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THE COPPER T 380 INTRAUTERINE DEVICE

A Summary of Scientific Data

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The Population Council, an international, nonprofit organization established in 1952, undertakes social and health science programs and research relevant to developing countries and conducts biomedical research to develop and improve contraceptive technology. The Council provides advice and technical assistance to governments, international agencies, and nongovernmental organizations, and it disseminates information on population issues through publications, conferences, seminars, and workshops.

FOREWORD

Intrauterine devices are the most widely used of all reversible contraceptive methods worldwide. Modern IUDs, particularly those with large copper surface areas like the Copper T 380, are among the most effective and long-acting methods of family planning and are suitable and acceptable options for many women.

The Copper T 380 Intrauterine Device: A Summary of Scientific Data presents highlights of the clinical performance of this IUD over eight years, including the latest data on effectiveness, expulsions, and continuation rates. It incorporates the combined data from the Population Council and World Health Organization studies that were submitted to the US Food and Drug Administration, as well as important work by scientists at Family Health International and in several countries.

Clinical studies over many years of the three models of the Copper T 380—the Copper T 380A, Copper T 380Ag, and Gyne T 380 Slimline—have provided substantial evidence of the safety, effectiveness, convenience, acceptability, and long-acting quality of this IUD.

This monograph is a collaborative effort of staff from the Population Council's Center for Biomedical Research, Programs Division, and Office of Communications.

The publication's introductory section describes the development of the family of Copper T IUDs by the Population Council and includes a chronology. Next, a brief profile of the method, suitable for easy reference and reproduction, focuses on information of particular interest to family planning providers. The bulk of the work presents the preclinical and clinical performance, including mechanisms of action, effectiveness, outcome of accidental pregnancy, rates of expulsion and ectopic pregnancy, side effects, continuation rates, return to fertility, and lactation and IUD use. There is also extensive discussion of the data on IUD use and pelvic inflammatory disease, and the importance of performing skilled insertions under aseptic conditions. The work contains a substantial bibliography and glossary of terms.

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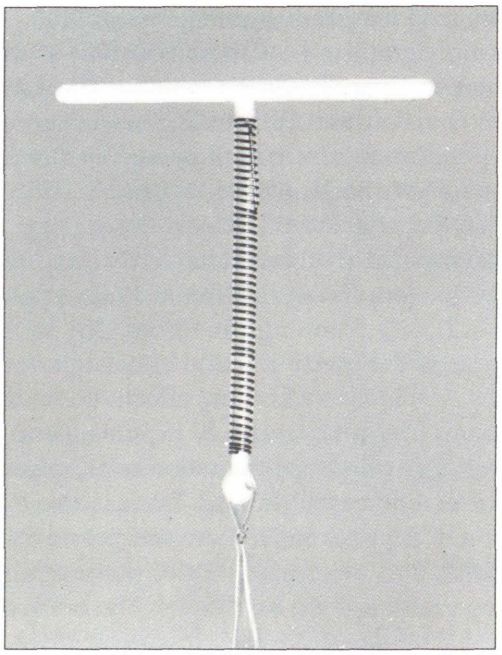
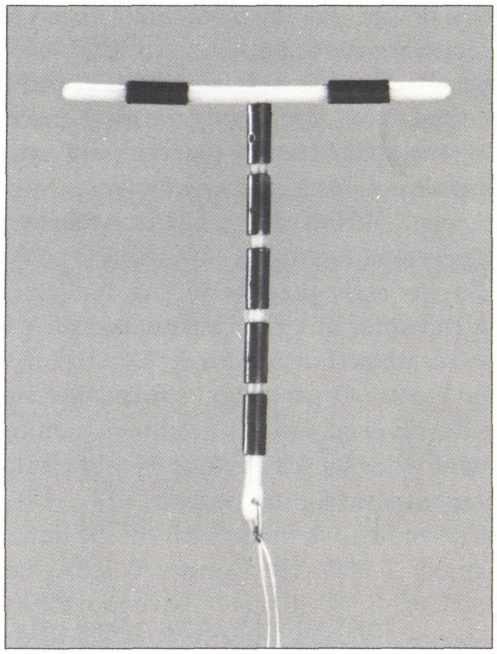
Figure 1: Evolution of the Copper T IUD



Copper T 200



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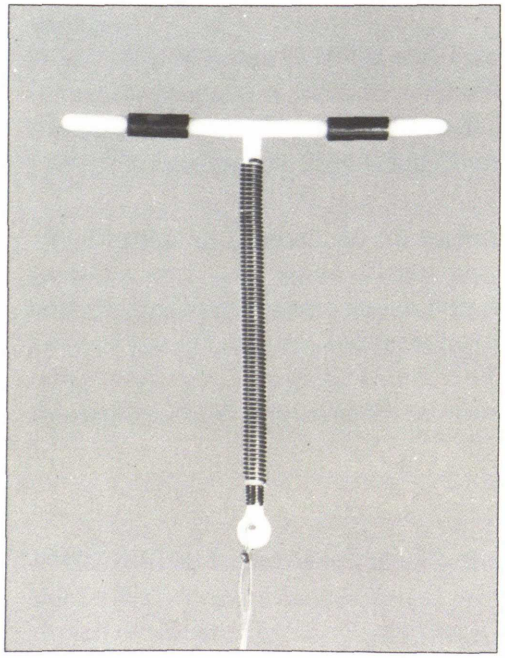
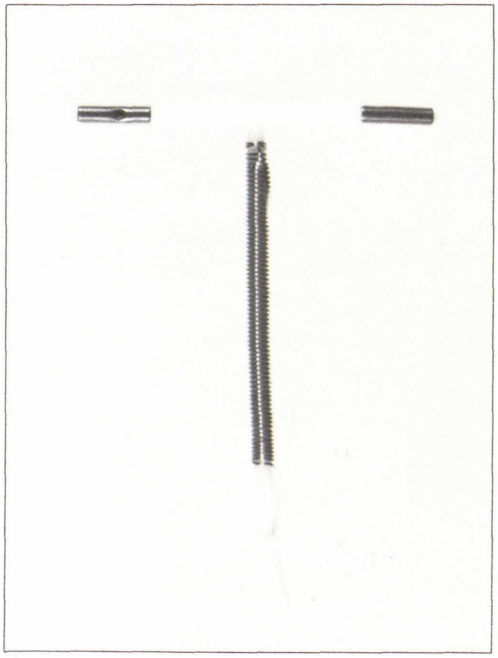


Copper T 380A (Ag)



Copper T 380 Slimline

CHRONOLOGY: COPPER T FAMILY OF IUDS

1962 First International Conference on Intrauterine Contraception is convened in New York by the Population Council.

1963 Christopher Tietze, for the Population Council, initiates a large-scale cooperative statistical program to evaluate IUDs—the most comprehensive and thorough study of a contraceptive method made to that date.

1964 Second International Conference on Intrauterine Contraception is held, with more than 400 participants from 38 countries.

1967 Howard J. Tatum of the Population Council develops a plastic IUD in the shape of a T.

1968 Jaime Zipper of Chile, a former Council fellow, reports on contraceptive effects of copper added to the plastic T.

1970 International Committee for Contraception Research is formed by the Council to identify, develop, and test new contraceptive leads.

1972 Clinical trials begin for Copper T 380 IUD.

1974 Third International Conference on Intrauterine Contraception is held under Population Council auspices in Cairo, Egypt.

1976 US FDA approves the Copper T 200 IUD for distribution in the United States.

1978 US FDA issues its Second Report on Intrauterine Contraceptive Devices, providing guidelines for clinical management of IUDs.

1980 Copper T 220C is marketed, mainly in Mexico.

1984 Copper T 380A is approved for marketing by the US FDA. Conference on Intrauterine Contraception: Advances in Future Prospects is convened in the US by Program for Applied Research on Fertility Reduction, Northwestern University.

1985 USAID begins distribution of Copper T 380A to developing countries.

1987 WHO scientific group on the safety of IUDs concludes, "The use of IUDs in both developed and developing countries should continue to be supported as a reliable and safe method of reversible fertility regulation." United States Centers for Disease Control issues guidelines for informed decision-making and use of IUDs.

1988 ParaGard 380/Copper T 380A IUD is marketed in the United States by GynoPharma, Inc.

1989 Duration of effectiveness of the Copper T 380A is extended to six years by the FDA.

1991 Duration of effectiveness of the Copper T 380A is extended to eight years by the FDA.

1992 International Conference, "A New Look at IUDs—Advancing Contraceptive Choices," is convened in New York by the Population Council and publishers of the journal *Contraception.*

The Population Council played a major role in the development, clinical testing, and statistical evaluation of modern forms of the intrauterine device, starting with the First International Conference on Intrauterine Contraception convened in 1962. This conference attracted 48 scientists and clinicians from eleven countries. Two years later, the Second International Conference on Intrauterine Contraception was attended by more than 400 scientists and public health officials from 38 countries. By 1964, the Council had provided 81 grants totaling nearly US$2 million to support research on the acceptability, effectiveness, safety, and mode of action of IUDs.

Several scientists were instrumental to the development process. The late Christopher Tietze directed the IUD conferences in the early 1960s. Starting in 1963, the Council supported Dr. Tietze in conducting a large-scale Cooperative Statistical Program, the first attempt in the history of contraceptive development to evaluate new methods from their inception. Dr. Tietze also adapted life table methods for evaluation of the use-effectiveness of contraceptives. Jack Lippes, of Buffalo, New York, in 1961 developed the plastic Lippes Loop (shaped like a double S) under a research grant from the Population Council. The device was first marketed in 1962. Dr. Lippes assigned the public sector rights to the Population Council, enabling the organization to encourage local manufacture of the Loop in a number of developing countries and to arrange for distribution at low cost in the United States and to national family planning programs in developing countries. In 1967, Howard J. Tatum, a scientist at the Population Council's Center for Biomedical Research, developed a plastic IUD in the shape of a "T". The next year, Jaime Zipper, a former Council biomedical fellow working in Chile, reported the contraceptive action of intrauterine copper. The IUD that combined these two discoveries was the Copper T 200, the first of the Copper T family of IUDs.

Since the 1960s, scientists at the Population Council's Center for Biomedical Research played major roles in the development of the Copper T intrauterine devices. They coordinated clinical studies; analyzed, reported, and published the data; developed the manufacturing prototypes and set manufacturing standards; prepared applications and reports for regulatory agencies; interacted with other institutions devoted to biomedical and contraception research; and obtained financial support for this work.

In 1970, the Council formed the International Committee for Contraception Research (ICCR), a group of experts in reproductive medicine from several countries dedicated to the development of improved contraceptive technologies. With intrauterine contraception among the Council's priorities, the ICCR tested the effectiveness and safety of the Copper T 200, a polyethylene T with copper wire wound around the vertical stem to provide 200 square millimeters of copper surface area. The Copper T 200 received US Food and Drug Administration (FDA) approval for distribution in 1976. Since then, over 50 million of these devices have been distributed worldwide.

The Council refined the Copper T design to increase contraceptive duration and effectiveness. Two advanced models resulted: the Copper T 220C, with copper collars on each transverse arm and on the vertical stem, and the Copper T 380, which has copper collars on the arms and copper wire coiled around the stem—the largest copper surface area of any marketed IUD. Today, there are three variations of this device: the Copper T 380A, the basic device, with 380 square millimeters of copper; the Copper T 380Ag, identical to the 380A but with a silver-cored copper wire on the stem; and the 380 Slimline, so-named because the copper collars are located at the tips of the horizontal arms of the T, permitting an easier fit in the inserting tube (see Figure 1 for photos of four IUD models). Since 1984, when the Copper T 380A IUD received US FDA approval for marketing, it has been widely distributed by the US Agency for International Development (USAID), the United Nations Population Fund (UNFPA), and other donors to family planning programs in developing countries. Finishing Enterprises of Tonawanda, New York, has been the major supplier for USAID international public sector programs since the early 1970s. As of January 1992, over 25 million Copper T 380A IUDs have been distributed by manufacturers through commercial channels and international public sector distribution programs.

The Council's introduction activities

The Council's Programs Division has focussed on introducing the Copper T380A IUD into family planning programs in developing countries, emphasizing the skills and information required to provide an advanced model of an established contraceptive method. The Council has worked with other international organizations, governments, and country health and family planning officials to encourage guidelines for safe provision of copper IUDs. The objective is to serve women better by establishing standards for client selection, service provision, and improved counseling. Training of service provid-

ers represents the chief vehicle for achieving these goals. Emphasis is on selection of appropriate IUD users; maintenance of aseptic conditions; retraining of providers accustomed to inserting the Lippes Loop; sensitive counseling of women to help them make the best contraceptive choices; and dissemination of information for users about how the IUD works, how it is inserted and removed, and advantages, possible side effects, and complications. Much of the introduction activity has been supported by the US Agency for International Development and the United Nations Population Fund.

