee and associates (29) in the other 1983 report, re-analysed the Women's Health Study (27) data in more detail. Compared with women not using contraception, IUD users had a relative risk of 1.9 for a first attack of PID, a statistically significant difference.

In 1984, Witoonpanich and associates (30) reported a large multicenter study sponsored by the World Health Organization and conducted in both developing and developed countries. Compared with women using no contraception and having never used an IUD, women using an IUD had a relative risk ranging from 2.3 to 11.5 (all statistically significant) depending on parity and type of country.

Finally, two case-control studies published in 1985 addressed the association between IUD use and primary tubal infertility, which may result from PID. Cramer and associates (31) in a multicenter study, used as cases infertile women with documented tubal disease; controls were women who delivered liveborn children during the years of the study. Compared with women who had never used contraceptives or who had used them for less than 3 months, women who had used IUDs had a relative risk of primary tubal infertility of 2.0, a statistically increased risk.

In the companion study, Daling and associates (32) in Seattle used as cases infertile women with documented tubal disease; population-based controls were women who gave birth the year after cases had started trying to conceive. Compared with women with no prior IUD use, women who had ever used any IUD had a relative risk of primary tubal infertility of 2.6, a statistically significant difference.

Cohort Studies

Two large prospective cohort studies corroborate the findings of the preceding case-control studies. In the first, Westrom (2) described his population-based study of laparoscopically-proven PID among women aged 20-29 years in Lund, Sweden (Table II). Compared with sexually active women not using contraception, women using IUDs had a relative risk of PID of 1.5, a statistically significant difference.

In the second study, Vessey and associates (33) reported the experience of women in the Oxford Family Planning Association contraceptive study. Compared with women using other methods of contraception, women using an IUD had a relative risk of acute "definite" PID of 10.5, a statistically significant difference.
Table II
Summary of recent cohort studies concerning intrauterine devices and pelvic inflammatory disease

<table>
<thead>
<tr>
<th>Authors (Ref. No)</th>
<th>Location</th>
<th>No. of Cases</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westrom (2)</td>
<td>Lund, Sweden</td>
<td>571</td>
<td>1.5</td>
<td>1.2 - 1.9</td>
<td>Referent group: sexually active women not using contraception</td>
</tr>
<tr>
<td>Vessey (33)</td>
<td>17 clinics, England and Scotland</td>
<td>42</td>
<td>10.5</td>
<td>5.4 - 32</td>
<td>Standardized for effect of age. Referent group: women using contraception other than IUD</td>
</tr>
</tbody>
</table>

PID and IUD Insertion

The increased risk of PID associated with IUD use centers around the time of insertion. Numerous studies (34,33,29,35) have documented that the risk of acquiring PID is inversely related to the duration of use. In the largest of these studies (29), the risk of PID (excluding women using the Dalkon Shield) was significantly elevated only during the first four months of use. The relative risk was highest (3.8) within the first month; for months 2 through 4, the risk fell to 1.7, which is only marginally significant statistically. By 5 months of use, the risk was not significantly higher than the baseline risk of PID. These data support the hypothesis that contamination of the endometrial cavity at the time of IUD insertion accounts for most cases of IUD-related PID.

PID and Type of IUD

The risk of PID appears higher with the Dalkon Shield than with other devices. Six reports published since mid-1980 have examined device-specific risks of PID or tubal infertility (Table III). Most published studies lack sufficient power to identify clinically important differences in risks of PID or infertility associated with various IUDs; hence, Table III provides a qualitative assessment of the risks, in decreasing order.

Vessey and associates (33) found the Dalkon Shield to be associated with the highest rate of PID (8.1 per 1,000 woman-years), but this rate was based on a numerator of only 3 cases. Hence, confidence intervals around this rate would be large. Nevertheless, this rate was 7 times higher than that with the Lippes Loop and nearly 9 times that with the copper devices.
Table III
Summary of recent studies concerning specific types of intrauterine devices and pelvic inflammatory disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Type of Study</th>
<th>No. of Cases</th>
<th>Rank Ordering of Risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessey et al.</td>
<td>17 clinics, England and Scotland</td>
<td>Cohort</td>
<td>42</td>
<td>Dalkon Shield, Saf-T-Coil, Other/Unknown Lippes Loop, Copper Device</td>
<td>Acute definite PID. Significance testing not reported</td>
</tr>
<tr>
<td>Kaufman et al.</td>
<td>U.S. and Canadian hospitals</td>
<td>Case-control</td>
<td>155</td>
<td>Dalkon Shield, Saf-T-Coil, Lippes Loop, Other, Copper</td>
<td>Risk with Dalkon Shield significantly higher than with copper device</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>16 U.S. hospitals</td>
<td>Case-control</td>
<td>657</td>
<td>Dalkon Shield, Progestasert, Copper 7, Saf-T-Coil, Lippes Loop</td>
<td>Risk with Dalkon Shield significantly higher than with other IUDs</td>
</tr>
<tr>
<td>Snowden &amp; Pearson</td>
<td>17 clinics in England, Scotland and Wales</td>
<td>Cohort not stated</td>
<td></td>
<td>Dalkon Shield, Lippes Loop 2D, Lippes Loop 3C</td>
<td>Differences not significant</td>
</tr>
<tr>
<td>Cramer et al.</td>
<td>7 U.S. and Canadian centers</td>
<td>Case-control</td>
<td>283</td>
<td>Dalkon Shield only, Lippes Loop, Saf-T-Coil only, Non-copper IUD, Other combination Copper device only</td>
<td>Primary tubal infertility as outcome. Risk with Dalkon Shield, Lippes Loop, and Saf-T-Coil significantly higher than with copper device</td>
</tr>
<tr>
<td>Daling et al.</td>
<td>King County, Washington</td>
<td>Case-control</td>
<td>159</td>
<td>Dalkon Shield, Lippes Loop, Saf-T-Coil, Copper IUD</td>
<td>Primary tubal infertility as outcome. Significance testing not reported</td>
</tr>
</tbody>
</table>
Kaufman and associates (23) found the same hierarchy of risks as did Vessey and associates. In this case-control study, the risk of PID among users of the Dalkon Shield was about 4 times that among women using the Lippes Loop and 6 times that among users of copper devices. The difference in risk of PID between users of the Dalkon Shield and users of copper devices was statistically significant.

Lee and associates (29) found that women using the Dalkon Shield had a statistically significant increase in the risk of PID (8.3) compared with women using no contraception. The risk associated with the Dalkon Shield was 5 times that associated with other IUDs. The other devices had similarly elevated increased risks; the study lacked sufficient power to distinguish between devices other than the Dalkon Shield.

Snowden and Pearson (36) in a cohort study from the United Kingdom, reported rates of pelvic infection associated with the Dalkon Shield, two sizes of Lippes Loop, and the Gravigard (Copper 7). Data for the Gravigard were too sparse for analysis. The gross cumulative rate of pelvic infection among women using the Dalkon Shield (5.8 per 100 women) was higher than the rates with the Lippes Loops (5.1 and 4.8), although these differences were not statistically significant.

Both studies of tubal infertility found the risk highest with the Dalkon Shield and lowest with copper devices. In the study of Cramer and associates (31), the increased risk of primary tubal infertility was statistically significant for users of the Dalkon Shield (3.9), Lippes Loop or Saf-T-Coil (2.9), and copper IUDs (1.0). For secondary tubal infertility, the risk associated with copper devices was not statistically significant. Of note, women with only one sexual partner had no increased risk of primary tubal infertility associated with IUD use.

In the study of Daling and associates (32), the relative risk of primary tubal infertility was 6.8 for users of the Dalkon Shield, 3.2 for users of the Lippes Loop or Saf-T-Coil, and 1.9 for users of copper devices. The risk associated with the copper devices was not statistically significant.

Methodologic Problems

Formidable methodologic problems face studies of the association between IUDs and PID. These have been reviewed in detail elsewhere (21,22,37,23,25,38). Several critical biases deserve mention here, however.

First, as described previously, many early studies included users of barriers or oral contraception in the reference group (23). Use of these contraceptives confers significant protection against upper genital tract infection in women (39). By comparing IUD users to these women, early investigations artificially elevated the risk of PID associated with IUD use. In recent studies, this effect can be seen in the high relative risk observed by Vessey and associates (33) (10.5) compared with other recent studies having women not using contraception as the reference group (Tables I and II).
Second, ascertainment bias is an important methodologic problem. PID is notoriously difficult to diagnose. For example, the predictive value of a positive clinical diagnosis of PID has been reported to be 0.65 (40). If diagnostic imprecision caused random misclassification, this would tend to obscure any relationship between IUD use and PID. In one study (10) when more rigorous diagnostic criteria for PID were used, the relative risk increased; in another (27) the opposite occurred.

The main concern, however, is the strong possibility of diagnostic bias introduced by the knowledge of IUD use. Physicians may be more likely to diagnose PID in IUD wearers than in women with similar complaints but without an IUD present. Overdiagnosis of PID in IUD users would spuriously increase the relative risk of PID among IUD users.

Three of the studies in Tables I and II minimize this bias by relying on objective evidence of the outcome measure. In the cohort study of Westrom (2), each patient thought to have PID underwent a diagnostic laparoscopy to confirm the diagnosis. Although this study cannot address "silent" PID that has few or no symptoms, this population-based investigation observed only a 50% increase in the risk of symptomatic PID among IUD users.

In both studies of tubal infertility (31, 32), objective evidence (laparoscopy, hysterosalpingography, or surgery) of tubal disease was required. The unique contribution of these studies is that they skirt the problems of overdiagnosis of PID among IUD users and omission of "silent" PID. In these studies, IUD use overall increased a woman's risk of tubal infertility from 2- to 2.6-fold. Thus, these three studies confirm an increased risk of PID (or its sequelae) among IUD users, although the magnitude of the risk is substantially lower than many previous estimates (23).

Third, women who choose an IUD for contraception may differ from other women in important - yet unmeasured - ways. These differences in personal lifestyles or sexual behaviour may influence their risk of acquiring PID. Previous PID, socioeconomic status, number of sexual partners, coital frequency, and the presence of sexually transmitted diseases have received the most attention. Although the role of parity remains unclear (38), the contribution of sexually transmitted pathogens appears important. In stable, monogamous relationships, IUD use carries little risk of PID.

**CONCLUSION**

Since the sixteen reports reviewed by Senanayake and Kramer in 1980 (23), nine additional reports have found a significantly increased risk of PID or tubal infertility among IUD users. These 25 studies, conducted in many different countries by different investigators with different diagnostic criteria, have all found an increased risk of PID or its sequelae among IUD users, which argues strongly for a causal relationship. The strength of this association in the most objective studies ranges from a relative risk of 1.5 to 2.6; these may be overestimates themselves due to selection bias and confounding.
Several lines of evidence support this being a causal association. The short sequence between insertion and development of PID is temporally correct, and the association between these two events is biologically plausible (41). However, the association between IUD use and PID is not specific; PID clearly has other etiologies and other risk factors.

