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Mechanism of action, safety and efficacy of intrauterine devices

Report of a
WHO Scientific Group

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SAFETY AND EFFICACY OF INTRAUTERINE DEVICES*

Geneva, 1-4 December 1986

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MECHANISM OF ACTION, SAFETY AND EFFICACY OF INTRAUTERINE DEVICES

Report of a WHO Scientific Group

1. INTRODUCTION

A WHO Scientific Group on the Mechanism of Action, Safety and Efficacy of Intrauterine Devices met in Geneva from 1 to 4 December 1986. The meeting was opened by Dr T.A. Lambo, Deputy Director-General, on behalf of the Director-General of WHO.

Two previous Scientific Groups have been convened by WHO to advise the Director-General on the subject of intrauterine devices (IUDs), in 1966 and 1967, and their reports were published in the *WHO Technical Report Series (1, 2)*. Since the second of these reports was published, data have become available on the use of IUDs in China and it is now known that more than 60 million women are using these devices. There have also been notable advances in the types of device now available; in particular, the recently introduced copper and hormone-releasing devices have not only reduced the incidence of certain side-effects but also result in lower pregnancy rates.

The IUD is highly effective in preventing pregnancy but, like other methods of contraception, has side-effects associated with it which may be either serious, such as ectopic pregnancy or pelvic inflammatory disease, or troublesome to the woman, such as pain and increased blood loss and anaemia. In the past decade, research on IUDs has been concentrated on the development of new devices that have both higher continuation rates and lower rates of expulsion and removal for bleeding abnormalities. In addition, a number of large-scale randomized multicentre studies have been undertaken by, both the WHO Special Programme of Research, Development and Research Training in Human Reproduction, and non-governmental organizations, such as the Population Council and Family Health International; these studies have covered both new IUDs and IUDs already in use in national family planning programmes.

Recently, the most important issue concerning the use and safety of IUDs has been that of a possible increased risk of pelvic inflammatory disease and subsequent tubal infertility associated with their use. In a number of countries, and particularly in the United States of America, this issue has been the subject of numerous law suits, in which judgements have been given both for and against the IUD; as a result, the two principal manufacturers have discontinued the manufacture and distribution of IUDs in the USA (3, 4). This, in turn, has resulted in considerable concern as to the safety of IUDs being expressed by governments, family planning agencies, the media and individuals in countries other than the USA, and WHO has received numerous requests from its Member States for advice on this subject.

It is for this reason, and to fulfil the recommendation of the WHO Global Advisory Committee on Health Research that the Organization should periodically review developments in the field of contraception, that the Director-General convened a Scientific Group on the Mechanism of Action, Safety and Efficacy of Intrauterine Devices.

2. BACKGROUND

2.1 Extent of present usage

The IUD is now probably the second most commonly used reliable reversible method of preventing pregnancy; only oral hormonal contraceptives are used more frequently. As already mentioned, it is estimated that more than 60 million women are using IUDs, of whom at least 80% are in China where, in some areas, more than 50% of women of child-bearing age have had an IUD inserted. IUD use in other areas of the world is very much less, ranging from about 6% in developed countries to 0.5% in sub-Saharan Africa (5) (see Table 1).

2.2 Development of IUDs

The first intrauterine device promoted specifically for purposes of contraception was described in 1909 (6); it was made of silkworm gut in the form of a ring. In 1931, Graefenberg (7) described a device consisting of a core of silkworm gut encircled by German silver—an alloy of copper, nickel, and zinc—which was said to be highly

Table 1. Estimated number of IUD users (1981)^a

Region	Estimated number of IUD users (in millions)	Proportion of married women of reproductive age (%)
Africa (sub-Saharan)	0.3	0.5
Asia (excluding Japan)	45.9 ^b	13
Developed countries	11.7 ^c	6
Latin America/Caribbean	1.8	2.2
South-West Asia/North Africa	0.8	2
World	60.5	8.7

^aSource: reference 5.

^bIncluding 42.3 million in China, or 35% of married women of reproductive age; in 1985, the figure was 39% (Gao Ji, personal communication).