IUD use in the world today

The IUD is the most popular reversible method worldwide, used by some 90 million women. In China, which manufactures a variety of steel rings and copper IUDs, over 65 million women use them. The method is also popular in Scandinavia, used there by from 20 percent to 40 percent of contraceptors, and by large numbers of women in Egypt, Germany, Hungary, Indonesia, Mexico, Taiwan, Tunisia, Turkey, and Vietnam (Mauldin and Segal, forthcoming). At one time, more than two million women in the United States used IUDs each year; this number declined following problems and liability concerns surrounding the Dalkon Shield in the 1970s. No copper or nonmedicated IUDs were distributed in the US for the two years before the Copper T 380A was introduced in 1988, although the Progestasert progesterone-releasing IUD has been available since 1976.

PROFILE: COPPER T 380 INTRAUTERINE DEVICE

THE COPPER T 380 IUD AT A GLANCE

- **EFFECTIVENESS:** The Copper T 380 IUD is among the most effective methods available, with fewer than one pregnancy per 100 women during the first year and during each subsequent year.
- **LONG-ACTING:** The Copper T 380A IUD may be used for up to 8 years.
- **SHELF LIFE:** The shelf life of the Copper T 380A is four years.
- **CONVENIENCE:** An IUD does not require daily attention from the user and does not interfere with sexual activity.
- **NONHORMONAL:** Because it contains no hormones, the Copper T 380 IUD does not affect lactation. The copper IUD also avoids side effects common to hormonal methods.
- **LOW COST:** Its low initial cost and long life make this IUD one of the least expensive methods available.
- **TIMING OF INSERTION:** An IUD may be inserted at any time during the menstrual cycle, provided the woman is not pregnant.
- **REVERSIBILITY:** Contraceptive protection is reversed when the IUD is removed.
- **REINSERTION:** If a woman has used her Copper T 380 IUD successfully for eight years and wishes to continue, a new IUD can be inserted immediately after the old device is removed.

Introduction

The Copper T 380 IUD is one of the most effective, long-acting reversible contraceptives available. It has more copper surface—380 square millimeters—than any other marketed IUD and is the most advanced of the family of T-shaped copper devices developed by the Population Council. The Copper T 380 is inserted high in the uterus, providing enhanced contraceptive protection for up to eight years.

More than 25 million have been distributed in over 70 countries. The US Food and Drug Administration approved marketing the Copper T 380A in the United States in 1984; the IUD was introduced into the US in 1988.

Copper T 380 models

There are three versions of the Copper T 380, which are known under different brand names in countries where they are manufactured and/or distributed. The original product developed by the Population Council is the Copper T 380A.

The Copper T 380Ag, identical to the T 380A except that its copper wire has a silver core, was developed in Finland and is approved in that country and distributed by Leiras Oy, a Finnish company. The Gyne T* 380 Slimline, developed by Ortho Pharmaceutical (Canada) Ltd., is approved in Canada and the United Kingdom. The Slimline is so called because its design permits the horizontal arms to fit more easily into the inserter tube. Many of the findings in this Profile apply to or derive from all three models.

Currently, no international criteria exist for regulatory evaluation of IUD devices or manufacturers. Individual manufacturers are subject to the rules of the regulatory authorities in their country. The Council has maintained close collaboration with manufacturers of the Copper T to ensure that the product they manufacture is of a standardized quality.

Manufacturers of one or more versions of the Copper T 380 are based in Canada, Finland, and the United States; producers for local use are located in China, Indonesia, and Mexico.

Components

The Copper T 380A IUD consists of a flexible polyethylene T-shaped body with a copper collar of approximately 66.5 mg of copper on each of its transverse arms and 176 mg of copper wire coiled around its vertical shaft. A monofilament polyethylene thread is tied through the bulb at the tip of the T, resulting in two threads to aid in detection and removal of the device.

The silver core in the copper wire wound around the stem of the Copper T 380Ag slows the rate of wire fragmentation. The Slimline differs from the others in that the copper sleeves are placed at the recessed ends of the arms and have the same diameter as the plastic.

Research and testing

The Copper T 380 IUD has been rigorously studied both before and after marketing. Clinical trials of the Copper T 380A began in the United States in 1972, sponsored and coordinated by the Population Council's International Committee for Contraception Research. The Copper T 380 in its three models has been studied in more than 9,500 women in randomized international and national clinical trials, conducted by the Population Council, the World

Health Organization, Family Health International, and by investigators in Brazil, China, India, and Indonesia.

Mechanisms of action

Various hypotheses have been advanced over the years about mechanisms of action of IUDs, including interference with sperm transport, ovum transport or development, fertilization, and implantation. Until about 1980, it was believed that the IUD worked mainly by causing an inflammatory response to a foreign body in the uterus, thereby interfering with implantation of a fertilized egg in the uterine wall. The consensus of informed opinion now has changed.

Studies support the conclusion that Copper IUDs prevent fertilization by reducing the number and viability of sperm reaching the egg, and by impeding the number and movement of eggs into the uterus. It is believed that the continuous release of copper from the coils and sleeves of the Copper T 380 into the uterine cavity enhances the contraceptive effect of the IUD.

Effectiveness

The annual pregnancy rate of the Copper T 380 is well below one per 100 users, within the range of implantable and injectable contraceptives and surgical sterilization. In actual use during the first year, the Copper T 380 IUD is more effective than most other IUDs, oral contraceptives, condoms, barrier methods, and periodic abstinence. The data contained in the US FDA labeling show cumulative pregnancy rates at three, five, and eight years of 1.5, 1.9, and 2.3 per 100 users respectively. The effectiveness of the Copper T 380A IUD was found to be related to age, with pregnancy rates decreasing for older women.

Duration of effectiveness

The US Food and Drug Administration first approved the Copper T 380A in 1984 for a duration of four years. In 1989, based on data submitted by the Population Council from its and WHO studies, the FDA approved the Copper T 380A as a contraceptive device effective for six years. On the basis of further data, in 1991 the US FDA approved use of the Copper T 380A for eight years. The eight-year duration applies to the Copper T 380A IUD governed by US FDA labeling. Approvals by regulatory agencies in other countries may apply to different models and for different durations of effectiveness.

Shelf life

The shelf life of the Copper T 380A IUD is four years. If the date on the individual IUD sterilized packaging has expired, discard the device and its inserter.

Potential users of a Copper T IUD

The Copper T 380 IUD is a safe, effective, and appropriate method for a woman who:

- wishes a long-term reversible contraceptive that does not require daily pill-taking or special action prior to intercourse;
- cannot use or wishes not to use a hormonal method;
- is in a stable and mutually faithful relationship that does not place her at elevated risk of contracting a sexually transmitted disease;
- has no history of pelvic inflammatory disease (PID), an infection of the upper genital tract; and
- is breastfeeding.

While a woman who has no children can use the Copper T 380, this method should not be a first choice. Women who have had no children generally have higher expulsion rates and more bleeding and pain than do other IUD users.

Who should not use a Copper T IUD

The Copper T 380 IUD should not be inserted in a woman who:

- is pregnant or is suspected to be pregnant;
- still retains a previously inserted IUD;
- has a known or suspected malignancy of the genital tract, including undiagnosed vaginal bleeding, or a severe uterine abnormality.

Many of the contraindications to IUD use have to do with infections. An IUD is not an appropriate method for a woman who:

- has a sexually transmitted disease (STD) including a lower genital tract infection, such as gonorrhea or chlamydia;
- is at a high risk for STDs because she or her partner has multiple sexual partners;
- has active or recurrent pelvic inflammatory disease.

If a woman cannot predict reliably whether she or her partner will be in a monogamous relationship, it would be prudent for her to adopt another contraceptive. A woman at risk for a sexually transmitted disease may also be at risk for transmission of the HIV virus; she should have her partner use a condom, since an IUD does not protect against AIDS.

Other considerations

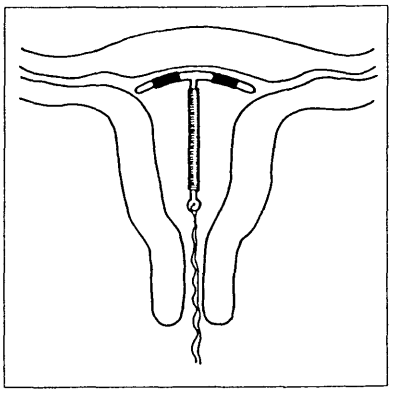
The Copper T 380 IUD should not be the method of first choice for a woman who has:

- painful or long menstrual periods;
- severe anemia;
- cervical stenosis or narrowing of the cervical canal;
- a recent postpartum or postabortion infection;
- an unresolved abnormal pap smear;
- no access to a health center for follow-up care;
- a condition associated with increased susceptibility to infection, such as leukemia, AIDS, and those requiring chronic corticosteroid therapy;
- a history of ectopic pregnancy.

A woman with one or more of these conditions who uses an IUD should be carefully counseled and be examined regularly for potential problems.

Insertion and removal

Insertion and removal of the Copper T 380 IUD are easily performed by trained physicians, nurse-midwives, and other paramedics, but providers must become thoroughly familiar with the procedures before attempting them. Since the withdrawal technique for inserting a Copper T 380 IUD differs from the push-in technique used for some other IUDs, providers must have appropriate training. Strict adherence to aseptic practices is vital to inhibit introduction of bacteria into the uterus. Some clinicians administer antibiotics just before insertion, although research has not demonstrated that this practice is effective. Following good clinical practice and using aseptic techniques in insertion and removal are critical to avoidance of infection.



Before insertion, the clinician will perform a pelvic examination to determine the size, shape, depth, and position of the uterus. The Copper T 380A should remain in its sterile packaging until insertion; the packaging has been specially designed so the device can be loaded inside the sterile wrapping. The IUD should be loaded into the inserter tube no more than five minutes before insertion.

The provider guides the Copper T 380 through the vagina and the cervix to place it at the fundus or top of the uterus. As the Copper T is inserted, the arms of the T will unfold. The woman may feel some pain or cramping at this time. After the inserter is removed, the threads attached to the end of the Copper T will be clipped. The threads will extend into the vagina from the cervical opening. The Copper T must be removed by a trained healthcare provider. This can be done easily and safely in the clinic and only takes a few minutes.

The importance of counseling

Adequate counseling is important in the selection of any family planning method; it is essential for informed, appropriate use. All women should be offered a choice of contraceptive methods and be informed of the advantages and disadvantages of each. Brochures developed for potential users in different settings are useful in providing information, particularly when clients are semi-literate. Prototype brochures utilize drawings and easily understood language.

A complete medical and sexual history should be taken to determine conditions that might influence the selection of an IUD and to make sure the woman is not pregnant. A physical examination should include a pelvic examination and Pap smear.

The healthcare provider should give the woman information about:

- who can use and should not use an IUD;
- comparison of IUDs to other methods;
- safety and effectiveness of the Copper T 380;
- how copper IUDs work;
- insertion and removal process;

- how to check for the IUD string and what to do if it cannot be felt;
- identification and management of minor side effects;
- importance of using a condom and/or spermicide in addition to the IUD if at risk of STDs;
- signs of potential complications, including pregnancy;
- where to seek help should problems occur;
- reasons for removal;
- a schedule for routine check-ups and reminder card for date of removal;

Assure clients they are welcome to return to the health facility if they are concerned about any aspect of IUD use.

Timing of insertion

The Copper T 380 IUD may be inserted at any time during the menstrual cycle, provided the woman is not pregnant and has been consistently using an effective contraceptive since her last menses. Many clinicians prefer to insert an IUD within seven days of the onset of menstruation because the cervical opening is slightly dilated during this time, making insertion easier and pregnancy very unlikely. Insertion during these days also is likely to result in less discomfort, cramping, and/or spotting for the patient.

With special training and careful technique, a clinician can insert a Copper T 380 postpartum within minutes after expulsion of the placenta. Expulsion rates tend to be at least two times higher when an IUD is inserted immediately postpartum than those found during interval insertion. In addition, clinicians need to ensure that appropriate client counseling and screening have taken place before the birth. Many clinicians prefer to insert an IUD six weeks or later postpartum, when the woman returns for a checkup. Special care should be taken when inserting an IUD in a lactating woman because of the possible increased risk of uterine perforation during lactation.

The Copper T 380 IUD may be inserted immediately after an uncomplicated first trimester miscarriage or an induced abortion. A provider must ensure that time is available for counseling and appropriate STD screening.

Use during lactation

The Copper T 380 IUD may be used by breastfeeding women. Studies have shown no adverse effect on quantity or composition of breastmilk. Multicenter clinical trials found no increased risk of adverse effects for breastfeeding women using the Copper T 380 as compared to their nonbreastfeeding counterparts. Breastfeeding women had fewer problems with bleeding and pain following IUD insertion; they had higher continuation rates than women who were not breastfeeding in the six months following insertion.

Reasons for removal

The Copper T 380 should be removed whenever the woman wishes, for whatever reason, and at the end of eight years. In addition, these conditions are cause for removal or concern:

- pregnancy;
- unexplained, severe, or prolonged vaginal bleeding or discharge;
- severe pelvic or lower abdominal pain or cramps;
- unexplained fever with pelvic tenderness;
- disappearance of the IUD's strings; or
- continued pain during sex.