Most IUD-related PID can be attributed to the insertion of the device. With the exception of users of the Dalkon Shield, PID that develops more than 4 months after insertion appears to be due to other factors, such as acquisition of a sexually transmitted disease.

The existing literature also supports the hypothesis that the Dalkon Shield carries a greater risk of PID than do other devices. Unlike other IUDs, the Dalkon Shield appears to continue to increase a woman's risk of PID beyond 4 months after insertion (29). When the Dalkon Shield is segregated from the other IUDs in published studies, the risk of PID associated with IUDs in general is substantially lower than was previously thought.

The public health impact of IUD use on PID depends on the incidence of PID in the community, the prevalence of IUD use, and the magnitude of the relative risk. For example, an estimated 2,153,500 women in the United States used IUDs in 1982 (42). If one assumes an incidence of PID of 1% among women of reproductive age (2), then 21,500 cases of PID per year would be expected in a cohort of this size. If the relative risk associated with IUD use is assumed to be 2.0, then an additional 21,500 cases per year could be attributable to IUD use.

An alternative way of assessing the contribution of IUD use to PID is calculation of the population attributable risk. This figure is the proportion of PID in the community attributable to IUD use. If one assumes that 4% of women of reproductive age in the United States used an IUD in 1982 (42) and that the relative risk associated with IUD use was 2.0, then 4% of all PID in the United States in that year was attributable to IUD use.

Epidemiologic data (27) can identify appropriate candidates for IUDs and thus minimize the risk of PID. For example, in the United States white women aged 25 years or older, who have only one sex partner and who have coitus 5 or fewer times per week can be expected to have little risk of PID.

In conclusion, IUD use appears related to a small but real risk of PID, which appears due to endometrial contamination at insertion. Careful selection of candidates for IUDs may reduce the risk of PID. However, this risk must not be considered in a vacuum; it must always be balanced against the benefits of highly effective contraception and protection against ectopic pregnancy (43). Moreover, for women who are unwilling or unable to use alternative methods of contraception, the risk of PID must be weighed against the risks associated with pregnancy and its complications.
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IMMUNOLOGIC APPROACH
TO CONTRACEPTION

Nancy J. Alexander, PhD
Vaccines have been successfully used for over 150 years to control infectious diseases and this approach has long been considered in other aspects of medicine, including fertility regulation. Until recently, problems of identification, mass production and testing have seemed insurmountable. But recent biotechnologic advances have alleviated some of these difficulties. With the emergence of hybridoma and recombinant DNA technologies, previously rare vaccine antigens, including human proteins can potentially be mass produced in pure form. Advances in understanding of adjuvants and immunoregulation assure a more effective immunization. One major concern is that the effectiveness of fertility control must be in the 95% range and this level is rarely achieved with viral or bacterial antigens even though these pathogenic agents are usually high immunogenic.

The two prerequisites for a contraceptive vaccine are that the antigen be unique for the reproductive tract and, secondly, that the antigen have a fertility-related function. Thus, the antigen must be absent from other tissues or cells and it must have an action that can be blocked by antibody or located on a cell that can be lysed by complement.

Research emphasis has focused on methods for immunizing women to prevent fertilization or disrupt early pregnancy. Many reproductive hormones as well as antigens isolated from the zona pellucida, sperm, embryonic tissue and fetal tissue appear to qualify as possible targets for vaccine. The most advanced approach involves antibodies based on synthetic peptides of the carboxyl-terminal region of beta-hCG. This hormone is produced in the cytoplasm of the syncytiotrophoblast cells and provides gonadotropin support to the corpus luteum
during early gestation. Antibodies to hCG have been shown to neutralize the endocrine activity of the hormone when injected into laboratory animals. The hCG appears on the surface of trophoblast cells and thus these cells are a good target for a contraceptive vaccine. Since antibodies develop to the intact hCG molecule cross-react extensively with luteinizing hormone (hLH), the beta subunit (B-hCG) has been considered as a vaccine antigen. Although antibodies raised against B-hCG in rabbits and baboons cross react to some extent to hLH, the reaction is much weaker than when the whole molecule is used as the immunogen. Use of this B-hCG immunogen has resulted in pronounced infertility in baboons and marmosets. Since the molecule is not highly immunogenic, various processing and coupling procedures have been tried. Recent approaches employ a synthetic molecule, the C-terminal portion; lack of any carbohydrate moiety does not appear to affect the immunological properties of the molecule. The B-hCG peptides, however, are even more weakly immunogenic and must be conjugated to a larger carrier molecule to raise significant antibody levels. Phase I clinical trials involving immunization with B-hCG peptide have been completed and Phase II studies are being planned.

Antibodies to FSH have been used in male monkeys and they result in infertility due to elimination of complete spermatogenesis. Whether this effect is transient or can be long lasting remains a question.

Antibodies to the zona pellucida have excellent potential in the contraceptive vaccine arena. Successful fertilization of a mammalian oocyte requires a complex series of interactions between the sperm and the zona pellucida (ZP), a protective extracellular matrix surrounding the mature ovum. Oogenesis occurs during fetal life, but final maturation is completed shortly after ovulation. During this maturation there is a production of specialized
antigenic substances that could provide targets for immune contraception. Specific glycoproteins are involved in sperm binding as well as sperm transport through the zona pellucida. Elegant studies by Wassarman and associates have demonstrated that the zona pellucida, in mice, is composed of 3 different glycoproteins. ZP3 possesses receptor activity responsible for binding sperm to unfertilized mouse ZP. Acrosome intact mouse sperm recognize and interact with specific O-linked oligosaccharides of ZP3 resulting in sperm-egg binding. Binding causes sperm to undergo the acrosome reaction. Bound acrosome-reacted sperm are able to penetrate the zona pellucida. The ZP3 molecule is approximately 30% N-linked oligosaccharides and 10% O-linked saccharide. Most probably the O-linked saccharide is the ligand for the sperm receptor. Recent studies in guinea pigs have shown that animals immunized with an antigen found on the surface of the sperm thought to be associated with the zona receptor prevent fertilization. Other studies involving immunization with zona antigens have resulted in ovarian damage. Studies to determine whether more purified antigens can alleviate the problems of ovarian involvement are underway in several laboratories (Table ).

Table Current Nomenclature of Zone Pellucida Glycoproteins in Mammals

<table>
<thead>
<tr>
<th>Species</th>
<th>Glycoprotein nomenclature</th>
<th>Mol. wt. range (kD)</th>
<th>Isolation and protein detection methods</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig</td>
<td>PZ1</td>
<td>40-110</td>
<td>2D-PAGE, reducing gradient gels, Coomassie blue, silver stain</td>
<td>Dunbar et al. (1986)</td>
</tr>
<tr>
<td></td>
<td>PZ3</td>
<td>70-110</td>
<td>2D-PAGE, nonreducing, 7% acrylamide, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>SDK</td>
<td>68-98</td>
<td>2D-PAGE, reducing gradient gels, 10% acrylamide</td>
<td>Subramanian et al. (1981)</td>
</tr>
<tr>
<td>Pig</td>
<td>ZP1</td>
<td>92-118</td>
<td>2D-PAGE, reducing gradient gels, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>ZP2</td>
<td>88-98</td>
<td>2D-PAGE, nonreducing, 7% acrylamide, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>ZP3 (FPZ2)</td>
<td>40-74</td>
<td>2D-PAGE, reducing gradient gels, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>ZP4</td>
<td>21</td>
<td>2D-PAGE, nonreducing gradient gels, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>BZK (ZP1/ZP2)</td>
<td>77-97</td>
<td>2D-PAGE, reducing gradient gels, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>SKK</td>
<td>40-70</td>
<td>2D-PAGE, reducing gradient gels, Coomassie blue</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>(dephosphorylated with TPMS)</td>
<td>35</td>
<td>1D-PAGE, reducing, 10% acrylamide, Coomassie blue</td>
<td>Skinner and Dunbar (1986)</td>
</tr>
<tr>
<td>Pig</td>
<td>(dephosphorylated with Endo-β galactosidase)</td>
<td>35</td>
<td>1D-PAGE, reducing, 10% acrylamide, Coomassie blue</td>
<td></td>
</tr>
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</table>
Sperm antigens may also be appropriate candidates for vaccine development (Figure). Many experimental and clinical studies have shown that exposure to sperm antigens can result in the development of antibodies. Sensitization occurs in males if the blood-testis barrier is breached as a result of physical or chemical trauma or infection. In man, antisperm immunity frequently develops after vasectomy, when leakage of sperm antigens may occur from the rete testis, epididymis, and efferent ductules. Experimentally induced or naturally occurring isoimmunization of females with sperm antigens has also been examined. It is apparent that under certain circumstances immune responses against sperm can be induced by systemic or local immunization with whole sperm or sperm components. The effect on fertility of deliberate immunization in the female is quite variable. In some studies there is no effect, immunization with other antigens impairs fertility because of reduced sperm viability or inhibition of some sperm function. Some immunization protocols lead to reduced fertility due to pre- or postimplantation embryo loss.
To identify relevant sperm antigens, the specificity of antibodies from individuals with putative immunologic and fertility have been examined. Immune complexes formed between antisperm antibodies and labeled solubilized sperm antigen preparations have been examined. More recently, reactions between electrophoretically separated sperm components and antibodies have been detected using western immunoblotting. Both methods have shown rather complicated binding patterns, but the results demonstrate that 1) normal sera contain sperm binding antibodies, 2) IgM antibodies from normal and infertile individuals often show identical sperm binding reactions, 3) no one specific antigen is uniformly recognized by IgG antibodies from patients with infertility, 4) antibodies in the sera from infertile males and females can recognize identical antigens indicating that certain sperm components can be both auto and isoantigenic, and 5) some sera known to contain antisperm antibodies do not show antigen antibody reaction, indicating that important antigenic determinants may be destroyed or modified during the preparation of solubilized sperm antigens.
Monoclonal antibodies to sperm specific antigens have been developed and tested for their ability to block specific functions using in vitro assays (e.g., sperm agglutination and immobilization assays, migration through cervical mucus, penetration of zona pellucida free hamster eggs, and in vitro fertilization). If the antigens are evolutionarily conserved, the ability of monoclonals to inhibit fertilization by passive immunization of female mice can provide an indication of the in vivo antifertility potential of the monoclonals. The monoclonal antibodies can be used to purify antigens by affinity chromatography. These purified antigens can be tested for a contraceptive effect by active systemic and/or local immunization regimes. This approach has been demonstrated successfully in guinea pigs immunized with the sperm antigen, PH20.