^cIncluding 1 million in Japan, or 5% of married women of reproductive age.

effective in preventing pregnancy. This was followed in 1934 (8) by the Ota ring—a gold or gold-plated silver ring to which a small disc in the centre was attached by three spokes. Both devices enjoyed some local success but the strength of medical opinion prevented their large-scale adoption. In 1959, Oppenheimer (9) reported on the use of the Graefenberg ring in 1500 women; in the same year, Ishihama published an account of the use of the Ota ring in 20 000 women (10).

In the following year (1960), the first of the so-called “second generation” IUDs was launched—the Margulies Spiral (11). This device was made entirely of plastic, without any metal, barium sulfate being added to the plastic to render it radio-opaque. In 1962, Dr Jack Lippes introduced the Lippes Loop, which is still one of the most widely used IUDs in national family planning programmes (12). This IUD has a serpentine “double S” configuration and was the first to have a nylon thread attached to the lowest part of the device; this made it easier to remove, and it was also possible to verify by simple vaginal examination that the IUD was in the uterine cavity.

Copper-bearing devices. Following the observation that a small length of copper wire within one uterine horn of a rabbit dramatically reduced the number of implantation sites as compared with the sham-operated contralateral horn (13), Zipper and others in 1974 reported on subsequent clinical trials in Chile (14). It was shown that, while the plain T carrier without copper had a pregnancy rate of 18 per 100 woman-years, the addition of copper wire with a surface area of approximately 200 mm² to the device reduced the rate to approximately 1 per 100 woman-years.

A number of copper-bearing devices are now commercially available, including the Copper-7, the Shanghai V, the Copper T in various forms, such as the TCu-200, TCu-220 C, and TCu-380 A, and those with a silver core wire (Nova T, TCu-380 Ag), and the Multiload devices. The numbers included in the names of the devices refer to the surface area (in mm²) of the copper on the device.

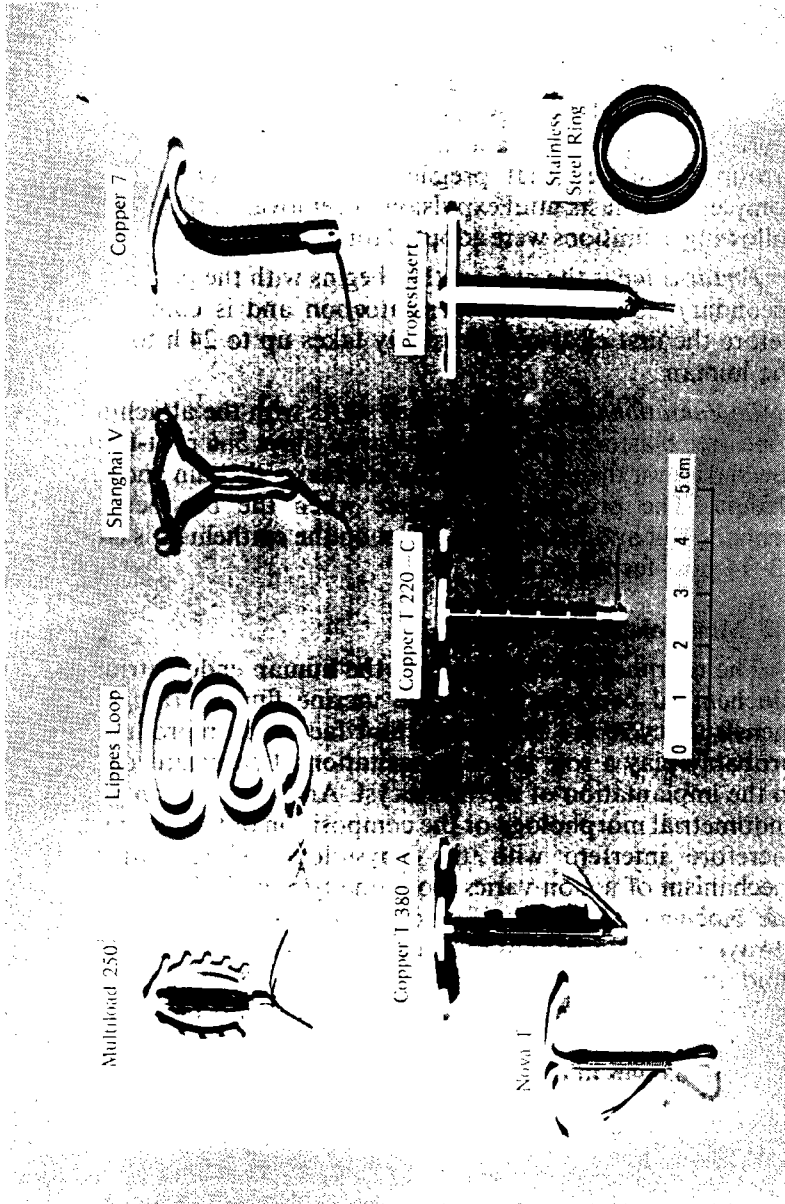
At least for the Copper T and Copper-7 devices, the expulsion rate would appear to be lower than for the larger non-medicated devices, such as the Lippes Loop (15, 16, 17), and the increased menstrual blood loss associated with intrauterine devices to be less than with the first generation devices, e.g., the Lippes Loop (18, 19).