If the IUD is removed and the woman does not wish to become pregnant, she should be provided with an alternative contraceptive.

Side effects and complications

PAIN AND BLEEDING: Most women have some bleeding following insertion of an IUD, and menstrual cramps may develop or worsen. Cramping is more severe in the first few months after insertion and usually diminishes over time. Menstrual bleeding may be heavier and longer than usual, and bleeding between menstrual periods can occur during the first two or three months after insertion. As with cramping, heavier bleeding generally decreases over time.

Pain and bleeding are the most common side effects reported by users of copper IUDs and are the most frequent reasons given for discontinuation in the first year or two of use. Randomized comparisons with other IUDs have shown little difference in removal rates for bleeding and/or pain among parous users. Copper IUD use may induce iron deficiency in some women; programs should be prepared to treat iron deficiency then or before a woman is given an IUD.

EXPULSION: Spontaneous expulsion of a Copper T 380 IUD is more likely to occur during the first three menstrual cycles following insertion than during any other time.

Expulsion rates are affected by the training and technical skill of the provider; the age of the IUD user and

whether or not she has ever had any children; and the timing of the insertion.

Nulliparous women and those with IUDs inserted immediately after expulsion of the placenta are more likely to expel an IUD than are other women. The IUD user should check the strings of the device after each menstrual period, to make sure the device has not been expelled.

Uterine perforation: Perforation of the uterine fundus is a rare complication of IUD insertion. This risk is lessened by careful insertion. An IUD in the abdominal cavity must be removed surgically. There is some evidence that the risk of perforation is greater early postpartum, before the uterus is fully involuted. Special care is required when the Copper T 380 is being inserted at this time, whether or not the woman is breastfeeding.

Pregnancy with IUD in place: Pregnancy with the Copper T 380A in place occurs at rates of less than one per 100 women per year. If a woman using an IUD becomes pregnant the IUD should be removed. The task is easily accomplished if the string is visible, and removal is routine.

If the IUD is left in place with the strings not visible, the woman runs a risk of an early spontaneous abortion or a later septic abortion, with possible life-threatening consequences, or premature labor. As a consequence of premature birth, the infant may be at increased risk. The woman should be counseled about the risks of continuing her pregnancy, and termination of the pregnancy may be considered and offered as an option.

Ectopic pregnancy: Ectopic pregnancy is an infrequent, but dangerous, type of pregnancy that develops outside the uterus. In about 4 percent of pregnancies with an IUD in place, the pregnancy is ectopic. Women with an increased risk of ectopic pregnancy are those who:

- have a history of ectopic pregnancy; or
- have ever had a pelvic inflammatory disease or sexually transmitted disease.

If a woman older than 35 becomes pregnant, she is more likely to experience an ectopic pregnancy than is a younger pregnant woman.

Because the Copper T 380 IUD is very effective, users of this device have a low risk of ectopic pregnancy, substantially lower than women not using contraception. If a pregnancy occurs with the Copper T 380 in place, however, it is more likely to be ectopic than a pregnancy after the failure of a barrier method or the combined pill. A pregnancy with the Copper T 380 is less likely to be ectopic than a pregnancy after failure of steroid-releasing IUDs, NORPLANT®, the minipill, or sterilization.

Pelvic inflammatory disease (PID): IUDs do not protect against PID infections, which are caused by gonorrhea, chlamydia, or other microscopic organisms. When PID occurs, it may be serious. PID can necessitate a hysterectomy and can damage the fallopian tubes, leading to ectopic pregnancy or infertility, or, rarely, death.

IUD use has been associated with increased risk of PID in the first one to four months of use. The risk is highest just after insertion when bacteria may be introduced into the uterus by the insertion process.

Exposure to sexually transmitted diseases also increases the risk of PID. Women who have multiple sexual partners, or whose partners have multiple partners, run a greater risk of contracting PID. The risk of PID decreases with long term IUD use.

Tarnishing of copper

Copper-bearing IUDs may show discoloration in their sterile packaging, but this should not cause alarm. The copper tarnishes because air passes through the sterile IUD package, causing an oxide or sulphide film to form on the surface. IUD packaging has to be permeable to gases used to sterilize the devices. If the package is not damaged, and the expiration date on the package has not passed, the IUD will be sterile even if the copper on the device is tarnished. Laboratory studies show the tarnishing does not affect the safety or effectiveness of the IUD. However, several steps have been taken in the manufacturing process to diminish the tarnishing.

Continuation rates

Continuation rates of IUDs have been among the highest of all reversible contraceptives. In combined data from the Population Council and World Health Organization studies, 77 percent of women continued using the Copper T 380A for one year. Sixty percent of the women continued for two years, and almost half for three years, with 29 percent continuing for eight years.

Prevalence of use

Worldwide, the IUD is the most widely used reversible contraceptive. IUD use varies from country to country, reflecting differences in culture, availability, and choice of contraceptives, attitudes and training of providers, and fertility goals of women. In Scandinavia, 20 percent to 40 percent of contraceptive users have IUDs, while about 60 million Chinese women use IUDs. A recent US sur-

vey showed that women who were using IUDs were more satisfied with the method than were women using other contraceptives.

Return to fertility

The contraceptive effect offered by the Copper T 380 IUD is reversed when the device is removed. Conception rates following removal for planned pregnancy are normal, with rates of successful planned pregnancy unaffected by duration of IUD use.

Postmarketing studies

In addition to numerous clinical studies, the Copper T 380 IUD is one of the devices being studied as part of a long-term postmarketing surveillance comparing health effects of NORPLANT® implants with IUDs and sterilization. The study, conducted by the World Health Organization, the Population Council, and Family Health International, compares 8,000 users of NORPLANT® with 1,500 sterilized women and 6,500 users of various IUDs, including the Copper T 380, over five years.

Active ingredient—Copper.

Effectiveness—Cumulative pregnancy rates, US Food and Drug Administration labeling: First year: 0.6 pregnancies per 100 users; three years: 1.5; five years: 1.9; eight years: 2.3.

Duration—Approved for eight years of use by the US Food and Drug Administration.

Mechanism of action—Copper ions dissolving into the uterine cavity from the IUD's copper collars and wire greatly enhance cytotoxic and phagocytic effects initiated in reaction to the plastic IUD platform. Copper IUDs inhibit sperm and ovum transport and/or the capacity of sperm to fertilize ova.

Side effects—Increased menstrual bleeding and pelvic pain; moderately increased risk of pelvic inflammatory disease; moderate decrease of hemoglobin during the initial two years.

Reversibility—Immediate upon removal.

Components

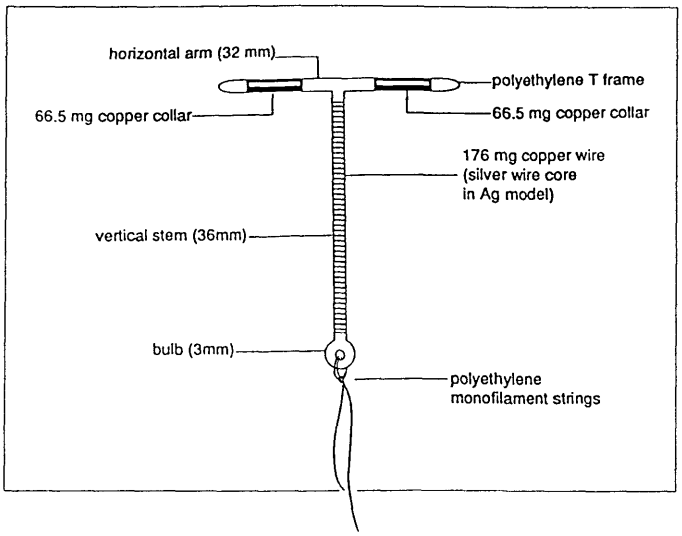
The Copper T 380 IUD (see Figure 2) has a T-shaped polyethylene frame with 380 square mm of surface area of copper — the most found on any commercially available copper IUD. Approximately 176 mg of copper wire is wound around its vertical stem, with 66.5 mg copper collars on each of its transverse arms. The device is 36 mm long and 32 mm wide, with the tip of the vertical arm enlarged to form a bulb 3 mm in diameter. A polyethylene monofilament is tied through the bulb, resulting in two threads that aid in detection and removal. As long as the device retains significant amounts of copper, it is radiopaque. Barium sulfate added to the plastic frame contributes to radiopacity.

The Copper T 380A model is packaged together with an insertion tube and a plunger in a pouch and then sterilized, either by ethylene oxide gas or by radiation. The insertion tube is equipped with a movable flange to aid in gauging the depth to which it is inserted through the cervical canal and into the uterine cavity. The shelf life of the Copper T 380A is four years.

The Copper T 380Ag was developed to increase the effective lifespan of the IUD. In this variant, the copper wire contains a silver (Ag) core to maintain the integrity of the wire for periods of eight or more years. This version of the Copper T 380 was developed by Outokumpu Oy, and is now marketed by Leiras Oy, of Finland.

The Gyne T* Slimline was developed by Ortho Pharmaceutical (Canada) Ltd. to enhance insertion by permitting the arms with collars to fit more easily into the insertion tube.

Figure 2: Copper T 380 IUD



Preclinical Evaluation

Toxicology and pathology

Copper ions are highly toxic to single-celled organisms, but mammals have effective buffering systems to cope with intakes far above their daily nutritional copper requirements.

Several studies have been directed to the effects on organs and tissues of animals exposed to copper *in utero* and intra-abdominally. Experiments in which copper was placed in the uterus and abdominal cavity of rats (Moo-Young, 1972) and monkeys (Moo-Young et al., 1973) have shown no important increments in copper contents of tissues. In a study conducted for the Population Council and Searle Laboratories, organs of monkeys exposed to copper *in utero* continuously for six to seven years were analyzed for copper content. The only significant increment as compared with control animals was in the uterus.

In one-year studies in monkeys, the only significant evidence of adverse effects was found in animals in which the devices were placed intra-abdominally. Marginal evidence of irritation in the vicinity of the devices was noted four years after placement *in utero*. A seven-year study of monkeys showed the duration of menstrual bleeding was increased by copper devices placed *in utero*. Some devices placed in the abdominal cavity penetrated pelvic organs and caused mild to severe lesions. More

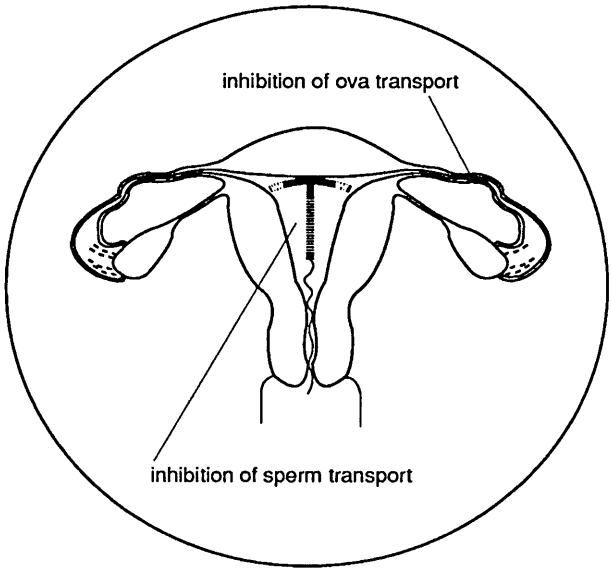
*Trademark GyneT380, Ortho Canada

endometriosis and adhesions were observed in IUD groups than in controls with no devices. No neoplastic changes attributable to the devices were observed.

Because copper wire may fragment after prolonged uterine use, the fate of copper fragments introduced into the uteri of monkeys was examined. Fragments were generally expelled, although recovery was not quantifiable. X-rays did not show that they had lodged in tissue. In one experiment, 100 mg of small copper fragments were placed in the uteri of monkeys a few days before menstruation and were studied after the first or second subsequent menstruation. Copper concentrations in the liver and lungs were not elevated above control levels.

Teratological studies have been conducted in rats, hamsters, and rabbits. Copper was introduced in the uterus after conception (Chang and Tatum, 1973). In initial studies, the only effects were in the reduction of the number of offspring delivered in rats and rabbits. Additional studies gave evidence of some fetotoxic effects, but no evidence of teratogenic effects. Other investigations found no evidence of teratogenic effects in mice. To date, human studies give no evidence of teratogenic effects or elevated rates of birth defects (Atrash et al., forthcoming).

Figure 3: Mechanisms of Contraceptive Action of Copper IUDs



Copper enhances the contraceptive effectiveness of IUDs. Few sperm reach the fallopian tubes and their capacity to fertilize eggs is reduced; fewer eggs are found in the tubes of women using copper IUDs. The principal action of IUDs occurs before an egg reaches the uterus. There is a marked reduction in the probability of fertilization.