The sperm surface is a mixture of integral and peripheral proteins associated with the phospholipid bilayer of the plasma membrane. Transmembrane proteins may be physiologically important for sperm survival in the female reproductive tract. Integral proteins, additionally, would be expected to be involved in gamete interactions. Peripheral proteins may affect in sperm passage, for example through cervical mucus, and may protect the sperm cells within the female tract.

A key feature of cell membranes is the ability of membrane lipids and proteins to diffuse laterally. The cell phospholipid bilayer is stabilized by a submembranous cytoskeleton that can control the mobility of proteins and glycoproteins. More than most cells, the sperm surface is organized into distinct, highly specialized regions. Specific regions of the sperm plasma membrane are related to important physiological events that occur during fertilization.
Recent studies of capacitation, the acrosome reaction and fertilization are demonstrating the importance of sugar moieties in the cell membrane. As the male and female gametes meet, specific sperm receptors present on the surface of the zona pellucida interact with those of the sperm. Attachment and recognition are due to carbohydrate-protein interactions.

A key event in fertilization is capacitation and subsequently, the acrosome reaction. Capacitation involves the removal of surface-bound proteins originating from the epididymis and seminal plasma. This dissociation from the sperm surface takes place during sperm transit in the female tract. Some of these proteins serve an important function in maintaining membrane stability during sperm storage before ejaculation. For example, a glycoprotein synthesized in the corpus epididymis, called acrosome stabilizing factor, prevents a premature acrosome reaction. This factor reduces lateral mobility of certain membrane proteins and blocks membrane changes associated with the onset of the acrosome reaction.

Before the acrosome reaction, cholesterol, a membrane stabilizer is removed which allows for a redistribution of intrinsic membrane proteins. A quilt-like pattern of protein-poor (areas of high membrane fluidity) and protein-rich domains (low fluidity) are found over the anterior part of the head. The acrosomal membrane is characterized by high fluidity and fusigenic properties.

Sperm-egg interaction is initiated by binding of sperm to the zona pellucida. Key in this binding are the carbohydrates bound to the surface of the spermatozoa and the glycoproteins in the zona. The sea urchin is the best studied example of fertilization. The sperm-specific protein, bindin, exposed during the acrosome reaction mediates sperm adhesion to the egg vitelline layer.
that is composed of glycoconjugates. On boar spermatozoa, similar lectin-like proteins bind to dextran sulfate and to fucose.

Detection of carbohydrate protein interactions in several species has been studied by means of competitive sugar and lectin binding inhibition experiments. Fucose, galactose, and N-acetylglucosamine and N-acetylgalactosamine are the carbohydrates involved on the sperm surface of the hamster. D-mannose or D-glucose may be involved in toad gamete interaction. In the mouse, a galactosyltransferase interacts with terminal N-acetylglucosamine residues present in the zona pellucida. ZP3 purified from the zona pellucidae of 2-cell embryos does not interfere with gamete binding. Sugar moieties, rather than proteins, are the recognition components of sperm and egg. With increased understanding of fertilization events, we can better develop treatments for infertility or consider contraceptive interventions.
MALE CONTRACEPTION-
MEDICAL APPROACHES

Ronald Swerdloff, MD
MALE CONTRACEPTION

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REFERENCES:


ROLE OF USAID IN WORLD POPULATION

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Program Objectives

The population program of the Agency for International Development (A.I.D.) began in 1965. A.I.D.'s population assistance is part of a much larger U.S.-foreign assistance effort to the Third World. Along side programs in agriculture, education, health, human resources, and energy, the population program is about four to five percent of the total development assistance. While this percentage is small, A.I.D. nevertheless has been, and still is, the single largest donor for population. Almost $3.4 billion has been provided since 1965. About half of this amount has been given since 1980.

The program has three objectives which encompass concerns for human rights, human welfare, and economic development. The three objectives of the population program are to:

1) enhance the freedom of individuals in developing countries to choose voluntarily the number and spacing of their children;

2) improve the health and survival of mothers and children by promoting adequate birthspacing; by encouraging
childbearing during the safest years for women; and, by reducing abortions; and,
3) encourage population growth consistent with the growth of economic resources and productivity. (A.I.D. 1982; Gillespie 1987)

The underlying principles of U.S. population assistance are voluntarism and informed choice. Population assistance is not conditional; rather the assistance is provided to those developing countries that request it. In 1988, the program provided assistance for population activities in about 90 countries.

The population program supports activities in two broad areas: family planning service delivery (about 75 percent of total funding) and research designed to improve family planning technology. Service delivery areas supported by A.I.D. include:

- policy dialogue in developing countries that can legitimate and promote family planning programs in both the public and private sectors:
support of voluntary family planning programs,
including a range of strategies for service delivery
(e.g. clinic-based, subsidized commercial marketing,
and community-based distribution);

training of program personnel in reproductive health
and fertility management;

assistance in population and contraceptive information,
education, and communication; and

provision of contraceptive supplies (including oral
contraceptives, IUDs, condoms).

A.I.D.'s research effort includes:

biomedical research on safer, less expensive and more
acceptable and effective methods of contraception;

operations research to improve the management and
operation of service delivery programs; and
Gillespie & Seltzer

social science and demographic research to increase knowledge of the social (including health) and economic consequences of population change and to improve information on population dynamics and contraceptive use trends. (A.I.D. 1989)

Organization of Assistance

A.I.D. is a mission-oriented agency with overseas Missions or representation in 69 countries and 13 regional development offices. Population assistance is provided through A.I.D Missions (under bilateral or country-to-country projects) monitored by the overseas A.I.D. Mission staff; through regional projects monitored by the three Regional Bureaus (Africa, Asia/Near East, and Latin America/Caribbean); and by the Bureau for Science and Technology's Office of Population through centrally-funded projects. The allocation of resources under the Agency's population account is:

- Bilateral programs, accounting for about 40 percent of population assistance, are carried out by A.I.D. Missions in 32 countries.
Office of Population accounts for 47 percent of the assistance. The assistance is provided through grant agreements and contracts (47 in 1988) with U.S. government and private agencies. The projects are developed by the Office of Population and carried out by these various organizations and are designed to complement A.I.D. Mission programs. The projects support activities that are not readily included in the A.I.D. bilateral programs. In countries that do not receive bilateral assistance, these projects are the primary, and in some cases, the only source of population support. In 1988, the Office of Population funded over 1,400 projects in about 90 countries.

Regional population assistance programs account for about 11 percent of assistance.

The remaining two percent supports special Agency initiatives in the population field.
Funding Trends

Congress appropriates funds for population assistance under the Population Planning Section of the Foreign Assistance Act. Funding has totalled nearly $3.4 billion over the last twenty-three years; $1.9 billion has been obligated since 1981. In 1988, the population budget amounted to $232 million. A reduction in population funds since 1985 largely reflects budgetary constraints throughout the Federal government. (See Table 1 for a summary of A.I.D. funding for 1965-1988.)

Program Innovations

A.I.D.'s population assistance can be described in terms of a number of innovative program endeavors which have benefitted the population programs in developing countries. Seven in particular are reviewed briefly (Dumm 1988):

1. Fertility and contraceptive prevalence surveys have been essential for documenting the need for family planning and the effectiveness of service delivery efforts. Between 1974 and 1988, surveys have been conducted in 69 developing
countries. This is clearly the largest social science effort ever undertaken.

2. Improved contraceptive methods have greatly enhanced the safety, effectiveness and acceptability of methods in developing countries. Several methods which have been greatly improved are female sterilization, copper IUDs, and low-dose oral contraceptives. In addition, a subdermal contraceptive implant (NORPLANT\textsuperscript{R}) is being evaluated in clinical trials.

3. An operations research program has supported pilot and experimental projects and has been critical in demonstrating that family planning services are wanted and that they can be delivered efficiently in a variety of settings. This research has found that services can be effectively provided through a variety of delivery modalities including clinics, community-based and household distribution, and pharmacies.
4. Community-based distribution programs are a particularly effective means of outreach and have increased use of contraceptive prevalence at less cost than clinic-based delivery would have been. For example, outside Khartoum in the Sudan, contraceptive prevalence rose from 10.6 percent in 1980 to 33.5 percent by 1987 when village midwives provided family planning. In Muslim areas of southern Thailand, contraceptive prevalence increased from 12 to 39 percent after one year in which field workers were employed to sell pills and condoms.

5. A concerted effort to engage the private sector in developing countries has shown that the private sector (both for-profit and PVO) can be an effective channel for expanding access to family planning. While the non-profit private sector has pioneered the delivery of services in many countries, the for-profit sector is playing a growing role in countries as diverse as Egypt, Peru and Zimbabwe through commercial marketing of contraceptives and employee-based health insurance programs.
6. The Contraceptive Social Marketing project is one example of a successful private for-profit initiative. This project uses marketing and advertising techniques to increase the availability of services through commercial channels. In Mexico, a social marketing project was started with a government-subsidized chain of 17,000 grocery stores to make low-cost condoms available to low income groups. Sales in the first year of this project yielded $100,000 in revenue which is being used to purchase additional advertising.

7. A population communications project capitalizes on the commercial private sector to reach millions of couples with strong family planning messages for a fraction of the cost of the actual mass media time used. One example is an experimental rock video and hit song with a family planning message for young adults, performed by rock stars, Tatiana and Johnny in Mexico. This experiment was successfully replicated in Nigeria and the Philippines by other rock stars.
Program Impact

Substantial declines in fertility have occurred in several regions of the world. Between the early 1960s and the early 1980s, fertility decreased by over 50 percent in East Asia (principally China) and by 25-30 percent in South Asia and Latin America. For the African continent, fertility declined by less than five percent. Most of this change occurred in North Africa since fertility in many African countries remained the same or increased somewhat. (Merrick, 1986) Vigorous family planning programs in combination with social and economic development efforts have been credited with bringing about dramatic declines in fertility. (Lapham and Mauldin, 1984) A number of countries which have experienced dramatic reductions in their birth rates have also benefitted from substantial A.I.D. population assistance. (See Table 2) Two such countries are Thailand and Indonesia. Survey data show that in Thailand, average completed family size dropped from about 6.3 children to 2.3 between 1965 and 1987. In Indonesia, the average completed family size declined from 5.6 to 3.4 children over the same period. (Knodel 1987; Chayovan 1987; and Central Bureau of Statistics, 1987)
Future Needs

Estimates of the future demand for family planning indicate that formidable challenges lie ahead. (Gillespie, et.al 1988) Not only is the level of contraceptive prevalence likely to increase, but the number of potential users will increase dramatically simply due to growing populations. The cost and effort to provide services to the increasing number of potential users over the next twenty years will be enormous. The annual estimate for the year 2010 is between $9 and $10 billion. This estimate is three to four times the amount of resources currently being invested in family planning.

Given that donor funding for population has leveled off or even declined in terms of constant dollars, where will the additional resources come from to meet needs?