Hormone-releasing devices. A device pioneered by Scommegna et al. (20) has now been shown to be just as effective in preventing pregnancy as copper-bearing IUDs. This T-shaped device, the Progestasert, is similar in size to the Copper T but consists of a permeable polymer membrane which releases progesterone at a predictable, controlled rate of 65 µg per 24 h over a period of 1 year (21). The advantage of this device is that, despite an increased frequency of intermenstrual vaginal spotting (22), there is significant reduction in menstrual blood loss, as compared with pre-insertion values (23). There are, however, two major disadvantages, namely the need to replace the device at yearly intervals and its relatively high unit cost. Similar devices containing larger amounts of progesterone but released at a lower rate, were expected to remain effective for at least 3–5 years, but when tested in a multicentre trial were found to have an effective life span of only 1.5–2 years (24).

Recent publications (25, 26) have shown that a device with a shape based on that of the Nova T IUD, releasing 20 µg/day of levonorgestrel from a reservoir in the form of a polymethylsiloxane collar, gives a low pregnancy rate (0.3 per 100 women at 1 year), a significant reduction in menstrual blood loss (27), and a reduction in dysmenorrhoea but an increased discontinuation rate on account of amenorrhoea (up to 10%). In view of the very low pregnancy rate, this amenorrhoea is almost certainly a local endometrial effect rather than an indication of accidental pregnancy (28). No changes were observed in serum lipids and high-density-lipoprotein cholesterol (29), breast-feeding or infant development following postpartum insertion (30), or blood pressure or weight (26).

A number of commonly used devices are illustrated in Fig. 1.

Fig. 1. Examples of commonly used IUDs



3. MECHANISM OF ACTION

3.1 Terminology

The Scientific Group noted that considerable confusion exists in the scientific and lay press as to the definition of certain key, early reproductive processes and as to the duration of pregnancy. The Group considered that pregnancy begins when implantation is complete, and lasts until expulsion or removal of the conceptus. The following definitions were adopted for fertilization and implantation.

Fertilization is the process that begins with the penetration of the secondary oocyte by the spermatozoon and is completed shortly before the first cleavage. It usually takes up to 24 h to complete in the human.

Implantation is the process that starts with the attachment of the zona-free blastocyst to the uterine wall (days 5-6 post-fertilization); the blastocyst then penetrates the uterine epithelium and invades the stroma. The process is complete when the blastocyst develops primary villi and the surface defect on the epithelium is closed (days 13-14 post-fertilization).

3.2 Morphological changes

The morphological changes in the human endometrium and the biochemical composition of the uterine fluid during the normal menstrual cycle are both important factors in reproduction. They probably play a role in the capacitation of spermatozoa as well as in the implantation of the blastocyst. Any agent which modifies the endometrial morphology or the composition of the uterine fluid may therefore interfere with the physiology of reproduction. The mechanism of action varies from one type of IUD to another, and the biochemical changes found in the endometrial tissue are not always the same as those found in the composition of the uterine fluid after the insertion of an IUD.