Mechanisms of Action

Effect on sperm and ova

Various hypotheses have been advanced for mechanisms of action of IUDs, including interference with sperm transport, ovum development, fertilization, and implantation. Until about 1980, it was thought that an IUD acted by preventing a fertilized egg from implanting in the uterus. The consensus of informed opinion has changed, however; it is now believed that copper IUDs greatly reduce the likelihood of fertilization. Recent data and analysis (WHO, 1987; Ortiz and Croxatto, 1987; Sivin, 1989b) indicate that the main antifertility effects of copper-bearing IUDs involve inhibition of egg or sperm transport and/or the capacity of sperm to fertilize eggs, through cytotoxic and phagocytic effects. Reduced gamete transport and capacitation inhibits fertilization and occurs before the ovum reaches the uterine cavity.

Figure 3 describes the mechanisms of contraceptive action of an IUD placed high in the uterine cavity and continuously releasing copper.

Continuous copper release into the uterine cavity from the wire and sleeves enhances the contraceptive effectiveness of the Copper T 380. In one study of women about to undergo sterilization, sperm were recovered from the fallopian tubes of women using no contraception 15 to 30 minutes after insemination, but no sperm were found in the tubes of IUD users at the same postcoital time (Ortiz and Croxatto, 1987).

Table 1 shows the lack of sperm and diminished numbers of ova in fallopian tubes of women undergoing sterilization. In two studies, spermatozoa were recovered from the upper reproductive tracts of non-contracepting women around 12 hours after sexual intercourse, but greatly reduced numbers were recovered from users of inert, non-copper IUDs, and none were found in the tubes of copper IUD users (Aref et al., 1983; Tredway et al., 1975). These differences were statistically significant. In another study of women about to undergo sterilization, investigators searched for ova in the fallopian tubes and uteri of non-contraceptors and of women using Copper T IUDs (Alvarez et al., 1988). Ova were found in the fallopian tubes of 56 percent of women using no contraception and 30 percent of Copper T IUD users ($p<.05$). No ova were recovered from the body of the uterus of any of the IUD users, indicating a contraceptive effect of the IUD before the ovum reaches the uterus. Of women from whom tubal ova were recovered, 20 nonusers of contraception and five Copper T IUD users had sexual intercourse during their fertile days. Microscopic features indicating normal preimplantation development of fertilized eggs were observed in half of the 20 ova of the non-contraceptors and in none of the eggs of the five copper IUD users who had intercourse. Thus, the likelihood of ova being fertilized en route to

Table 1 Presence of spermatozoa and ova in fallopian tubes of women undergoing sterilization

Presence of sperm 12 hours after coitus				
First author	Contraceptive	Specimens with sperm present	(N)	Percent with sperm
Tredway	None	6	(6)	100
	IUD	0	(4)	0*
Aref	None	11	(15)	73
	Nonmedicated IUD	4	(10)	40
	Copper IUD	0	(10)	0**
Presence of ova 37–132 hours after LH peak				
First author	Contraceptive	Women with 1+ ova present	(N)	Percent with ova
Alvarez	None	64	(115)	56
	Copper T 200 IUD	8	(27)	30*

*The difference between these rates is statistically significant at p<.05.
**The difference between these rates is statistically significant at p<.001.

the uterine cavity containing a copper-bearing IUD is much reduced.

Further evidence that the IUD acts by inhibiting fertilization is the absence or only rare presence of chorionic gonadotropin, a substance produced by developing embryos beginning at the blastocyst stage, in the blood of women using copper IUDs. Segal and colleagues (1985) took blood samples from three groups of normally menstruating young women: 30 Copper T 200 IUD users, 30 sterilized women, and 15 who were trying to become pregnant. The only women who tested positively for human chorionic gonadotropin (hCG) were attempting pregnancy; they were later found to be pregnant. In a larger study, Wilcox et al. (1985) employed highly sensitive and specific immunoradiometric assays to demonstrate that hCG rises were rare among IUD users as compared with controls.

Epidemiological studies of ectopic pregnancy shed light on how IUDs work. If the IUD were an abortifacient, preventing uterine implantation of fertilized eggs, ectopic pregnancy rates among IUD users would be at least as high as among women who did not use contraception. This is because ectopic pregnancies develop before the fertilized egg reaches the uterus. On the other hand, if IUDs tended to prevent fertilization, fewer ectopic pregnancies would be found than in women using no contraception. Both the Women's Health Study (1981) and the WHO case-control study of ectopic pregnancy (1985) found the risk of ectopic pregnancy among IUD users to be about one-half that of women who used no contraception. The risk of ectopic pregnancy among women with IUDs is directly correlated with the effectiveness of copper IUDs; the lower the accidental pregnancy rate, the lower the rate of ectopic pregnancy (Sivin 1991b). Since ectopic pregnancies develop before the egg can reach the uterus, these findings of significantly reduced rates of extrauterine pregnancy imply that IUDs act before the egg reaches the uterus, presumably by inhibiting fertilization.

The exact mechanisms by which sperm transport and/or fertilizing capacity are decreased in copper-bearing IUD users have not been fully elucidated. All types of IUDs increase the number of uterine leukocytes and

Tarnishing of Copper

The wire and sleeves of all types of copper-bearing IUDs occasionally discolor or darken within the package. This occurs because air can pass into the IUD package, causing a thin film of copper oxides or sulfides to form. Surface oxidation can produce a variety of colors depending on the thickness of the films that form (Evans, 1960). IUD packaging must be permeable to ethylene oxide gas used to sterilize devices. Laboratory studies as well as clinical experience show that these tarnished or darkened IUDs are safe and remain as effective as brighter Copper T 380s (Tsong and Nash, 1991).

For copper ions to be released from the metallic copper of the IUD into the uterine cavity, oxidation must occur. Tsong and Nash (1991) show that in the presence of serum whose composition closely resembles that of uterine fluids, tarnish is quickly dissolved. No differences can be detected in copper release from initially tarnished or from bright untarnished copper. Tarnish does not diminish the availability of copper ions *in utero*. In fact, dissolution of copper from the wire or sleeves proceeds through the same oxidative processes (Oster, 1972; Kosonen, 1980).

the amount of degradation products. Sperm may be destroyed through phagocytosis and through cytotoxic effects of copper or by cell degradation products. Copper is spermicidal and cytotoxic (Holland and White, 1988). Sperm incubated in media previously exposed to copper IUDs maintained normal motility, but exhibited reduced capacity to penetrate bovine cervical mucus (Shoham et al., 1987).

Clinical Pharmacology

Cytology

Data on initial and repeat Papanicolaou smears were available for 1,767 women in the Population Council study (Sivin and Stern, 1979). Percentages of women in class III (dysplasia) and higher ranked smears at insertion (1.3 percent) and at the last test (1.5 percent) were similar and within normal ranges. These data indicate that the presence of a copper IUD does not adversely affect the incidence of clinical carcinoma.

Clinical chemistry

Serum chemistry profiles of organ function for 15 women using the Copper T 380A followed through three years showed few abnormalities (New Drug Application submission). The most frequent deviations from normal were low glucose or potassium levels, which were not of physiological importance. In studies of more than 50 women using the Copper T 220C for at least four years, of 60 women using Copper T 200 for at least five years, and of 126 women using the Copper T 380Ag for three years, frequencies of abnormal serum chemistry measurements were well within expected incidences (NORPLANT® NDA submission, 1988). Serum copper levels among Copper T 380A users were also within normal limits and showed no trend over three years.

Clinical Overview

Extent of clinical experience

The initial clinical trials of the Copper T 380A, sponsored and coordinated by the Population Council, began in 1972 at several investigational sites in the United States. A total of 3,536 volunteers participated at clinics that maintained good follow-up. Of the total, 1,679 were in randomized trials with the Copper T 200. More than a thousand women who started use in 1972 in seven of the centers were followed for up to four years (Sivin and Stern, 1979; Sivin and Tatum, 1981). These Population Council trials provided the basis for the approval of the Copper T 380A by the US Food and Drug Administration in 1984.

COMPUTING RATES FOR PREGNANCY AND OTHER EVENTS

PREGNANCY and other event or termination rates are calculated in several ways from clinical trials and survey data, usually as lifetable gross event rates or lifetable net event rates, or the Pearl Index. Unlike annual pregnancy rates, which tend to decrease with time, cumulative pregnancy rates must either increase year by year or remain unchanged. Cumulative rates cannot decrease.

LIFETABLE or actuarial techniques are used to take into account the varying lengths of time that women remain in studies. Event rates are estimated on a daily or monthly basis for women continuing to use a method. These rates are then integrated to estimate annual or cumulative event rates. Lifetable rates are expressed in two ways: gross and net.

GROSS EVENT RATES are estimates of the annual or cumulative probability of an event, such as pregnancy or expulsion, that is unaffected, in theory, by the rates at which competing events occur. The gross rate is an estimate of the intrinsic rate at which an event occurs. Gross rates are most appropriate for comparing different devices in a single trial or for comparing the performance of the same device across various clinics or populations.

NET EVENT RATES allow for the presence of competing risks of termination; for example, some women may have expelled or removed the device before they had a chance to become pregnant. Net rates are most appropriate for estimating the relative importance of discontinuation for accidental pregnancy, bleeding and pain, planned pregnancy, expulsion, or medical reasons.

PEARL INDEX is a measure of incidence and represents the number of events, e.g. pregnancies, divided by exposure —the total duration of use by all women in the study. The Index is expressed as the number of pregnancies or other events per 100 woman-years of use. An overall Pearl Index does not take account of possibly changing risks of pregnancy or other events with time. An annual Pearl Index does this.

Subsequently, several international randomized trials of the Copper T 380 IUD (models A, Ag, and Slimline) have been conducted by the Population Council, the World Health Organization, and Family Health International, and single-country randomized trials have been conducted in Brazil, China, India, and Indonesia. All randomized trials published before 1992 are listed in Table 2, including the 1,679 women who participated in the randomized component of the initial US Population Coun-

Table 2 Randomized clinical trials of the Copper T 380 IUD

Authors	Sponsor	Country	(N)[a]	Years of follow-up
TCu 380A				
Sivin and Stern	Population Council	US	(1,679)	2
Roy et al.	Population Council	US	(391)	3
Díaz et al.	Population Council	Brazil	(159)	1
Chi et al.[b]	Family Health International	International	(589)	1
Rowe, Farley et al. (WHO)	World Health Organization	International	(1,396)	8
Sastrawinata et al.	Indonesian Fertility Research Program	Indonesia	(946)	2
Sivin et al.	Population Council	International	(298)	2
TCu 380Ag				
Cole et al.; Champion et al.	Family Health International	International	(737)	3
Cole et al.; Apelo et al.	Family Health International	UK and Philippines	(181)	3
Sung et al.; Tianjin	Tianjin Municipal Health Bureau;	China	(892)	3
Family Planning	Tianjin Family Planning	China	(892)	3
Sivin et al.	Population Council	International	(1,121)	8
Saxena et al. (ICMR)	Indian Council of Medical Research	India	(434)	3
Gyne T Slimline				
Sivin et al.	Population Council	International	(698)	2

[a] Number randomized to Copper T 380 users; approximately equal number used other IUDs.
[b] Four single clinic comparisons, each with a different comparative IUD.

cil trials. A total of 9,521 women who used the Copper T 380 have participated in the randomized trials. Published experience in these trials exceeds 20,000 years of use. Long-term randomized trials in excess of eight years of continuous use are currently being conducted by the WHO and by the Population Council.

Contraceptive effectiveness

The Copper T 380 is one of the most effective contraceptives in use, with an annual pregnancy rate, on average, of less than one per 100 users. Figure 4 shows annual pregnancy rates summarized from randomized trials of the variants of the Copper T 380 for each of the years that the devices have been approved.

The annual pregnancy rates observed in each trial, expressed as Pearl indices, appear in Table 3, as do the annual pregnancy rates for each variant of the Copper T 380. Each of the three variants—Copper T 380A, Copper T 380Ag, and Gyne T Slimline—has average annual pregnancy rates that are well below one per 100 woman-years, although, by chance, individual studies have been higher. The highest first-year rate was found in the Population Council's 1972–1975 US trials, in which 60 percent of the participants were under age 25 at admission. Accidental pregnancy rates among IUD users are highest among the youngest users. This is the case with most other types of contraception.