Greater emphasis is being placed on stimulating investments by developing-country governments and the private sector. A.I.D. is concentrating much of its funding on activities which are highly leveraged, that is, which have a multiplier effect.
Among such efforts are encouraging policy reforms and increasing the availability of more effective and inexpensive contraceptives. Finally A.I.D. population assistance is improving the efficiency of programs, for example, by training their program managers to improve their management skills and logistics management.
References


Table 1
Summary of A.I.D. Population Assistance
1965-1988
(in $000,000)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<td>Office of Population</td>
<td>259.7</td>
<td>942.3</td>
<td>133.5</td>
<td>115.0</td>
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<td>Regional Programs</td>
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<td>Africa</td>
<td>35.0</td>
<td>74.7</td>
<td>26.1</td>
<td>33.8</td>
<td>36.9b</td>
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<td>172.8</td>
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<td>46.8</td>
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<td>58.9c</td>
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<td>Near East</td>
<td>21.2</td>
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<tr>
<td>Latin Amer/Carib</td>
<td>92.2</td>
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<td>30.2</td>
<td>24.6</td>
<td>22.1</td>
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<tr>
<td>All Other</td>
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<td><strong>GRAND TOTAL</strong></td>
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<td><strong>1961.4</strong></td>
<td><strong>237.5</strong></td>
<td><strong>230.5a/</strong></td>
<td><strong>233.5d/</strong></td>
<td><strong>3382.5</strong></td>
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</tbody>
</table>

Note: During 1985, the previously separate Asia and Near East regions of A.I.D. were combined into a single Asia/Near East (ANE) region. Prior to 1986, the funding levels reflect the previous division of program responsibilities.

a/ Excludes reprogrammed prior year deobligations.
b/ Development Fund for Africa
c/ Includes $8 million for Afghanistan
d/ Includes funds from Population Account and Development Fund for Africa

Table 2. Twenty Most Populous Developing Countries: Changes in Crude Birth Rates, 1965 - 1988

<table>
<thead>
<tr>
<th>Country</th>
<th>1988 Population (Million)</th>
<th>1965 Crude Birth Rate</th>
<th>1988 Crude Birth Rate</th>
<th>Percent Change</th>
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<tr>
<td>1. China</td>
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<td>33</td>
<td>21</td>
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<tr>
<td>2. India</td>
<td>817</td>
<td>43</td>
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<td>-23.3</td>
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<td>3. Indonesia</td>
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<td>45</td>
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<td>4. Brazil</td>
<td>144</td>
<td>40</td>
<td>28</td>
<td>-30.0</td>
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<tr>
<td>5. Nigeria</td>
<td>112</td>
<td>51</td>
<td>46</td>
<td>-9.8</td>
</tr>
<tr>
<td>6. Bangladesh</td>
<td>110</td>
<td>50</td>
<td>43</td>
<td>-14.0</td>
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<td>7. Pakistan</td>
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<td>47</td>
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<td>-8.5</td>
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<td>9. Vietnam</td>
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<td>10. Philippines</td>
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<td>35</td>
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<td>11. Thailand</td>
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<td>12. Egypt</td>
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<td>13. Turkey</td>
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<td>14. Iran</td>
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<td>15. Ethiopia</td>
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<td>17. Burma</td>
<td>41</td>
<td>41</td>
<td>34</td>
<td>-17.1</td>
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<td>18. Zaire</td>
<td>33</td>
<td>48</td>
<td>45</td>
<td>-6.3</td>
</tr>
<tr>
<td>19. Colombia</td>
<td>31</td>
<td>42</td>
<td>28</td>
<td>-33.3</td>
</tr>
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<td>20. Morocco</td>
<td>25</td>
<td>50</td>
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<td>-28.0</td>
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<tr>
<td>Total Developing</td>
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<td>-22.5</td>
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<tr>
<td>Country Listed</td>
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<tr>
<td>Total Developing</td>
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<td>Countries</td>
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<td>Total World</td>
<td>5,128</td>
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<td>28</td>
<td>-20.0</td>
</tr>
</tbody>
</table>

* Countries receiving significant amount of A-I-D. population assistance during 1965 - 1988 are underlined.

Source: Population Reference Bureau, 1988
HEALTH BENEFITS AND RISKS
OF ORAL CONTRACEPTIVE USE

Ruby T. Senie, PhD
Epidemiologic Assessment of the Health Benefits of Oral Contraceptive Use

Assessment of Associations Through Epidemiologic Investigations

I. Methods employed to detect and quantitate the effects of oral contraceptives on health status

- Case Reports: Clinical recognition of adverse reactions
- Trend analyses and ecologic studies
- Clinical Trials
- Observational studies
  - Case-Control (Retrospective) Studies
    - Methodologic Considerations
      - Selection of Study Population
      - Data Collection Techniques
      - Potential sources of bias
    - Analytic Methods
    - Advantages & Disadvantages
  - Cohort (Prospective) Studies
    - Methodologic Considerations
      - Selection of Cohort
      - Completeness of Follow Up
      - Criteria defining endpoints
    - Potential sources of bias
    - Analytic Methods
    - Advantages & Disadvantages

II. Epidemiologic Criteria for Evaluating Causal Relationships

- Strength of the Association
- Biologic Gradient; Dose-Response Effect
- Consistency of Association
- Plausibility
- Temporality
- Specificity
- Coherence of Evidence

The Health Benefits of Oral Contraceptive Use

- Current statistics on oral contraceptive use
* Proven Protective Effect
  * Epithelial Endometrial Carcinoma
  * Ovarian Carcinoma
  * Benign Breast Disease
  * Iron Deficiency Anemia
  * Ovarian Cysts
  * Pelvic Inflammatory

* Potential Protective Effect
  * Uterine Fibroids
  * Osteoporosis

* No Protective Effect
  * Toxic Shock Syndrome
  * Rheumatoid Arthritis

* Cardiovascular Disease: current versus past use

Oral Contraceptives and the Risk of Breast Cancers

* Description of the Cancer and Steroid Hormone Study (CASH)
  Methodology
  Initial Reports
  Subgroup Analyses

* Inconsistent Reports Associated with Breast Carcinoma
  Review of current literature
References:


2. Centers for Disease Control Cancer and Steroid Hormone Study and the National Institute of Child Health and Human Development: Combination oral contraceptive use and risk of endometrial cancer. JAMA 1987; 257:796-800.


USE OF ORAL CONTRACEPTIVES IN 1989

David F. Archer, MD
The introduction of the oral contraceptive "pill" in 1960 was hailed as a major breakthrough in the ability for individuals to control their reproductive potential. The development of the oral contraceptive dates back to 1849 with the discovery of male hormones by Berthold.1 Oral contraceptives are the result of research in physiology, hormone effects (endocrinology), and steroid chemistry.1 (Figure 1) The orally active progestational agents synthesized in the 1950's were the principal innovation, since orally active synthetic estrogens had been available for approximately twenty years.2 Although the synthetic estrogens alone would inhibit ovulation, control of menstrual bleeding was poor. Oral progestational agents alone also inhibit ovulation, but had comparable results in terms of irregular bleeding. The combination of both an orally active estrogen and progestin into one tablet (the pill) was found to inhibit ovulation with a lower dose of each hormone, and to provide a better degree of menstrual bleeding control.1,2

The initial oral contraceptive formulations contained 0.150 mg. of estrogen and 9.850 mgm. of a progestin. Over the succeeding 28 years, the dosages of each hormone have been reduced, resulting in an equally effective contraceptive agent, but with evidence of a "safer" product. In the mid-1970's in Western Europe and England, oral contraceptives containing greater than 50 mcg. of estrogen were removed from the market in response to concern over thromboembolic and cardiovascular complications related to the higher dose formulations.3,4 The early epidemiologic reports from the late 1960's and early 1970's have been the subject of much debate, criticism and reanalysis.3,4 However, a significant reduction in the dosage of the contraceptive hormones followed these reports. (Figure 2)
unique phenomenon has been the continued use of higher dose estrogen containing formulations in older women.\textsuperscript{5}(Figure 3) This reflects the prescribing practices of physicians and the consumer attitude resisting change of an accepted well-tolerated product.

Overall, in the United States between 1971 and 1980, approximately 8 million women ages 12 - 54 representing approximately 15 percent of the population used oral contraceptives.\textsuperscript{6} In 1988, the United States Food and Drug Administration, acting on the recommendation of the Fertility and Maternal Health Advisory Committee, have requested the removal from the United States market of oral contraceptives containing greater than 50mcg. of estrogen. This move reflects the continuing surveillance by the FDA of oral contraceptive use. Pharmaceutical manufacturers in the United States have responded to this by withdrawing the higher dose estrogen formulations from the market. It is estimated that the higher dose contraceptives are less than 5% of the U. S. market. The removal of >50mcg oral contraceptives took place in Western Europe and England in the mid-1970's. As mentioned above, the reduction in steroid dosage should lead to comparable reduction in the incidence of adverse effects.

The U. S. Food and Drug Administration is the principal regulatory agency for both new drugs and older marketed drugs in the United States. Since 1960, the number of Investigational New Drug (IND's) applications for contraceptives has fallen markedly. This reflects the fact that the FDA has required a higher standard of animal toxicology testing and a very conservative approach to clinical investigations of contraceptive agents. Recent attempts to reduce the costs of preclinical animal toxicology for contraceptive agents by redefining the appropriateness of the animal models and dosage, have been initiated by the Special Program for Research in Reproduction of the World Health Organization. A schematic representation of drug development in the United States is presented below, modified after DiRaddo.\textsuperscript{6,7}(Figure 4) It can be appreciated that the problems which involve time and costs for new drug development are large.
The Fertility and Maternal Health Advisory Committee of the USFDA is often asked to participate in this process as an objective non-governmental group. This Committee monitors and evaluates reports related to adverse effects attributed to oral contraceptives. This Committee, principally composed of Obstetricians and Gynecologists, is convened to consider the evidence relative to potential adverse effects and other information relative to oral contraceptives, and to make recommendations based on the data presented. This Committee has been instrumental in deciding on safety of oral contraceptives. The Committee has been actively involved in the wording of both the physician package insert and the patient package insert for oral contraceptives.

Oral contraception utilization is extensive. It has been estimated that between 60 - 100 million women worldwide are using oral contraceptives for family planning. However, the percentage of use of oral contraceptives vary with the populations under investigation. In the United States, current estimates are that oral contraceptives are used by 16 percent of the population between 15 - 54 years of age. The impact of family planning programs with a variety of contraceptive methods shows significant changes in the birth rate. The long-term benefits are a reduction of population growth and improved health of the family unit, as exemplified in the population decline in Indonesia. (Figure 5)

Changes in Oral Contraceptives:

Oral contraceptives have been extensively modified since their clinical introduction in 1960. One of the major and most significant changes has been the decrease in hormonal content. The reduction in estrogen and progestin dosage has been greater than 50% of the dosage in the early contraceptive formulations. The rationale behind the decrease in hormone concentration is the data that indicate a dose relationship between the estrogen and progestin content and metabolic and clinical abnormalities.
Risks Factors Contraindicating Oral Contraceptives:

Although the hormonal content of oral contraceptives has decreased, the prescribing habits of physicians have not changed as extensively. Higher dose estrogen-containing pills are more likely to be prescribed to older women, while the lower estrogen content pills were used in younger women.\(^5\) The cause of concern with this finding is that aging increases the risk for cardiovascular disease and other serious illness in both men and women. It would be more appropriate to prescribe lower estrogen dose oral contraceptives in the older age groups, although all ages will benefit from the reduced hormonal contact.

Physicians should take into account clinical risk factors for cardiovascular disease when prescribing oral contraceptives (Table 1). The occurrence of myocardial infarction is not significantly different between healthy oral contraceptive users versus non-users when this was done.\(^{16,17}\) Concordant with this is the finding that smoking accounts for almost all of the excess cases of myocardial infarction in women ages 35 - 44.\(^{17}\) Therefore, it is apparent that modification of risk factors (smoking), as well as not prescribing oral contraceptives to women with risk factors can have a significant impact on the occurrence of clinical disease.

**TABLE 1**

Risk Factors in Oral Contraceptive Users

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 35 years</td>
</tr>
<tr>
<td>Blood pressure &gt;140/90</td>
</tr>
<tr>
<td>Cigarette use</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Migraine headaches</td>
</tr>
<tr>
<td>Coagulation disorders</td>
</tr>
<tr>
<td>Family history of early cardiovascular disease</td>
</tr>
<tr>
<td>Obesity &gt;50% of Ideal Body Weight</td>
</tr>
</tbody>
</table>
Reduction in Oral Contraceptive Dosage:

Low dose oral contraceptives in healthy women are not found to result in serious cardiovascular problems. These data argue for the use of low dose oral contraceptives in healthy women over 35 years of age.

Monophasic preparations with \( \leq 50 \text{mcg} \) of estrogen and triphasic preparations have acquired a greater market share in the last 5 - 8 years. This change in prescribing patterns represents new information being applied by the practicing physician. The advantage in using these new formulations is that there is little to no change in lipoprotein, carbohydrate, and clotting factors.14

Cholesterol and lipoprotein changes have been associated with increased cardiovascular risk. Elevation in cholesterol and low density lipoprotein-cholesterol (LDL-C) are known to be correlated with an increase in myocardial infarction. A decrease in high density lipoprotein (HDL) specifically HDL\(_2\) is also a risk factor for cardiovascular disease. Generally speaking, estrogen administration results in a good outcome by increasing HDL and lowering LDL-C, while progestins negate the effects of estrogens. Oral contraceptive formulations contain various estrogen and progestin combinations and doses. There are over 30 oral contraceptive formulations available in the United States. Each individual has a different metabolic or biochemical reaction to the oral contraceptive, while diet and smoking can have an adverse effect on lipoprotein parameters. Extensive investigation of cholesterol and lipoprotein changes indicate that the higher the dose of progestin the more likely there was to be an adverse effect, usually by elevating LDL-C and reducing HDL\(_2\) levels.14 The sub-50mcg estrogen monophasic and triphasic preparations have been found to have minimal or no effect on serum lipoproteins and cholesterol.

Recent evidence in cynomolgous monkeys fed an atherogenic diet have shown comparable adverse changes in total cholesterol, HDL-C and LDL-C when placed on oral contraceptives. Although these adverse cholesterol and lipoprotein changes have been associated with increased cardiovascular risk, this study showed an
unforeseen improvement in coronary artery plaque size. These data support a beneficial effect of ethinyl estradiol on endothelial plaque formation.\textsuperscript{18,19}

**Glucose and Insulin Changes:**

Carbohydrate (glucose) utilization has also been found to be abnormal in women using the high dose estrogen formulation of oral contraceptives. This glucose intolerance is associated with a concurrent insulin intolerance. Current low dose monophasic and triphasic preparations do not result in any significant alteration in glucose utilization or insulin response.\textsuperscript{15,20} These data reinforce the increased safety of the lower dose estrogen contraceptive.

**Coagulation:**

Thrombo-embolic phenomenon has also been linked to the estrogen dose in oral contraceptives. Lowering the steroid dosage improves clotting factors and fibrinogen concentrations.\textsuperscript{13} How these changes in coagulating factors relate to the occurrence of clinical thromboembolism is not known. It appears that the clinical diagnosis of deep vein thrombosis is highly inaccurate with a high false positive rate. The use of venography, Doppler ultrasound and impedance plethysmography have increased the accuracy for diagnosis of deep vein thrombosis.\textsuperscript{21} This fact renders suspect the epidemiologic studies of the late sixties and early seventies relative to an increased risk of deep vein thrombosis in oral contraceptive users, which was based on clinical diagnosis alone.\textsuperscript{21}

The epidemiologic studies related to thrombosis and thromboembolism also evaluated women in one age group (15-44) and their oral contraceptive use. Current investigation would indicate the need for evaluating these women with narrower age ranges, as well as considering other risk factors. A more objective documentation of deep vein thrombosis could alter the current concept of increased risk of thromboembolism associated with oral contraceptives.

**Clinical Considerations:**

The change from high dose monophasic preparations to low dose monophasic or triphasic preparations can be accomplished without any change in contraceptive
efficacy. This change should be done by all practitioners for their patients in
the next 4 - 6 months. Appropriate counseling is necessary stressing the
benefits derived from the low dose hormonal preparations, as long as contra-
ceptive efficacy is maintained.\textsuperscript{22} It is important to understand that changing
doses, like changing formulations, may result in an increase in side-effects such
as breakthrough bleeding, headaches, and non-specific symptoms such as bloating
or nausea. However, anticipation of these problems in the counseling session is
of benefit to the consumer. Changes in menstrual flow and even lack of menses
can occur and in the latter instance, pregnancy should be considered and ruled
out with appropriate pregnancy tests, even though the contraceptive efficacy is
high.

New oral contraceptive users and women being changed from high to low dose
formulations should be placed initially on the triphasic preparations or the 30
and 35mcg monophasic estrogen formulations. The 50mcg monophasic formulations
should be used as backup for persistent breakthrough bleeding or other withdrawal
bleeding problems.\textsuperscript{23}

\textbf{Summary:}

In conclusion, the late 1980's bring to the physician and the consumer a
significant change in oral contraceptive use pattern. The removal of high dose
hormonal oral contraceptives have benefits to the consumer without loss of
contraceptive efficacy. The problems related to oral contraceptives in the
seventies have resulted in increased knowledge and improved safety for the
population using oral contraception. The history of oral contraceptive develop-
ment and refinement can be traced back over 100 years. Continued investigation
and evaluation have made the oral contraceptive preparations in use today
effective and safe.
REFERENCES


SEX STEROID HORMONES AND MANAGEMENT OF CARDIOVASCULAR DISEASE IN WOMEN

Robert H. Knopp, MD
A. Effects of sex steroids on lipoprotein physiology
   o Normal
   o Estrogens alone
   o Progestins alone

B. Effects of natural sex steroids at puberty:
   o No change in girls' HDL-C.
   o HDL-C in boys changes from a "female" to a "male" pattern at puberty.
   o Effects of lipoproteins on the fatty streak lesion in coronary arteries and aortas.
   o ASCVD risk in young men vs. young women.

C. Effect of birth control pills on lipoproteins:
   o High dose pills - raise LDL and may lower HDL, depending on formulation.
   o Significance for ASCVD is established for the older pills.
   o Lower dose pills - differences in HDL-C, especially in HDL2 are of lesser magnitude among the formulations; LDL-C raising effect is largely eliminated.
   o Persistent significance for ASCVD?

D. Effects of natural progestin, estrogen increases on lipoproteins in pregnancy:
   o Increases in estrogen and progestin.
   o Linear increases in TG and LDL-C.
   o HDL-C pattern is biphasic with a rise by 20 weeks and then a slight decline but remaining at elevated levels.
   o Apo A-I concentrations remain elevated.
   o No firm evidence of ASCVD increase proportional to parity.
   o Significance exists for fetal growth and development.
   o Treatment of massive hypertriglyceridemia.

E. Effects of postmenopausal hormones:
   o Estrogens lower LDL-C, raise HDL-C, including HDL2.
   o Effects on cardiovascular disease:
     a. case control studies
     b. prospective cohort studies
     c. role of HDL-C
   o Effects on total life expectancy.
   o Progestins have an opposing effect on lipoproteins and an unknown effect on ASCVD.
F. Patient evaluation:

- Determine number of risk factors: high blood pressure, smoking, diabetes, family history of premature vascular disease, evidence of ASCVD in the patient, male gender, HDL-C <35 mg/dL.
- Guidelines for lipid screening (National Cholesterol Education Program)
  a. All adults should be checked, childhood guidelines are still pending.
  b. Chol < 200; recheck every five years.
  c. Chol 200-239:
     0-1 risk factors - general diet, recheck yearly
     2 or more risk factors - get HDL, TG and calculate LDL-C
  d. Chol ≥ 240: Get HDL, TG and calculate LDL-C.

G. Conditions having deleterious effects on lipoproteins

- Diseases:
  a. diabetes
  b. obesity
  c. hypothyroidism
  d. uremia/nephrotic syndrome
  e. liver disease
  f. dysgammaglobulinemias

- Drugs:
  a. thiazides
  b. beta blockers
  c. androgens
  d. progestins (see below)

- Habits:
  a. smoking

H. Guidelines for treatment:

- Diet:
  0-1 risk factors; LDL-C ≥ 160 mg/dL
  2 or more risk factors; LDL-C ≥ 130 mg/dL

- Drug:
  0-1 risk factors; LDL-C ≥ 190 mg/dL
  2 or more risk factors; LDL-C ≥ 160 mg/dL
Estrogens and Lipoproteins

Robert H. Knopp, M.D.
NW Lipid Research Clinic
University of Washington

Abstract:

Recent studies show that arteriosclerotic cardiovascular disease is associated with high low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol concentrations and, further, that reversal of these abnormalities can prevent cardiovascular disease. Since postmenopausal estrogen therapy favorably changes LDL and HDL cholesterol concentrations, it is hypothesized that reductions in cardiovascular disease will be observed in estrogen-using postmenopausal women. At least 22 population-based reports have been published that address this question. Of the case-control studies, six of eight showed reductions in unadjusted cardiovascular disease risk ratios ranging from 0.4 to 0.8. In a seventh study, the risk ratios were 1.0 to 1.2, not significantly different from unity; and in an eighth study, arteriosclerotic risk was increased 4.2-fold. In that study, however, selection of the controls was criticized. In case-control studies in which adjustments for cardiovascular risk factors were made, relative risk ranged between 0.4 and 1.2 in all studies.