Figure 4: Annual Pearl pregnancy rates per 100 woman-years for Copper T 380 models in all randomized studies

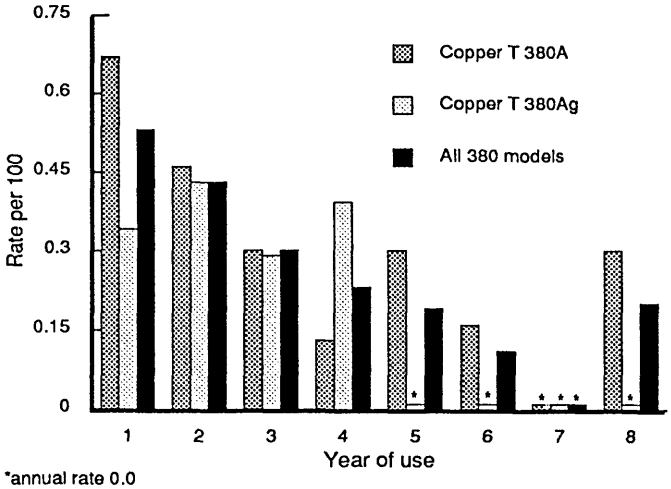


Table 3 Annual Pearl pregnancy rates per 100 woman-years in randomized trials, Copper T 380 IUD, years 1–3

Authors	Mean/Median age	Pregnancy rates Year 1	Year 2	Year 3	(N)
TCu 380A					
Sivin and Stern	22.6	1.3	0.0	—	(1,679)
Roy et al.	23.5	0.6	0.5	0.0	(391)
Diaz et al.	26.5	0.0	—	—	(159)
Chi et al.	—	1.0	—	—	(589)
Rowe, Farley et al.(WHO)	28.7	0.3	0.4	0.3	(1,396)
Sastrawinata et al.	26.0	0.5	0.8	—	(946)
Sivin et al.	28.4	0.4	1.5	—	(298)
Total TCu 380A	**26.2**	**0.7**	**0.5**	**0.3**	**(5,458)**
TCu 380Ag					
Cole et al.; Champion et al.[a]	26.7	0.3	0.3[a]	0.0[a]	(737)
Cole et al.; Apelo et al.[a]	28.7	0.7	0.0[a]	0.0[a]	(181)
Sung et al.	32.0	0.1	0.4	0.7	(892)
Sivin et al.	26.6	0.3	0.5	0.2	(1,121)
Saxena et al. (ICMR)	25.9	0.8	0.3	0.0	(434)
Total TCu 380Ag	**26.7**	**0.3**	**0.4**	**0.3**	**(3,365)**
Gyne T Slimline					
Sivin et al.	27.8	0.3	0.0	—	(698)
All variants	**26.6**	**0.5**	**0.4**	**0.3**	**(9,521)**

Note: Dash (–) = not published or not studied.
[a] Subset of clinics in Cole et al., 1985.

In individual randomized trials, the Copper T 380 had significantly lower first-year pregnancy rates than the Copper T 200 (Sivin and Stern, 1979; Chi et al., 1990), the Copper T 220C (WHO, 1990), the Lippes Loop D (Diaz et al., 1982), the Mahua steel double ring used in China (Sung et al., 1984), and the MLCu 375 (Sastrawinata et al., 1991; Rowe 1992). In other randomized studies, the Copper T 380 has had lower first-year pregnancy rates than the Multiload MLCu 250 (Chi et al., 1990), the Multiload MLCu 375 (Cole et al., 1985; Champion et al., 1988), and the Cu7 (Cole et al., 1985; Apelo et al., 1989), but the individual comparisons were not significant (see Table 4). In the 19 comparisons shown in Table 4, the Copper T 380 had the lower pregnancy rate in 15 studies. In no comparison has another IUD had a significantly lower pregnancy rate than that exhibited by the Copper T 380 at any duration of use. The slightly different rates of pregnancy of the Copper T 380 in the randomized studies reflect chance occurrences, the differing characteristics of the study groups, and the different investigators and clinics. The Copper T 380 is more effective than non-medicated and most other copper IUDs (WHO, 1987; Sivin and Schmidt, 1987).

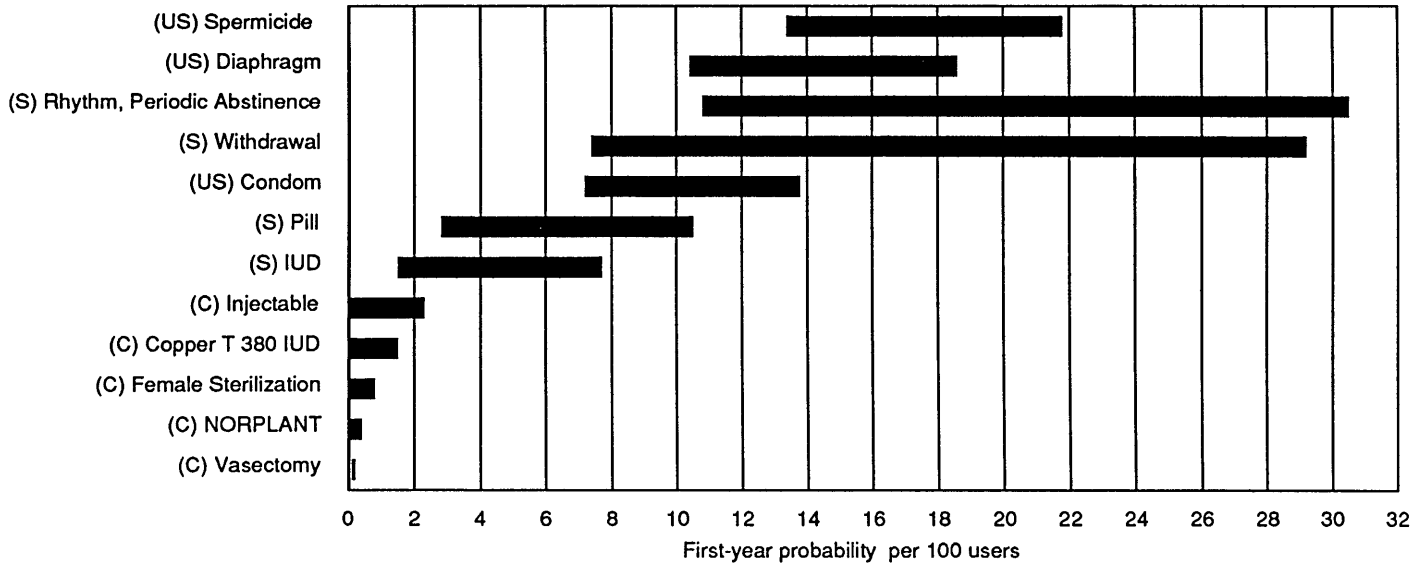
The first-year pregnancy rate of the Copper T 380 IUD is within the range of effectiveness of implantable or injectable hormonal contraceptives and surgical sterilization. Actual use of IUDs shows them to be more ef-

Table 4 First-year gross pregnancy rates per 100 women in randomized comparative trials

First author	TCu 380 rate	Other device Rate	Name
Nonmedicated IUDs			
Sung	0.1*	3.3	Mahua
Diaz	0.0*	4.1	Lippes
Sastrawinata	0.4	1.4	Lippes
Chi	1.5	1.8	Lippes
Copper IUDs			
Sivin and Stern	1.2*	3.6	TCu 200
Chi	0.8*	6.2	TCu 200
Saxena (ICMR)	0.8	0.9	TCu 200
Cole	0.6	3.8	Cu 7
Chi	0.7	2.1	MLCu 250
Cole	0.3	0.8	MLCu 375
Sastrawinata	0.4*	1.4	MLCu 375
Rowe (WHO)	0.5*	1.2	MLCu 375
Rowe, Farley (WHO)	0.3*	1.1	TCu 220C
Roy	0.5	1.1	TCu 220C
Chi	0.7	2.2	TCu 220C
Sung	0.1	0.4	TCu 220C
Saxena (ICMR)	0.8	0.0	TCu 220C
Levonorgestrel IUDs			
Saxena (ICMR)	0.8	0.0	LNg 20
Sivin	0.3	0.2	LNg 20

*The difference between these rates is statistically significant at $p<.05$.

Figure 5: Probability of experiencing a pregnancy in the first year of contraceptive use, per 100 users



US=Surveys of Family Growth
S=15 national Demographic and Health Surveys (DHS)
C=Clinical studies

Note: In computing ranges for the survey -derived data, the highest and lowest failure rate reported for each method have been omitted, i.e.. the range represents an 87 percent interval for each method.

fective in the first year than are oral contraceptives, condoms, barrier methods, and periodic abstinence, as judged by national sample surveys of women in 15 countries (Moreno and Goldman, 1991). Long-term (five or more years) pregnancy rates have been lower than that observed in studies of NORPLANT® implants (Population Council data, reflected in the US labeling).

A comparison of first-year accidental pregnancy rates of various methods is shown in Figure 5. The data derive from national surveys of contraceptive failure in 15 developing countries (Moreno and Goldman, 1991) and the United States (Trussell and Kost, 1987; Trussell et al., 1990). For some methods, like NORPLANT® implants, national sample survey data do not yet exist, and clinical trial data have been used.

US FDA approval of continuous use of the Copper T 380A for eight years (1991) was based on combined data from two sources: the original trials conducted in the US by the Population Council representing 3,536 women in randomized and non-randomized trials and the WHO randomized study involving 1,396 users of the Copper T 380A in 13 clinics in nine countries. The cumulative gross pregnancy rates for the combined data are shown in Figure 6.

Cumulative pregnancy rates of the Copper T 380A in the WHO study at nine years were 2.1 per 100 users (WHO 1990; Rowe, forthcoming). In an eight-year Population Council study, the cumulative rate at the end of the period was 1.4 per 100 users of the Copper T 380Ag.

Long-term follow-up in the WHO study of the Copper T 380A and in the Population Council study of the Copper T 380Ag has continued. Ten-year data have been submitted to the US FDA for review and possible extension of approved life of the IUDs.

Large randomized trials and cohort studies have found pregnancy rates of the Copper T 380 and other IUDs to decrease with age (Tietze and Lewit, 1970; Vessey, 1982; Sivin and Stern, 1979; Sivin et al., 1990a). Pre-

Figure 6: Cumulative gross pregnancy rates per 100 Copper T 380 users, through 8 years

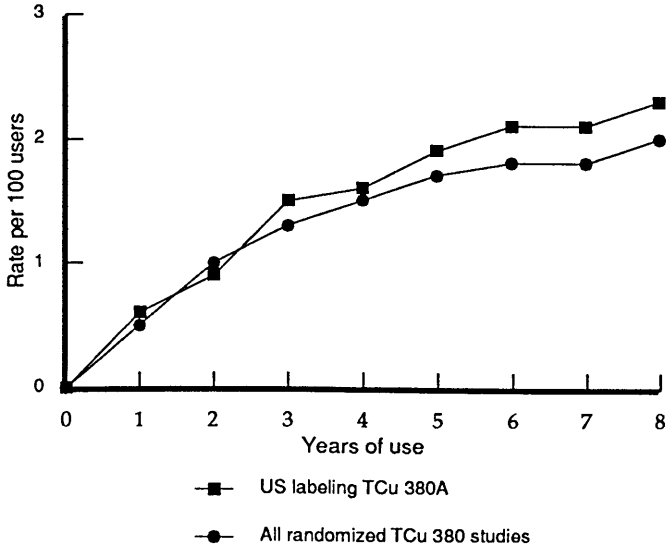
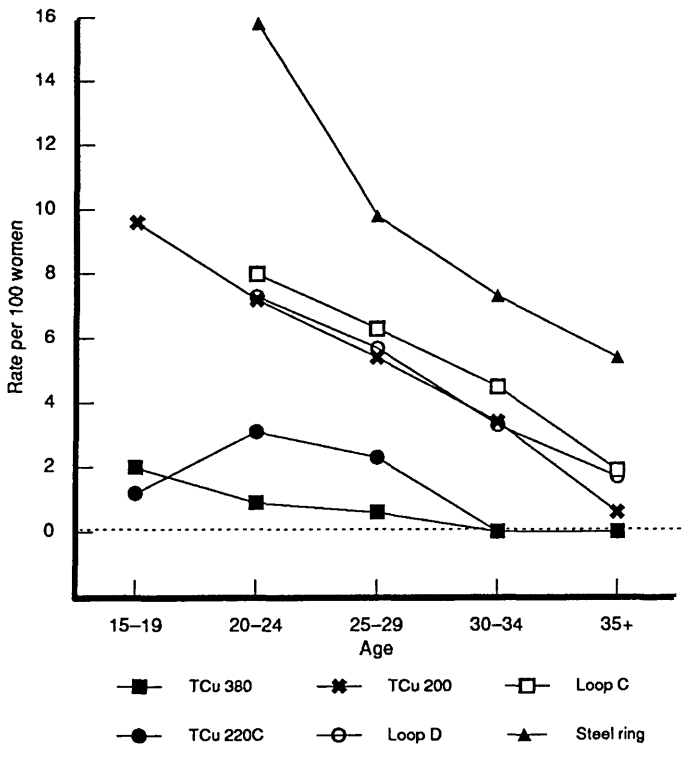


Figure 7: Two-year gross cumulative pregnancy rates per 100 women, by age of user and type of IUD



sumably this occurs because younger women have a greater frequency of intercourse. Figure 7 shows two-year cumulative gross pregnancy rates by age for various IUDs. The two-year cumulative pregnancy rate among women less than 20 years of age at acceptance was 2.0 per 100, whereas it was 0.6 per 100 for women aged 25 to 29, and 0.0 for women aged 30 or older when they started to use the Copper T in the initial Council study (Sivin and Stern, 1979). The very low pregnancy rates among women aged 35 or older who used copper devices or the Lippes Loops C and D provide a partial explanation of the low pregnancy rates observed at 6 to 10 years of Copper T 380 use, even when the devices are releasing less copper. The very long-term users tend to be above age 35.