In the prospective studies, there are 11 reports of calculations of crude unadjusted relative risk for arteriosclerotic cardiovascular disease, with estrogen use ranging between 0.2 and 0.5. Two additional studies showed little difference and a third showed increased risk. In this last study, from the Framingham cohort, the relative risk for cardiovascular disease with estrogen use was 1.76, with one third of the endpoints being angina pectoris, which is an unreliable diagnosis in women. Indeed, reanalysis of these data, omitting angina as an endpoint and stratifying for age, showed a beneficial trend in postmenopausal women in the 50-60 year age range.

Increased risk among estrogen using women persists in the age 60-69 group, but this is a small, select group of women. Two of the most important prospective studies determined that arteriosclerotic disease risk among estrogen users is one third of that in the nonuser group. These differences withstand adjustment for important cardiovascular disease risk factors. Indeed, in the study of Bush and associates, HDL cholesterol and LDL cholesterol account for about half of the protective effect of estrogen, thus supporting the view that arteriosclerotic disease prevention with estrogen therapy is mediated in part by alterations in lipoprotein lipid concentrations. The remainder of the estrogen benefit may be mediated by a direct effect of estrogen on the arterial wall. Under these assumptions of benefit, estimates of quality-adjusted life expectancy show that reduced arteriosclerotic cardiovascular disease overshadows any increased mortality attributable to endometrial cancer. Nonetheless, induction of endometrial cancer is an unacceptable health risk and mandates the coadministration of cyclic progestin therapy with postmenopausal estrogen therapy in women with an intact uterus. The extent of the adverse effect of progestins on lipoproteins and heart disease depends on the therapeutic regimen and dose; an ideal program with known effects on heart disease remains to be determined.
TABLE 1

Effect of Estrogen on Postmenapausal ASCVD: Case Control (Cross-Sectional) Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Journal</th>
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<td>Hosp.</td>
<td>Crude</td>
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<td>1) Rosenberg/Jick</td>
<td>1976</td>
<td>NEJM</td>
<td>+</td>
<td>0.5</td>
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<tr>
<td>2) Pfeiffer</td>
<td>1978</td>
<td>Am J Epi</td>
<td>+</td>
<td>0.6</td>
</tr>
<tr>
<td>3) Jick</td>
<td>1978</td>
<td>JAMA</td>
<td>+</td>
<td>4.2†</td>
</tr>
<tr>
<td>4) Rosenberg</td>
<td>1980</td>
<td>JAMA</td>
<td>+</td>
<td>1.0–1.2**</td>
</tr>
<tr>
<td>5) Ross</td>
<td>1981</td>
<td>Lancet</td>
<td>+</td>
<td>0.4*</td>
</tr>
<tr>
<td>6) Bain</td>
<td>1981</td>
<td>Circ</td>
<td>+</td>
<td>0.7</td>
</tr>
<tr>
<td>7) Adam/Vessey</td>
<td>1981</td>
<td>Br Med J</td>
<td>+</td>
<td>0.8</td>
</tr>
<tr>
<td>8) Seklo</td>
<td>1984</td>
<td>Prev Med</td>
<td>+</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Relative risk ratios are for current estrogen users, when available; otherwise relative risk is for current or past use and is marked with an *.

† Interpretation complicated by few cases, age < 50, 90% smoking rate.

** Current and ever users are represented by the first and second values respectively.
### TABLE 2

**Effect of Estrogen on Postmenapausal ASCVD:**
*Cohort (Prospective Studies)*

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Journal</th>
<th>Populations</th>
<th>Relative Risk</th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Birch 1974</td>
<td>Am J Ob Gyn Surg. Prac.</td>
<td></td>
<td></td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Gordon/Kannel 1978</td>
<td>Ann Int Med. Town</td>
<td></td>
<td></td>
<td>1.0-1.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Hammond 1979</td>
<td>Am J Ob Gyn Univ. pts.</td>
<td></td>
<td></td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) Petiti 1979</td>
<td>JAMA</td>
<td>Kaiser Perm.</td>
<td></td>
<td>1.2**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petiti 1986</td>
<td>NEJM</td>
<td>Kaiser Perm.</td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5) Bush 1983</td>
<td>JAMA</td>
<td>LRC</td>
<td></td>
<td>0.4†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bush 1987</td>
<td>Circulation</td>
<td>LRC</td>
<td></td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6) Nachtigall 1979</td>
<td>Obst Gyn</td>
<td>Chr. Dis. Hosp.</td>
<td></td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7) Criqui 1984</td>
<td>Am J Epi</td>
<td>Comm.</td>
<td></td>
<td>0.22***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8) Henderson 1985</td>
<td>J Repr Med</td>
<td>Comm.</td>
<td></td>
<td>0.54††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9) Wilson 1985</td>
<td>NEJM</td>
<td>Town</td>
<td></td>
<td>3.2-1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10) Eaker 1986</td>
<td>NIH Sympx.</td>
<td>Town</td>
<td></td>
<td>&lt;1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11) Stampfer 1985</td>
<td>NEJM</td>
<td>Nurses</td>
<td></td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12) Colditz 1987</td>
<td>NEJM</td>
<td>Oophx.</td>
<td></td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Fatal and non-fatal CHD respectively.
** Hysterectomized women with nonfunctioning ovaries were not determined.
*** Smokers only; all cause mortality estimated to be 0.67.
† About 75% of the reduction in all-cause mortality is related to HDL-C.
†† Smoking and diabetes tended to obliterate the estrogen effect.
Smokers vs. non-smokers respectively.
Subjects given estrogen 2.5 mg daily and 10 mg provera 7 days/mo.
**TABLE 3**

**RISK FOR CARDIOVASCULAR DEATH WITH POSTMENOPAUSAL ESTROGEN USE***

<table>
<thead>
<tr>
<th></th>
<th>Non-Users</th>
<th>Users</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n):</td>
<td>1677</td>
<td>593</td>
<td></td>
</tr>
<tr>
<td>CVD death:</td>
<td>44</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age adj. rate</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>10,000:</td>
<td>38.1</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Adjusted for</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>age, SBP,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoking:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;H.S.</td>
<td>39.6</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>H.S.</td>
<td>37.0</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>&gt;H.S.</td>
<td>23.5</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

DELIVERY SYSTEMS

FOR CONTRACEPTIVES

Henry L. Gabelnick, PhD
DELIVERY SYSTEMS FOR CONTRACEPTIVES

Henry L. Gabelnick, Ph.D.

Abstract

For more than two decades, research on sustained release formulations for contraceptive drugs has been a major component of both public and private sector R&D programs. The reasons for this interest include: 1) increased safety because of lower body burden of drug; 2) increased compliance and, therefore, efficacy because of reduced frequency of administration; and 3) greater acceptability because of improved aesthetic features, e.g. diaphragms containing slowly released spermicides.

This lecture will cover the fundamentals of the design of drug delivery systems -- the advantages and disadvantages of various types, e.g. biodegradable vs. nondegradable, implants vs. injectables, etc. A review of ongoing research, both laboratory and clinical, will also be presented.
CLINICAL UTILITY OF
SYSTEMIC LONG-ACTING
CONTRACEPTIVES
David F. Archer, MD
CLINICAL USE OF SYSTEMIC CONTRACEPTIVES

DAVID F. ARCHER, M.D.
Contraceptive Research and Development Program
The Jones Institute for Reproductive Medicine
Eastern Virginia Medical School
Norfolk, Virginia

Systemically administered contraceptives have not been available in the United States since 1970. Prior to that time, Depoprovera, a microcrystalline preparation had briefly been available for contraception. Systemically administered contraceptives have some advantages over the oral route of administration. These are:

A. Bypasses the gastrointestinal tract and first pass through the liver where extensive metabolism can take place.
B. Potentially reduces the daily total hormone exposure to the body.
C. Can be developed to result in a near zero order release, with concentrations within the therapeutic range
D. Has a long duration of action
E. Significantly reduces the need for consumer compliance
F. With a reduced daily hormone exposure, has the potential of less metabolic alterations.

There are currently available several techniques involving biodegradable and non-biodegradable formulation of steroids. These delivery systems will be further discussed in this symposium by Dr. Gabelnick. Although none of these formulations are in the United States market, it is anticipated that in the next 1-3 years, several of these contraceptive techniques will be available.

This is a brief listing of systemic contraceptive agents:

I. Progestin only
   A. Injectables
      1. Depoprovera - 3 month
      2. Norethindrone enanthate - 2 month
B. Biodegradable (norgestrol/norgestimate/norethindrone)
   1. microcapsules - polylactide/coglycolide - 1-12 month
   2. capronor - E-caprolactone - 12 months
   3. fused pellets - cholesterol - 12 months

C. Non-biodegradable
   1. Norplant - levonorgestrol - 5-7 years

II. Estrogen and progestin

A. Injectable
   1. Estradiol valerate - Norethindrone enanthate - 1 month
   2. Estradiol cypionate - Depoprovera - 1 month
   3. Estradiol enanthate - Deladroxate - 1 month

We have had experience with the use of both injected microcapsules and pellets containing norethindrone and norgestimate for contraception. These methods appear to be acceptable to women and their motivation and compliance have been good. It should be pointed out that our use of the compounds have been under clinical research protocols. For this reason, I thought that I would briefly discuss the two techniques that we have had practical experience with. These are a 90-day biodegradable microcapsule containing norethindrone at two dose levels, 65 and 100 mg. The second is a pellet of norethindrone fused with cholesterol.

Microcapsules are made with a polymer of polylactide-coglycolide that is the same material available in the biodegradable suture Dexon. The microcapsules are of various sizes ranging from 10 - 125 mm. in diameter. The norethindrone is released by both a diffusion across the polymeric membrane, and also by the erosion of the polymer. The microcapsules are suspended in Dextran and injected intramuscularly immediately after vigorous shaking to prevent settling of the microcapsules. Limited discomfort at the injection site is the only problem that we have seen to date related to the injection itself. These injections are
repeated every 90 days. Based on the pharmacokinetics, we believe there is a window of 7 days on either side of the 90 day interval, but beyond this window escape ovulation can occur. There has been no evidence of accumulation of norethindrone in these women based on the Phase II studies.

There are at least three (3) mechanisms of contraceptive action from the injected progestin.

A. inhibition of ovulation
B. Altered cervical mucous - hostile to sperm
C. Altered endometrium

Ovulation may not be inhibited in all instances. Four different ovarian response patterns have been found with orally administered norethindrone 300 mg. per day. These are:

A. Low serum estradiol and progesterone compatible with follicular inhibition
B. Elevated estradiol without evidence of a subsequent progesterone rise - suggesting some follicular activity.
C. Elevated progesterone with evidence of a short luteal phase.
D. Estradiol rise followed by reasonably normal serum progesterone levels in terms of concentration and duration

The contraceptive efficacy of the 90-day injection in ongoing Phase III trials performed by Family Health International have been very good with a Pearl Index of 2.2 by life table analysis with a wide confidence interval.