Duration of use

The original 1984 approval of the Copper T 380A was for four years based exclusively on the Population Council's US clinical trials. Approval for eight years (1991) is based on both the US trial data and those of WHO. The eight-year approval for the Copper T 380A applies to the labeling approved by the US FDA. Versions of the Copper T manufactured in other countries may have been approved for different durations and are subject to the national regulatory requirements of the concerned countries. Therefore, the Copper T 380A may not be approved for eight years in each country.

Outcome of accidental pregnancy

If a pregnancy occurs with an IUD in place, the device should be removed. Removing the IUD decreases the risk of an early spontaneous abortion and of later septic abortion with its possible consequence of septicemia, septic shock, and death. When the IUD string is visible, removal during pregnancy is easily accomplished, and may improve chances of carrying to term if that is desired. The WHO recommends that if removal proves difficult or if the strings are not visible, the woman should be told about the risks of continuing with the pregnancy (WHO, 1987). Termination of pregnancy may be offered as an option. If the IUD is not removed, the woman should be followed more closely than other pregnant women. Long-term effects on the fetus or child have not been exhaustively documented. Atrash et al. (forthcoming) report that an IUD *in situ* is not associated with congenital malformations, even if the device is not removed and the fetus is carried to term.

In 1978 after the occurrence of pregnancy-related deaths associated with, but not limited to, the Dalkon Shield IUD, the US FDA instructed physicians to remove an IUD, whenever possible, following an accidental pregnancy. Since implementation of the FDA recommendation, cases of IUD-associated septicemia and septic shock have become extremely rare. There have been no IUD-associated, pregnancy-related deaths in the US since 1977 (Atrash et al., forthcoming).

Ectopic pregnancy

The Copper T 380 is more effective than most contraceptives in preventing ectopic pregnancy. It does this by preventing pregnancy. If a pregnancy occurs with the Copper T 380 in place, it is *less* likely to be ectopic than with steroid-releasing IUDs, NORPLANT®, the minipill, or sterilization and *more* likely to be ectopic than a pregnancy after the failure of barrier or rhythm methods or the combined pill.

Women with a history of ectopic pregnancy may have increased risk of another ectopic pregnancy; women who have had a pelvic inflammatory disease or sexually transmitted disease also may have increased risk of an ectopic pregnancy. If a woman older than 35 becomes pregnant, she is more likely to experience an ectopic pregnancy than is a younger woman. Women using a copper IUD whose menstruation is delayed two or more weeks should immediately visit a clinic or physician to be evaluated for pregnancy and for ectopic pregnancy.

Most IUDs protect against ectopic pregnancy, but greater protection is offered by the more effective IUDs such as the Copper T 380. An analysis of 42 randomized IUD trials of medicated IUDs confirms that both preg-

nancy rates and ectopic pregnancy rates vary inversely with the surface area of copper on the devices (see Table 5). The more copper, the fewer pregnancies. Ectopic pregnancy ratios in women generally increase with age, but IUD failure rates decline with age; thus, the annual rate of ectopic pregnancy both for older and younger users is about 4 in 10,000 per year or lower. Risks for IUD users depend upon whether the IUD releases copper or a steroid, the amount released, and the age of the user (Sivin, 1991b).

Women who use no contraception have a greater risk of ectopic pregnancy than do copper IUD users. Large case-control investigations demonstrated that IUD use significantly reduces a woman's risk of ectopic pregnancy as compared with the risks of nonusers of contraception (Oryet al. 1981; WHO, 1985). In these studies the reduction in ectopic pregnancy risk among IUD users was 50 to 60 percent. The IUDs in these studies were far less effective in reducing the incidence of ectopic pregnancy than the Copper T 380. The Copper T 380 reduces the risk of ectopic pregnancy by about 90 percent in comparison with nonusers of contraception (Sivin, 1991b).

Expulsion

Expulsion rates of IUDs are typically highest in the first three months following insertion, and decline thereafter. Generally, expulsion rates in the second and third years of use are much lower than in the first year. Gross cumulative expulsion rates from the long-term trials of the Copper T 380A used in the official labeling of the device in the United States are shown in Figure 8. In the first year, the expulsion rate was 5.7 per 100 users.

Many factors affect rates of expulsion. These include familiarity with the technique of insertion of the particular device and the training, technical skills, and hand skills of the provider inserting the IUD, the timing of insertion in relation to the preceding pregnancy, the age of the woman accepting the IUD, and the number of full-term pregnancies the woman has had.

The technique developed for insertion of Copper T IUDs differs markedly from that for most other IUDs. IUD providers must be trained in the specific insertion technique of the Copper T 380 before attempting placement. The Copper T should be placed at the uterine fundus; proper training helps avoid perforation and partial or complete expulsion by ensuring correct placement.

First-year expulsion rates in randomized studies of Copper T IUDs are shown in Figure 9. Lower expulsion rates in more recent studies probably reflect improved familiarity with the insertion techniques.

The timing of insertion can affect expulsion rates. The Copper T 380 IUD may be inserted at any time during a woman's menstrual cycle, provided the woman is not pregnant and has been consistently using an effective contraceptive since her last menses. Many clinicians prefer to insert an IUD within seven days of the onset of menstruation because the cervical opening is slightly dilated during this time, making insertion easier and pregnancy very unlikely. Insertion during these days also is likely to result in less discomfort, cramping, and/or spotting for the patient. The most frequent timing of insertion is interval insertion—three or more months postpartum. Most of the insertions in the randomized trials of the Copper T 380 conducted in the 1980s were interval insertions. Insertion after elective first-trimester abortion has been associated with expulsion rates similar to those following interval insertion.

Table 5 Pregnancy and ectopic pregnancy rates per 1,000 woman-years in the first 2 years of randomized, non-postpartum trials, by copper surface area

Device and surface area	Woman-years (000s)	Pregnancy rates	Ectopic rates
All	**53.4**	**12.4**	**0.5**
350–380 mm²	**13.1**	**4.1**	**0.2**
TCu 380	9.9	3.4	0.2
MLCu 375	2.5	5.9	0.0
Fincoid 350	0.7	7.3	0.0
220–300 mm²	**19.9**	**9.1**	**0.4**
MLCu 250	4.5	9.4	0.4
TCu 220	15.5	9.0	0.3
200 mm²	**20.3**	**21.2**	**0.8**
Nova T 200	7.0	13.4	0.9
TCu 200	8.2	24.9	0.6
Cu7 200	5.1	25.8	1.0

Sivin, 1991b.

Figure 8: Gross cumulative expulsion rate per 100 Copper T 380A users, through 8 years

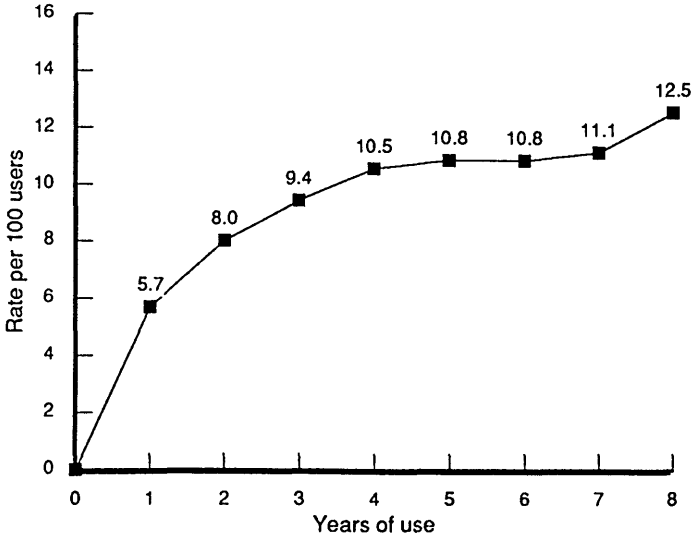
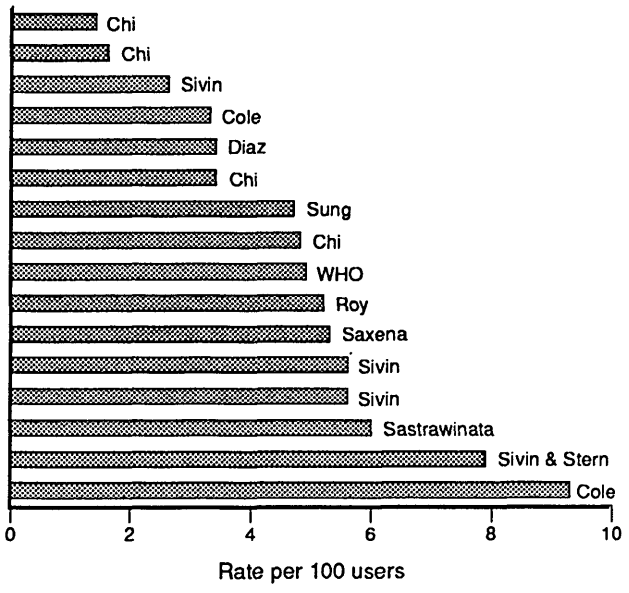


Figure 9: First-year gross expulsion rates per 100 users for the Copper T 380 in randomized trials



Immediate post-placental IUD insertion before the woman leaves the delivery room is associated with expulsion rates that have not been lower than 10 per 100 at one year, and have reached 41 to 46 per 100. They show remarkable variation by clinic, reflecting the skill and experience of the healthcare provider. In the most recent study of the Copper T 380 inserted within ten minutes after spontaneous expulsion of the placenta, Van Kets and colleagues (1991) reported a one-year gross expulsion rate of 13.3 per 100. Among the four clinics participating in the study, the range of the one-year expulsion rate was 3.8 to 45.7 per 100. Studies of insertions of the Copper T 380 more than ten minutes after delivery of the placenta but before hospital discharge have not been reported.

Insertion of the Copper T 380 in the second postpartum month has been associated with low rates of expulsion in the six-month period following (Chi et al., 1989; Mishell & Roy, 1982) and in the year following (Population Council data). Insertion during the second postpartum month may have programmatic and personal advantages, as many women visit a provider for a six-week postpartum check-up.

Bleeding and pain

In the initial years of use, menstrual problems and pain constitute the major single reason for removal of the Copper T 380 IUD. Similar findings apply to other IUDs (Rybo, forthcoming). The combined Population Council 1972–1976 and WHO data in the US labeling show gross cumulative termination rates for bleeding and pain as 11.9 per 100 users in the first year and 20.6 at two years. Termination rates attributable to menstrual problems and pelvic pain vary inversely with both age and parity. The first two randomized studies of the Copper T 380A (Sivin and Stern, 1979; Roy et al., 1979) included a majority of women under age 25 who were nulliparous. Women with these characteristics tend to have the highest rates of IUD removal. Thus, the early studies showed relatively high rates of removal for bleeding and pain and led to the belief that high rates of bleeding and pain are associated with the Copper T 380 IUD, as compared to other IUDs.

Thirteen years after those early publications, numerous randomized trials of the Copper T 380 show something quite different. Few nulliparous women have participated in randomized trials initiated in 1979 or later. In consequence, rates of removal of the Copper T 380 for menstrual problems and/or pain in ten later randomized trials were less than half the rates reported by Roy et al. or Sivin and Stern in 1979 (Table 6).

Users of the Copper T 380 had lower rates of removal for menstrual problems or pain than did users of non-T devices in seven of ten one-year randomized comparisons with non-T IUDs.

Table 6 First-year gross removal rates per 100 woman-years attributed to menstrual problems and/or pain, in randomized comparative trials

First author	TCu 380 rate	Other device Rate	Other device Name
Non-medicated IUDs			
Diaz	5.9	10.7	Lippes Loop D
Chi	3.1	4.9	Lippes Loop D
Sastrawinata	1.6	1.9	Lippes Loop D
Sung	7.4*	4.8	Mahua
Other medicated IUDs (not Copper T)			
Chi	1.5	2.0	MLCu 250
Cole, Champion	3.6	3.6	MLCu 375
Sastrawinata	1.6	1.1	MLCu 375
Cole, Apelo	3.1	4.2	Cu 7
Sivin	6.8*	10.4[a]	LNg 20
Saxena (ICMR)	7.5*	14.7[a]	LNg 20
Copper T IUDs			
Sivin and Stern	15.6*	12.9	TCu 200
Chi	6.6	3.2	TCu 200
Saxena	7.5	6.9	TCu 200
Roy	16.3	15.6	TCu 220C
Chi	0.9	1.5	TCu 220C
Rowe, Farley (WHO)	5.9	6.3	TCu 220C
Sung	7.4*	3.6	TCu 220C
Saxena	7.5	6.8	TCu 220C

*The difference between these rates is statistically significant at $p<.05$.
[a]Terminations attributable to amenorrhea are included.

Comparisons of the Copper T 380 with the other Copper T models show few substantial differences. Reviewing the published data, Rowe (forthcoming) concluded that it is unlikely that important differences exist among standard copper IUDs available today with respect to removal rates for bleeding/pain problems.

Annual rates of removal for bleeding and pain are highest in the initial year of use and decline thereafter. In the first year, the rate was 7.7 per 100 woman-years for all variants. This decreased to 6 per 100 woman-years in the second year of use. In years three through eight the rate varied narrowly between 3 and 4 per 100.

As with other nonhormonal IUDs, users of the Copper T 380A experience, on average, increased menstrual blood loss (MBL) in the initial year. Copper IUD use may induce iron deficiency in some women. Programs should be prepared to treat iron deficiency then or before a woman is given an IUD. In a short-term study (Gallegos et al., 1978), the average increase in blood loss was approximately 43 ml, accompanied by a significant decrease of hemoglobin. In a longer term study of the Copper T 220, MBL diminished with time (Andrade and Pizaro, 1987), and by the end of two years of its use, MBL was not greatly elevated above baseline. A study of the Copper T 380Ag (Sivin et al., 1984) showed an average decrease in hemoglobin of 3.6g/L at one year of use and of 1.3g/L in the first two years. After the first two years, however, continuing users of the Copper T 380Ag IUD experienced modest increases in hemoglobin that were statistically significant when compared with their status at two years of use (Sivin et al., 1991b), or at admission.

Other medical reasons for removals

Clinical studies record all medical reasons women give for removal of an IUD; some may be method-related, some not. In the US FDA-approved labelling for the Copper T 380A, gross cumulative medical terminations for reasons other than bleeding or pain were 2.5 per 100 users at one year, 5.9 per 100 users at three years, 7.6 at five years, and 9.0 at eight years.

A detailed tabulation of reasons for termination during the first two years of the first large Council study is given in Table 7. The overall rate of medical removals for the two-year period was 3.17 per 100 woman-years of exposure. Pelvic inflammatory disease and endometritis (1.27 per 100 woman-years) and vaginitis (0.46 per 100 woman-years) were the principal "other medical" removals during the first two years. Apart from these two, no single condition had a removal rate above 0.2 per 100 woman-years. Accidental removals and reported discomfort to the IUD user's husband caused by the IUD strings ranked third and fourth, respectively, in rate of removal.

IUD use and pelvic inflammatory disease (PID)

From the very first, the relationship of IUDs to pelvic inflammatory disease (PID) has received substantial attention. Studies of the possible association multiplied in the 1970s in the US in the wake of problems related to the Dalkon Shield, a plastic IUD introduced in 1971.

IUD use has been associated with increased risk of PID in the first one to four months of use, with the risk highest just after insertion of the device due to the insertion process itself. Insertion of an IUD may introduce microorganisms from the vagina into the uterus. To minimize the possibility of infecting the upper reproductive tract, insertion must be performed under strict aseptic procedures. Risk of PID thereafter is associated with exposure to sexually transmitted diseases (STDs). Infections of the uterus or adnexa caused by sexually transmitted organisms or other infectious agents are called PID. Rates of PID vary enormously, depending on the age and parity of the women, the degree of mutual monogamy practiced, the frequency of medical observation, and criteria used to diagnose or characterize PID. Any person can be exposed to sexually transmitted diseases by having multiple sex partners, or having a partner who has multiple sex partners. IUDs are most appropriate when exposure to sexually transmitted disease is minimal, that

Table 7 Pearl rates of termination for medical reasons other than bleeding and pain during first two years of use of the Copper T 380A IUD (3,536 acceptors), US 1972–1975

Reason	Rate per 100 woman-years
Total	**3.17**
Pelvic inflammatory disease[a]	1.27
Vaginitis, etc.	0.46
Perforation of uterus	0.05
Perforation of cervix	0.14
Internal displacement	0.05
Carcinoma of cervix	0.02
Abnormal cytology	0.12
Ovarian cysts	0.17
Fibroids	0.02
Other genital pathology	0.02
Diseases of urinary tract	0.05
Surgery	0.02
Psychiatric problems	0.05
Miscellaneous medical problems	0.31
Discomfort to husband	0.12
Pregnant at admission	0.05
Unintended or erroneous removal by patient or physician	0.24

Sivin and Stern, 1979.
[a] Includes PID, salpingitis, and endometritis.

is, for women in stable, mutually monogamous relationships. Women in such relationships are at minimal risk of PID, whether or not they use an IUD (Lee et al., 1983, 1988; Stone et al., 1986; Struthers, 1985). In a major analysis from the US Women's Health Study (WHS), conducted from 1976–1978, currently married or cohabiting IUD users with only one partner did not have a significantly increased PID risk compared with monogamous women using no method of family planning (Lee et al., 1988).

Case control studies have provided an opportunity to estimate the relative risk of PID among IUD users in comparison with women from the same population groups who have used no contraception. Burkman et al. (1981) and Lee et al. (1983) found in the WHS that women using various IUDs (excluding the Dalkon Shield) were 1.6 times more likely to develop PID than were women using no contraception. In the first month after insertion, they were four times more likely to develop PID. Two to four months after insertion, the relative risk decreased in non-Dalkon Shield users. Thereafter, IUD users were not at significantly higher risk of developing PID than were women using no method. A case-control study conducted by the WHO in 12 developing countries found that parous IUD users were 2.3 times more likely to develop PID than were women using no contraception (WHO, 1984). The same case-control study at three developed country sites also found an elevated relative risk of 4.1 for parous IUD users.

In the 1972–1976 Population Council clinical trials of the Copper T 380A, the termination rate for PID was 1.27 per 100 woman-years in the first year. The rate decreased to 0.71 per 100 woman-years in the second year and to 0.0 per 100 woman-years in the third year of use. The majority of women in this study were under age 25 and nulliparous. In marked contrast, in the eight year WHO study of the Copper T 380A, undertaken principally in traditional, developing country settings, there were no reported cases of PID in the first two years of use. The overall rate of occurrence (and termination) due to PID in the WHO study was minuscule, 0.05 per 100 woman-years (WHO data submitted to the FDA). In all WHO studies of the Copper T 380A, the rate has been 0.05 per 100 woman-years (Farley et al., 1992), about six percent of the rate of 0.93 per 100 found in the first three years of use in the US studies of the early 1970s (Sivin and Stern, 1979).

Some physicians may consider use of the prophylactic administration of antibiotics before insertion. There is no evidence from studies that such administration is beneficial in preventing PID. A Nigerian study (Ladipo et al., 1991) compared a dose of 200 mg of doxycycline with a placebo, and found no significant difference in PID rates between regimens. Indeed, the placebo-treated regimen had the lower observed rate. The investigators concluded that emphasis on aseptic conditions during IUD insertion, follow-up visits with short intervals to monitor health, and treatment of opportunistic infections may have reduced the potential of PID within this population. Sinei et al. (1990) studied the efficacy of prophylactic doxycycline at insertion in a large randomized clinical trial in Kenya, but also did not find a statistically significant difference in PID rates between the group given antibiotics and those given a placebo. Given the negative findings of these two studies, some argue that routine use of prophylactic antibiotics at IUD insertion would burden the method with additional costs without providing a benefit.

Uterine or cervical perforation

Although rare, partial or total perforation of the uterine fundus or cervix may occur following insertion of a Copper T 380 IUD (Sivin and Tatum, 1981). In the initial Population Council study of the Copper T 380 IUD, two uterine perforations—one associated with pregnancy—were reported among 3,536 women. Apart from unintended pregnancy, the consequences of uterine fundal perforation can be severe. The IUD may cause adhesions or may puncture organs in the peritoneal cavity, or cause sepsis if the bowel is punctured. The consensus treatment is to remove copper devices that have perforated the uterus and provide an alternative contraceptive method, if desired.

There is evidence (Tietze and Lewit, 1970) that the risk of fundal perforation is greater early in the postpartum period before the uterus is fully involuted. Special care is required when inserting postpartum, whether or not the woman is lactating. This has been discussed by Heartwell and Schlesselman (1983) and Sivin (1984). Further discussion of insertion while the woman is breastfeeding appears below under *Lactation and IUD* use. Insertion of the Copper T 380 or any other IUDs in the first two to three months postpartum is best done only by highly trained providers.

Cervical perforation is believed to be a more common phenomenon than uterine perforation. This appeared to be the case in the initial studies of Copper T devices when the Copper T 380A was manufactured without the ball tip. Six cervical perforations among 3,536 women were reported (Sivin and Stern, 1979). Cervical perforations usually occurred in conjunction with partial expulsion of the IUD. When the US FDA approved the Copper T 200 in 1976, it required that the polyethylene be molded into a bulb and placed at the lower vertical tip of the IUD to reduce the likelihood of cervical perforation. It is believed that this bulb lowered the rate of

cervical perforation of these two IUDs.

In all randomized trials of the Copper T 380, the rate of uterine perforations was 0.4 per 1,000 women and the rate of cervical perforation was 0.6, based on 9,521 women.

Allergy

There have been few cases of allergy associated with use of a copper IUD. A study of 1,121 users of Copper T 380 IUDs over an average of four years of use reported no cases of allergy to copper (Population Council data).

Continuation rates and acceptability

Continuation rates are one indication of the acceptability of a method after its use has been initiated. Continuation rates of IUD users are among the highest found in users of modern reversible contraceptives, including implants, oral contraceptives, and injectables (Trussell et al., 1990).

Cumulative continuation rates for the Copper T 380A used in the FDA-approved labeling are shown in Figure 10. The continuation rate was 77 per 100 users at one year. At the end of six years, 35 per 100 of the original acceptors were continuing, and at the end of eight years, 28.5 percent were still using the same IUDs. Average duration of use is 3.85 years. For the Copper T 380Ag in the Population Council study, the one year continuation rate was 82 per 100. At the end of eight years, 25 per 100 women were still using their original Copper T 380 (Sivin et al., 1990a, and Population Council data).

One-,two-, and three-year continuation rates in each of the randomized studies of the Copper T 380 variants are shown in Table 8. In six of the seven published three-year trials, the cumulative continuation rate at three years was 50 per 100 women or higher.

Because younger women and those with no children or only one child are more likely to want additional children, continuation rates vary with age and parity. Continuation rates also vary remarkably with the setting of the study or family planning program. The rates depend on the attitudes and experiences of the users, the attitudes and skill of the providers, as well as on the degree of availability of other methods of highly effective, reversible contraception. Hardy and Goodson (1991) have shown an association between the contraceptive method accepted and the perception of the information received during counseling.

IUDs are the most popular reversible method worldwide. Nevertheless, acceptance of the method varies from country to country. From 20 percent to 40 percent of contraceptors in Scandinavia use IUDs. In China, where over 65 million women choose from a selection of steel rings and copper IUDs, the method is a favored contraceptive; over 40 percent of Chinese contraceptive users choose IUDs. Other countries with large percentages of IUD users among all contraceptive users include Vietnam, Jordan, Egypt, Tunisia, and Indonesia. IUDs also are popular in Germany, Mexico, Turkey, Taiwan, and Hungary (Mauldin and Segal, forthcoming). American women's attitudes about the IUD have changed dramatically from the early 1970s, when four in ten married women viewed the method with favor. In 1991, US women were more likely to have an unfavorable attitude about IUDs than about any other method then available (Forrest, 1992). This reflects the adverse publicity given to all IUDs because of concerns with the safety of the Dalkon Shield. However, the 1991 Ortho Annual Birth Control Study showed that among those using the IUD, the proportion reporting satisfaction with the method is higher than among users of any other method (Ortho, 1991).

Return to fertility

Reversible contraceptives should not impede the speed at which women become pregnant or have children after they stop contracepting. Tietze and Lewit (1970) showed that, for a variety of nonmedicated IUDs, lifetable estimates of pregnancy rates were close to the values demographers considered normal. Vessey and colleagues (1976) in Oxford found that in the two years after removal for planned pregnancy, birth rates among former users of IUDs were as high or higher than among women using combined oral contraceptives or barrier methods.