The principal metabolic derangement is alteration in lipoproteins. Decreased high density and low density lipoproteins were found in the Phase II NET study. HDL levels declined 9.7 mg/dl (17.6%) in the 65 mg group and 7.7 mg/dl (14.4%) in the 100 mg. group. The mean LDL levels declined 10.3 and 26.5 mg/dl (9.2 and 22.1%) in the 65 and 100 mg. groups respectively.
A major clinical problem with systemic contraceptives has been irregular vaginal bleeding. The uterine bleeding is not heavy, but can be persistent and a nuisance. The etiology is unknown. Bleeding patterns from the Phase II study of NET microcapsules indicate a significant change in bleeding and spotting during the study. The daily bleeding calendars were analyzed with 90-day reference periods. Prolonged bleeding (>8 days) decreased from 40 to 17% in the 65 mg. NET group and from 43 to 23% in the 100 mg. group. The occurrence of amenorrhea increased from 10 and 7% to 33 and 39% in the 65 and 100 mg. groups respectively. These values are not different from those reported with other systemic progestin-only contraceptives. The mechanism(s) of the bleeding will be further addressed below. To date, we have undertaken office hysteroscopy in four (4) women who have complained of persistent bleeding on the NET microcapsules. The uterine cavity has been normal in configuration, while the lining of the uterus appears atrophic with visible venous lakes with teleangiectasis beneath the endothelial surface. There has been a pink-tinged fluid present in the uterine cavity, but no evidence of any active bleeding site(s).

To date, 16 months into the Phase III study, we have had 38 of 100 women discontinue the method. Our greatest loss is due to failure of the women to return within the 7 day window for reinjection, and/or moving out of the area. Discontinuation for bleeding problems has occurred in only 8 of the 38 women.

We have also used pellets containing norethindrone and cholesterol in a Phase II protocol in volunteers who have had a prior tubal ligation. The pellets, four (4) in number, each containing approximately 10 mg. of norethindrone, have been placed under the skin of the forearm. They are not visible, but are palpable. There has not been any effect on movement or work efficiency.

The pellets are designed to release norethindrone for at least twelve (12) months. They are biodegradable, but can be surgically removed if necessary. We have removed pellets from 14 of 35 volunteers, principally due to non-compliance
or a planned move from the area. Only two women had removal for bleeding problems. This study is ongoing at present and none of the data have been analyzed. Irregular vaginal bleeding based on diary cards continues to be a clinical problem, but is well tolerated by the volunteers.

The last formulation, of which I have no practical experience, is with Norplant(R). These are silastic capsules or rods which contain levonorgestrel. The silastic does not biodegrade, and for this reason, surgical removal is required. The initial Norplant devices are compared to six capsules containing norgestrel. They are placed in a fan shape subcutaneously in the inner-upper-arm.

The new formulation consists of two silastic rods covered with a silastic capsule. The rate-limiting membrane is the outer silastic sheath. These devices have the potential for a five (5) to seven (7) year contraceptive efficacy.

The insertion of these devices is readily accomplished under local anesthetic using an inserter. Removal requires surgical intervention under local anesthetic and through a small incision. However, the staff require special training for these procedures. Dr. Irving Sivin will address this issue on Saturday.

Monthly injectables containing both estrogen and progestin are under development by the World Health Organization (WHO). The decision to initiate these studies was the need for a systemic contraceptive without the associated bleeding problems of the progestin-only formulations. The monthly injectable preparations have a regular bleeding pattern, which makes them more acceptable to women. The drawback to this method is the need of a monthly visit to the clinical staff for reinjection. Monthly injectables are available in Mexico, and are used by an estimated 8% of the women.

A major advantage of these systemic agents is the reduction of consumer motivation. Daily oral medication can be forgotten or presents a problem for
storage. Injectable methods free the consumer from these inconveniences, and replaces it with an infrequent visit to the health provider. This also allows for a more precise documentation of contraceptive use.

The mechanism(s) by which uterine bleeding occurs are not well understood. Several possible mechanisms related to the uterine bleeding are being considered. They are:

A. Prostaglandins
B. Macrophage related factors such as cytokines
C. Paracrine effects of other stromal factors

The initiating events of normal menstruation are not clear at present. Markee's early experiments of endometrial explants placed in the anterior chamber of the Rhesus monkey eye indicate that there was an initial stasis of blood in the spiral arterioles followed by intense vasoconstriction that lasted from 4-24 hours. Bleeding began when vasodilation became apparent. Whether or not this is the series of events that occurs in women is not known.

It is well known that estrogen given alone and then stopped can initiate menstrual bleeding, but it can be prolonged. Progestin alone without estrogen priming does not result in bleeding. Withdrawal of both estrogen and progesterone results in limited endometrial bleeding. In the normal cycle, it is the withdrawal of hormones that result in the initiation of bleeding. Endometrial progesterone receptors are induced by estrogens and are present in the luteal phase of the cycle. Using a specific antibody to the progesterone receptor, only the luteal stroma after day 21 of the cycle has been found to be positive for progesterone receptor activity, while the glands have limited to no staining for progesterone receptor.

Prostaglandins play a key role in menstruation. Prostaglandins can cause both vasoconstriction and vasodilation. Endometrial tissue in vitro has the capacity to produce both PGF2α and PGE2. Prostaglandins are found in menstrual
blood, and these levels are increased in systemic circulation during the luteal phase. Estrogens in vitro increase endometrial prostaglandin production while some investigators have found that progesterone inhibits prostaglandin. It is hypothesized that declining progesterone levels and/or lack of receptors would result in an increase in prostaglandin synthesis. Clinically a reduction in menstrual blood loss has been found with the use of non-steroidal anti-inflammatory agents, arguing for a major role of prostaglandins.

Endometrial macrophages could be involved in the initiation of menstrual bleeding. The macrophages are found to cluster around the base of spiral arterioles in the luteal phase of the cycle. These macrophages could be cytotoxic by the releasing peroxides, tumor necrosing factor, and various lysosomal enzymes. The macrophages may also influence capillary integrity by acting on the endothelium via the production of plasminogen activating factor (PAF), tumor necrosin factor-B (TNF), and interleukin 1 (IL-1). They could also promote vaso-dilation by the release of PGE2. The event that initiates the macrophage secretion is not known. Prolactin has been found to cause release of TNF by macrophages. Prolactin (PRL) is secreted by the stroma (decidua) and high concentrations of prolactin are present in intrauterine fluid in the luteal phase of the cycle. It is possible that PRL could be a hormonal stimulus for macrophage secretion.

Macrophages could be involved in the reparation of the shed endometrium by the production of growth factors such as transforming growth factor-B, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF). The increased nitotic activity of the basal endometrium in regeneration implies the increase in growth factors.

It is apparent that multiple systemic and local factors could be involved in the bleeding that occurs during progestin contraception. Readily apparent is a role of prostaglandins in uterine bleeding. How the prostaglandins initiate or
modulate the bleeding is unknown. Stromal factor(s) on an autocrine or paracrine basis may well play a major role in the initiating events of uterine bleeding. How progestational-only contraceptive agents cause the irregular bleeding is unknown at present.

Summary:

Systemic progestin-only contraceptive agents could be available within the United States in the next 3 - 4 years. They have a very good use effectiveness ratio. The major drawback has been irregular vaginal bleeding and the changes in serum lipoproteins. The mechanisms involved in normal menstrual bleeding and the irregular bleeding of the progestin-only agents is under investigation.
REFERENCES


NORPLANT CONTRACEPTIVE IMPLANTS:

A NEW MODALITY

Irving Sivin, MA
The Method

NORPLANT\textsuperscript{R} implants are a set of six flexible Silastic\textsuperscript{R} capsules, each containing 36 mg of the progestin, levonorgestrel. Each capsule is 2.4 mm in diameter and 34 mm in length. The capsules are inserted in a superficial plane beneath the skin of the upper arm. Contraceptive effectiveness begins the first day and continues for five years.

Release Rate and Plasma Concentrations

The levonorgestrel dose is estimated to be about 80 mcg/day during the first few weeks, and declines to about 34 mcg/day at 6 months, and then gradually to about 25 mcg/day at five years. These doses may be compared with triphasics which step up from 50 to 125 mcg of levonorgestrel plus 30 mcg of ethynylestradiol, or with the 37.5 mcg of levonorgestrel supplied by the mini-pill.

Mean levonorgestrel concentrations among NORPLANT\textsuperscript{R} users were estimated at 0.32 ng/ml plasma at 12 months and 0.26 ng/ml at 48 months. These compare with peak concentrations of 5 to 7 ng/ml observed among users of low dose combination orals containing levonorgestrel. Concentrations vary over a wide range. Large differences between individuals in levonorgestrel clearance rates have been reported in the literature. In part, these differences in plasma levonorgestrel levels are weight related. We estimate a decrease in circulating levonorgestrel of about 0.003 ng/ml with each kg increment in weight.
After placement of implants, maximum or near maximum circulating concentrations of levonorgestrel are reached by 24 hours. This implant system, thus, becomes effective by the end of the first day.

Effectiveness

Studies of NORPLANT™ implants began in 1974. The Population Council has now conducted seven trials of NORPLANT™ capsules involving 2,470 women of whom about 400 have completed five years of uninterrupted use. About 6,000 woman years of experience have been accumulated. Participants in the trials had to be sexually active, cohabiting women, with no contraindications to the use of combined oral contraceptives. They were age 18 to 40 at enrollment, agreed to randomization with other implants when required, and agreed to use no adjunctive mode of contraception during the trial. Two of the Population Council trials included IUD control groups. Mean age was around 26, mean parity was 2, and mean weight was less than 60 kg. Cumulative loss to follow-up was 6.8 percent among NORPLANT™ users over the course of the studies.

In addition to the 2,470 women in Population Council studies, published studies of NORPLANT™ capsules include data on 14,400 other women. In these studies, mainly from developing countries, some 450 women have completed five years of continuous use. More than 10,000 women in these trials were studied in the People's Republic of China. Five of the studies included IUD controls.

Because release rates and plasma levels of levonorgestrel are highest during the first months and years of use, the corresponding pregnancy rates are lowest in the first two years. Gross annual pregnancy rates have been significantly below 1 per 100 in each of the first two years of NORPLANT™ use and have not been significantly different from 1 per 100 in each of the third,
fourth or fifth year of continuous use.