Figure 10: Cumulative continuation rates for Copper T 380A IUD per 100 users, through 8 years

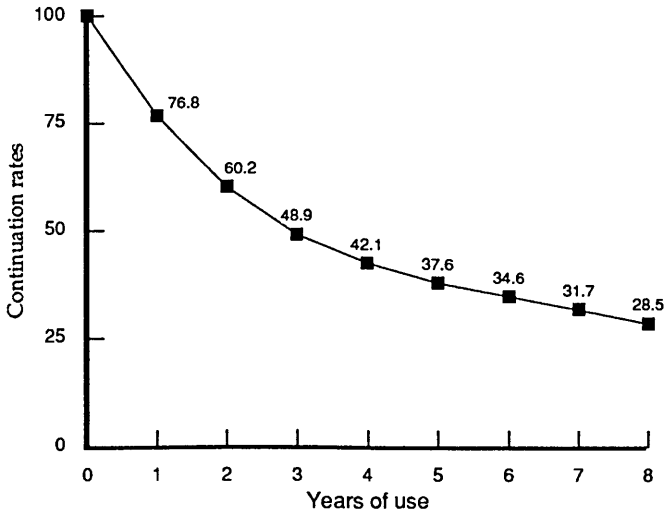
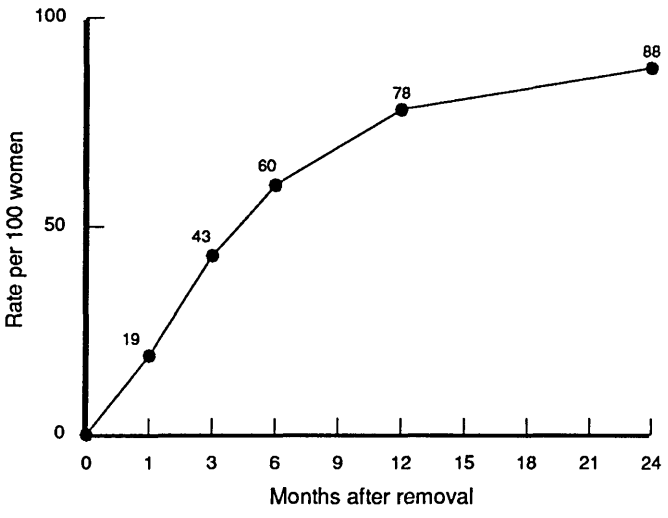


Table 8 Cumulative continuation rates per 100 women in randomized studies

Authors	Year 1	Year 2	Year 3
TCu 380A			
Sivin and Stern	69.7	50.1	—
Roy et al.	72.1	50.0	37.8
Diaz et al.	82.5	—	—
WHO	86.7	75.6	66.4
Sastrawinata	90.3	85.5	—
Sivin et al.	79.7	68.9	—
TCu 380Ag			
Champion et al.	89.5	79.7	67.4
Apelo et al.	85.6	80.8	74.3
Sung et al.	88.4	83.9	75.8
Sivin et al.	81.8	69.0	59.3
Saxena (ICMR)	83.5	69.9	50.4
Gyne T Slimline			
Sivin et al.	79.1	64.7	—

Figure 11: Cumulative rate of planned pregnancy after removal of Copper T 380



Studies of the Copper T 380A and Ag also indicate normal pregnancy rates after IUD removal and normal pregnancy outcomes. In a study with substantial loss to follow-up, 80.3 per 100 parous women who had used the Copper T 380A became pregnant within a year of removal of their IUD as did 76.1 per 100 nulliparous women (Sivin and Stern, 1979). Limiting analysis to clinics with good follow-up, Belhadj et al. (1986) and Sivin et al. (1986) showed that the pregnancy rates of former Copper T 380Ag users were normal at one and two years (see figure 11). Sivin et al. (1992) also showed that the rates of successful planned pregnancy were unaffected by duration of use. Age at IUD removal for planned pregnancy was a significant factor affecting rates; women who were 30 years of age or older at IUD removal had substantially lower rates of planned pregnancy than did younger women. This is also true in the general population. Women who said they wanted more children at the time of IUD insertion had significantly higher pregnancy rates post-removal than did women who were not sure, or who thought they wanted no more children but subsequently removed the IUD (Sivin et al., 1992). Pregnancy rates following removal of the Copper T 380Ag were similar at one and two years to those observed among women with NORPLANT® capsule or rod implants.

Studies that follow cohorts of women desiring pregnancy do not provide a complete picture of the effects of IUDs or other contraceptives on the reproductive capacities of former users. Because women with PID, endometritis, accidental ectopic pregnancy, or other conditions that may compromise future fertility are not included in the group of women followed for a planned pregnancy, rates of successful planned pregnancy may be overstated. To address that problem, several investigators have studied women who removed IUDs following a "complication" of use, and then sought pregnancy, as well as removals for planned pregnancy. All the cohorts studied (Sandmire, 1986; Skjeldestad, 1988; and Wilson, 1989), no matter which group they were from, were deemed to have normal pregnancy rates.

A different approach has been taken in case-control studies of tubal infertility. The concern has been that with elevated risks of PID, IUD users may also have increased risks of tubal infertility. The study groups have consisted of women who sought medical help to overcome infertility of one year's duration (Cramer et al., 1985; Daling et al., 1985; Daling et al., 1992). These studies found that the risk of primary tubal infertility varied with both the type of IUD and the number of sexual partners the women had. The studies of Daling and Cramer, taken together, now indicate a significantly increased risk of primary tubal infertility among women with copper devices then used in the US (principally the Copper 7 IUD). But these case-control studies suffer from the same limiting features as do the cohort studies of planned pregnancy. The women who sought medical help for fertility are self-selected from among upper economic groups. At the time of the studies, it was widely believed that IUDs might affect future fertility, and so women with IUDs might have sought medical evaluation more frequently than their peers, thereby introducing a bias in the results, as Skjeldestad has shown. Non-response or refusal to be interviewed or give data reached 30 percent. Whatever their exact merit, these studies strongly suggest that an IUD is not the method of first choice for nulliparous women.

Table 9 Insertion event rates per 1,000 women by breastfeeding status

Events/Authors	Status at insertion: Breast-feeding	Women	Nonbreast-feeding	Women	Proba-bility
Uterine perforation					
Chi et al.	0.0	559	0.0	590	NS
Sastrawinata	2.7	744	0.0	203	NS
Sivin et al.	0.0	222	0.0	773	NS
Total	1.3	1,525	0.0	1,566	NS
Moderate or severe pain at insertion					
Chi et al.	8.9	559	27.1	590	<.05
Sivin et al.	45.0	222	99.6	773	<.05
All insertion events*					
Chi et al.	16.1	559	47.5	590	<.01

*Included cervical laceration, dilatation required, and uterine perforation.

Lactation and IUD use

IUD use does not decrease either the quantity or quality of breastmilk in lactating women (Labbok, 1985). Because it does not affect breastmilk, a woman may choose to initiate IUD use while nursing her baby. During breastfeeding, contraception with combined oral pills is not recommended, because the estrogen component of the pills is known to affect the quantity and quality of breastmilk. Chi and colleagues (1989a) investigated insertion events and termination event rates in breastfeeding and nonbreastfeeding women using the Copper T 380. Sivin and colleagues (1990b) and Sastrawinata and colleagues (1991) also compared Copper T 380 insertion and termination events and rates. Data from each of these studies and their combination appear in Table 9 as do data on perforation rates from an on-going Population Council study of IUDs.

The FHI investigators found significantly lower rates of required dilation and of moderate or severe pain at IUD insertion in the breastfeeding women, as compared with nonbreastfeeding women. There were no uterine perforations in either group. At six months of use, breastfeeding women had significantly lower rates of removal for bleeding and pain and higher continuation rates, although it is not clear how much of these differences derive from different starting points within pregnancy intervals.

The findings in the Population Council study of the Slimline and Gyne T*380 were similar to Chi's with respect to a significant reduction in the occurrence of moderate or severe pain at insertion in the breastfeeding group and the absence of perforation in either group.

In the context of a multicenter randomized trial in Indonesia, Sastrawinata and colleagues (1991) showed that neither expulsion nor removal rates for bleeding and pain were elevated when use of a Copper T 380A IUD was initiated during breastfeeding, and the latter rate may be reduced in comparison with insertion at other times. There were, however, two uterine perforations in the breastfeeding group. (See Uterine Perforation section.)

Overall rates of moderate or severe insertion pain were significantly lower in the breastfeeding groups. Rates of perforation were not significantly higher in these comparative studies, but that these rare events requiring surgical removal of the IUD occurred at all to lactating women places emphasis on the great need for skilled care in inserting an IUD at this juncture.

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GLOSSARY

Abortifacient An agent that produces abortion.

Barium sulfate A non-soluble powder sometimes added during the manufacturing of IUDs so that they will show up on x-ray.

Blastocyst A mass of cells that become the *embryo* and supporting structures. It implants in the uterine lining seven to nine days after fertilization.

Carcinogenic Cancer causing.

Cervical canal The part of the uterus leading through the cervix and into the vagina.

Chorionic gonadotropin A hormone produced by the developing *embryo* that becomes detectable in the mother's serum around the time of *implantation*. Pregnancy tests are based on the detection of human chorionic gonadotropin (hCG).

Cohort A group of individuals having factors in common, such as age, *parity*, education, or economic status.

Congenital anomaly A birth defect that begins during fetal development, before the birth of the baby.

Copper ions Copper atoms carrying electrical charges.

Cytology The study of the anatomy, physiology, pathology, and chemistry of the cell.

Cytotoxic Harmful to cells.

Degradation products Created when a chemical compound breaks down into a less complex compound.

Dermatitis Irritation or inflammation of the skin.

Dysplasia Alteration in size, shape, and organization of an organ's cells.

Ectopic pregnancy A pregnancy occurring extrauterine, that is, outside the uterus; most commonly in the *fallopian tubes*.

Embryo An organism in the early stages of development; in human beings, this is considered to be from conception to approximately the end of the second month.

Endometriosis The presence of functioning endometrial tissue outside its normal site in the lining of the *uterine cavity*.

Endometritis An infection of the endometrium (the mucus membrane lining the uterus).

Epidemiology The study of incidence, risk, and exposure factors, distribution, and control of disease in a population.

Extrauterine pregnancy (See *Ectopic pregnancy*.)

Fallopian tubes Organs that carry the egg from the ovaries to the uterus; also called oviducts.

Fertility Ability to conceive or to give birth after 12 to 24 months of trying.

Fertilization Fusion of spermatozoa and ovum to form a zygote or pre-embryonic cell, usually in the *fallopian tubes* within one day of ovulation.

Fetotoxic effects Toxic or causing harm to the fetus.

Glucose A simple sugar; the most common form of carbohydrate used by animals.

Gross event rates (See page 10.)

Hemoglobin A protein in red blood cells that carries oxygen.

Immunoradiometric assays A sensitive procedure for measuring hormones (such as hCG) using antibodies and radioisotopes.

Implantation The embedding of the fertilized egg into the wall of the uterus.

In situ In place.

In utero In uterus.

Intrauterine In the uterus.

Lactation The production of milk by the breasts after childbirth.

Leukocytes White blood cells.

Lifetable (See page 10.)

Monofilament A single synthetic thread or filament, tied to the bottom of the IUD and used in detection and removal.

Net event rates (See page 10.)

Nulliparous Never having borne children.

Ova Female eggs or germ cells; plural of ovum.

Papanicolaou smear test or "Pap smear" Examination of a smear of cells, usually from the cervix, used to detect cancer or precancerous changes in cervix that may indicate pathology.

Parity The number of children borne by a woman.

Pathology The study of the essential nature of diseases and the causes and development of abnormal conditions.

Pearl Index (See page 10.)

Pelvic Inflammatory Disease A general term for inflammation or infection of the ovaries, oviducts, or fallopian tubes.

Perforation As used here, refers to holes or tears in the walls of the uterus or cervix.

Phagocytosis The process of ingestion and digestion by cells.

Polyethylene A form of plastic used in manufacture of the T-shaped platform of the Copper T IUD.

Postpartum After childbirth.

Radiopaque Impenetrable by x-rays and therefore visible when x-rayed.

Randomized trial A clinical study in which the volunteers are assigned a treatment, such as use of a contraceptive method, in a random way that is not determined by the volunteers or those conducting the study.

Septic Infected or contaminated; not sterile.

Septicemia Systemic disease caused by the presence of microrganisms in circulating blood.

Spermicidal Causing the death of spermatozoa.

Spermatozoa Mature male reproductive cells; sperm.

Syncope Fainting.

Teratogenic Causing malformations or serious deviations from normal development.

Toxicology The scientific study of the relative safety of substances, including those in drug and food products.

Tubal infertility Infertility-related pathology of the *fallopian tubes*.

Tyvek® A material widely used in sterile packaging; a component in the Copper T packaging.

Uterine cavity The space within the uterus.

Vaginitis Inflammation of the vagina.

Wilson's disease An inherited disease characterized by abnormal metabolism of copper.

Appendix A

Statements by American and international organizations about the IUD

World Health Organization
Mechanism of action, safety and efficacy of intrauterine devices
Technical Report Series 753, 1987

> "In summary, the Scientific Group considered the IUD to be an important method of fertility regulation with high continuation rates and significant advantages in convenience of use. The newer copper-releasing devices are comparable to oral contraception in terms of safety and efficacy, and the use of IUDs in both developed and developing countries should continue to be supported as a reliable and safe method of reversible fertility regulation."

International Planned Parenthood Federation
Statement on intrauterine devices (IUDs)
International Medical Advisory Panel 1987, 1989

> "After more than two decades of widespread use, IUDs are now used by some 60 million women world-wide. They do not interfere with sexual activity and, for properly selected women, are a safe, effective and convenient reversible method of contraception."

American College of Obstetricians and Gynecologists
Technical Bulletin, No. 164—February 1992

> "The IUD is an excellent form of contraception for selected patients. As with all methods of contraception, the benefits and risks of the method and the needs of the patient must be considered. Counseling is an important part of the selection process and will identify those for whom the IUD is a suitable contraceptive choice."

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