In four of the Population Council's seven trials of NORPLANT\textsuperscript{R} capsules, there were no pregnancies in the first year. Of the few pregnancies reported during the first year, almost all have been reported in the first month and appear to have been initiated before implant placement. No first year pregnancies were registered in published preintroduction studies in Colombia, India, Ecuador, Finland, and Singapore. In China, the first year pregnancy rate was 0.1 per 100. More than 4,000 Chinese women had completed one year of use. In Population Council studies the highest first year pregnancy rate was 0.6 per 100. In non-Population Council published studies of NORPLANT\textsuperscript{R} capsules, the highest first year gross rate was 1.2 per 100 in Assiut, Egypt. The investigator in Assiut has determined that all pregnancies he had reported in the first year were conceived prior to implant placement.

The gross cumulative five-year pregnancy rate was 3.5 per 100 in all Population Council studies (Cut-off date of Sept. 30, 1988). At three years, the rate cumulated to 1.9 per 100; at four years the cumulative pregnancy rate was 3.1 per 100 and at the end of five years of use the cumulative rate was 3.5 per 100.

The Interaction of Pregnancy Rate with other Factors

Age, parity, and weight. Pregnancy rates have not varied significantly by age of subject or by parity nor by location of implant in the arm. Pregnancy rates have varied significantly by the weight of the subjects. Women who, at admission, weighed less than 50 kg have experienced a five-year pregnancy rate of 0.2 per 100. Women weighing 50-59 kg and 60-69 kg have experienced cumulative five-year pregnancy rates of 3.0 and 4.3 per 100, respectively. Women
who weighed 70 kg or more have experienced pregnancies at a rate of 8.6 per 100 continuing users in the five-year period of use (Cut-off date 30 Sept. 1988).

**Tubing used in manufacture.** Two types of tubing have been used in NORPLANT\textsuperscript{R} studies. They differ only in the amount of inert silica filler they contain. Pregnancy rates have been much lower with implants with the tubing containing less filler (P<0.05). Future manufacture will be exclusively from the tubing with less inert filler.

**Mode of Action**

NORPLANT\textsuperscript{R} capsules attain contraceptive effect through a variety of mechanisms. The principal mechanism appears to be its effect on cervical mucus, rendering it essentially impenetrable by sperm. Ovulation is suppressed in many cycles, and progesterone values at ovulation are low.

**Adverse Effects**

**Sources of data.** Data on adverse effects associated with NORPLANT\textsuperscript{R} capsule implants in Population Council studies derive from two IUD controlled clinical trials and from the five other Population Council studies of NORPLANT\textsuperscript{R} capsule implants.

In the seven Population Council studies, information on adverse effects derives from a variety of sources. These include reasons for terminations; questions asked and examinations and observations recorded at each visit; specific inquiries at one year of use; measurements of weight, blood pressure, and hemoglobin; records of bleeding patterns; a number of special studies of metabolic parameters; and recordings of complications of removal. Use of
NORPLANT \textsuperscript{R} implants, or of any contraceptive, is made at the election of the subject. Medical reasons ascribed for terminations serve to identify those conditions considered sufficiently bothersome or serious by the women or clinicians to change her election of contraception.

**Menstrual Problems.** Terminations ascribed to menstrual pattern changes have been the most frequently cited medical reason for discontinuation of implant use. In Population Council studies, the five year gross termination rate for menstrual problems was 25.2 per 100 women as compared with 20.6 for all other medical reasons. Menorrhagia was cited in the majority of menstrual terminations and, together, with metrorrhagia, accounted for ninety percent of all menstrual terminations. One percent of all subjects discontinued use because of amenorrhea. This was approximately six percent of women citing menstrual problems.

Menstrual diaries indicate that menstrual patterns are most disturbed in the first year of use. Thereafter a general, but far from universal, return occurs toward more normal patterns. Gross annual termination rates for menstrual problems decreased with time. They were 9.1, 7.9, 4.6, 3.7 and 2.5 per 100 for years one through five, respectively.

As recorded in menstrual diaries, bleeding patterns differed by the weight of the women. Women who weighed less than 50 kg at admission reported, on average, fewer bleeding events than did heavier women.

Despite the fact that many women experienced menorrhagia, menstrual problems have not been associated with decreased average hemoglobin readings. Mean hemoglobin readings in fact have risen significantly at one year. Women who terminated NORPLANT \textsuperscript{R} use citing menstrual problems did not have decreased
mean hemoglobin levels. Longer term use has also been associated with increased hemoglobin levels.

In preintroduction studies, altered menstrual patterns have been the dominant reason for termination in the first year of NORPLANT® use. In these studies, too, however, there was a clear tendency for hemoglobin values to rise.

Terminations for Medical Reasons other than Menstrual Problems. About 14 percent of subjects in the Population Council's seven studies of NORPLANT® capsules had discontinued either at a physician's recommendation or because of adverse conditions which the subjects considered might improve after removal of implants (Oct. '87 analysis).

Only a few conditions or classes of conditions - other than menstrual problems - were associated with terminations by one percent or more of all women.

Placement "related" events led to terminations by 1.2 percent of women. These include terminations because of infection at the site of placement, expulsion of one or more implants, and complaints of pain, of appearance of implants, of motion limitation, etc., which might be attributable to the specific placement of NORPLANT® capsules. The overall incidence of terminations for infections and expulsions has been 0.7 percent of subjects in the Population Council studies and 0.3 percent in the preintroduction studies.

Common complaints were cited at termination (7.4 percent of subjects) (Sept. '87 cut-off). These include four "specific" conditions cited by one or more percent of women as their reason for wishing to discontinue. The most
common "specific" complaint leading to removal of implants was headache (1.9 percent). The next most frequent complaint concerned changes of weight (1.7 percent), including both increases and decreases. Changes of mood led to the termination of 1.1 percent of the women, and an additional 0.9 percent of subjects asked that the NORPLANT\textsuperscript{R} capsules be removed because they felt depressed. 1.8 Percent of women stopped for a variety of "other" conditions.

All conditions for which the percentage of women terminating was 0.4 or more, corresponding to 10 or more cases, are discussed below.

Terminations for hypertension generally reflected moderate elevations of blood pressure. Because blood pressure above 140/90 was regarded as a contraindication to implant use in the trials, investigators often used this standard in deciding whether or not a subject should continue use. There were removals, however, at subjects' requests at levels below 140/90. A total of 24 women ceased use because of hypertension.

Functional ovarian cysts occur among women using implants. In a few instances women experienced pain and requested removal of implants. More often the cysts were found on pelvic examination. Cysts may persist for as long as 6-10 weeks before spontaneously regressing. Occasionally physicians have intervened before regression occurred. Fourteen women ceased use because of ovarian cysts.

IUD users meeting the same criteria for eligibility as required for implants were enrolled in two studies. Termination rates for specific reasons were generally too low to differentiate between regimens. The conditions expected to be more frequent reasons for discontinuation among IUD users such as abdominal pain and dyspareunia were confined to that group, while headache
and other common complaints have led to a higher rate of removal among implant subjects.

Adverse Reactions Indicated by Complaints and Conditions. At each clinic visit women were asked "How have you been feeling since the last visit?"

Significantly higher percentages of NORPLANT\textsuperscript{R} users reported headache, nervousness, change in appetite, weight gain, dermatitis and acne in both controlled studies. When the two studies were considered jointly, the implant users had or reported four other conditions more frequently than did IUD acceptors. These were ovarian enlargement, nausea, mastalgia, and hair conditions. IUD users had higher complaint rates of pelvic pain and pain at intercourse.

A second approach to evaluating conditions was to ask each subject at one year or at earlier termination whether she had noted an increase, decrease or no change in a specified condition. In contrast to the analysis of frequency of complaints and diagnosed conditions, headache, nervousness, nausea, dizziness, and acne were not perceived to have increased by significantly more NORPLANT\textsuperscript{R} than IUD users.

Serious Conditions. In the Population Council studies, which reflect 2,470 subjects with a mean of about 2.5 years use per subject, the most frequently reported severe conditions were hypertension (24 cases), ovarian cysts (14 cases), cervical cancer (8 cases), gall bladder problems (7 cases), and anemia (5 cases). Two deaths occurred in the Population Council studies; one was judged to be a result of an aneurism, one was attributed to complications of cholecystectomy.
Implant Removal Problems. Problems associated with removal were specifically recorded. Approximately seven percent of NORPLANT® removals were associated with any difficulties affecting the subjects. The most frequent problem has been extended time for removal of all the implants. This has resulted from implants severed at placement, or deep placement. Other categories were multiple incisions, failure to recover the implants completely, and pain. Removal, like placement, is performed after local anesthesia.

Time required for removal of capsule implants was recorded in 320 cases in Population Council Study 21/25. Forty-four point five percent of removals were completed in less than ten minutes. More than two-thirds of all removals, 67.5 percent, were accomplished in less than 20 minutes. Median removal time was 10-14 minutes. The 75th percentile for removal was between 20 and 29 minutes, while the 90th percentile was at 45-59 minutes.

Outcome of Pregnancies. The outcome of accidental pregnancies in the Population Council's studies has been normal. The ectopic pregnancy rate was 1.1 per 1,000 woman years among NORPLANT® users in the Population Council studies, and far less in the preintroduction studies. Since ectopic pregnancy rates vary greatly among cultures, it is difficult to evaluate the effect of implant use. As one guideline, the ectopic rate in the United States among women aged 15-44 based on the National Hospital discharge survey was 1.5 per 1,000 woman years in 1987. The rate in the preintroduction studies has been remarkably low.

There has been only one known instance of birth defect among births to women using levonorgestrel implants. A boy in a preintroduction study in the Dominican Republic was born with ambiguous genitalia. It seems unlikely that
the defects were due to NORPLANT since, based on the known slight androgenic effects of levonorgestrel and on its effects on rats in reproduction studies, one would expect, if anything, enhancement of male characteristics.

**Conception After Implant Removal.** There has been no evidence of delayed conception after implant removal. Life table rates of conception among women who had implants removed in order to become pregnant have been 85-88 per 100 or higher. High and nearly identical pregnancy rates were found among NORPLANT and IUD users in Indonesia who continued contraception to become pregnant.

**Continuation of Use**

In Population Council studies of NORPLANT capsules, one year continuation rates by area have ranged from a low of 76 per 100 in Scandinavia to 90 per 100 in Chile. At the end of two years, 60 percent or more of the women were still using their first set of implants. In the pre-introductory studies continuation rates have been even higher. The lowest one year continuation rate, 87 per 100, was in Ecuador. All other countries in the studies have reported one year continuation rates above 90.

**Summary**

NORPLANT capsule implants represent a new low dose, progestin-only modality, that users find convenient, that is highly effective and that has had few serious adverse effects. The greatest problem to users of the method is its disruption of normal menstrual function. In most countries, however, even in the face of menstrual problems, continuation of use for one or more years has been at very high rates.