Whenever a foreign body is introduced into the uterine cavity, biochemical and cellular reactions take place, characterized by specific changes in the endometrial tissue, such as increased vascular permeability and oedema, and stromal infiltration of leukocytes, including neutrophils, mononuclear cells and macrophages (31, 32).

All IUDs stimulate an increase in leukocytes in the endometrial tissue and in the intrauterine fluid environment. The presence of leukocytes in the endometrium, however, is not unique to IUD use.

In the normal menstrual cycle, extensive leukocyte infiltration occurs about 24–48 h prior to the onset of menstruation (33).

It should be emphasized that the foreign-body reaction seen with both medicated and non-medicated IUDs can take place in the absence of bacterial infection (34, 35) and is most pronounced in the area adjacent to the device.

The foreign-body reaction should not be confused with endometritis, which is a bacterial inflammatory condition. The morphological features in the endometrium indicating endometritis include necrosis and disintegration of the tissue architecture of the endometrium, with extensive leukocyte infiltration, the number of plasma cells being of diagnostic importance. Endometritis should be confirmed by specific staining of histological material or bacterial culture.

3.3 Biochemical changes

The true foreign-body reaction occurs in the presence of inert IUDs, where leukocytes have been shown to migrate through superficial ulcerations in the endometrium (35). It has been suggested that the antifertility action of inert IUDs is directly related to the presence of increased numbers of intrauterine leukocytes in general (36, 37) and macrophages in particular (38). The high levels of intrauterine protein reported in IUD users (39) might reflect the cellular degradation of these neutrophils and macrophages (35) and thereby further contribute to the antifertility effect (39).

The foreign-body reaction caused by non-medicated devices is enhanced by the addition of copper to the IUD (40, 41). In addition, copper-bearing IUDs affect endometrial enzymes, the amount of DNA in endometrial cells, glycogen metabolism and estrogen uptake by the uterine mucosa (42). The copper ions released from the device may also inhibit sperm transport in the cervical mucus and in the endometrial cavity (43).

A foreign-body reaction has also been reported in the endometrium exposed to steroid-releasing devices (28, 44, 45). In addition, steroid-releasing IUDs have specific morphological effects on the endometrium, such as suppressed proliferation and atrophy of glands, and extensive decidual transformation of the stroma. A biochemical reaction occurs together with the morphological changes, in the form of a generally lower enzymatic activity, as compared with normal cyclical endometrium and with endometrium exposed to copper-bearing IUDs (44, 46).

3.4 Prostaglandins and allied substances

Prostaglandins are very active biological substances that are potentially capable of affecting many steps in the reproductive process.

In some non-primate animal species, the IUD has been shown to increase prostaglandin (PGF_2) production in the uterus and induce luteolysis (47). Many of the cellular and vascular changes observed in the IUD-influenced endometrium and in the uterine fluid can, in principle, be induced by arachidonic acid metabolites. Moreover, cells attached to the surface of IUDs, both inert and copper-bearing, have the capacity to produce both PGF_2 and PGE_2 (48).

Arachidonic acid metabolites produced by the lipoxigenase pathway, such as leukotrienes and lipoxins, are known to be a product of human polymorphonuclear leukocytes (49). These compounds produce a variety of biological effects, such as cytotoxicity, chemotaxis and increased vascular permeability (49). The possible relevance of these effects from the point of view of IUDs has not yet been explored.

Data on the endometrial levels of the classical prostaglandins in the IUD-influenced endometrium are incomplete. Three studies have been published, of which the first was concerned with the endometrial levels of PGF_2 and 13,14-dihydro-15-keto PGF_2 before and after insertion of the Dalkon Shield. No changes were found as a result of IUD insertion (50). In the second study, this result was confirmed for PGF_2 levels but an increased level of PGE_2 was found in the luteal phase of women using copper-bearing and inert IUDs (51). In the third study, no changes were reported in endometrial PGF_2 levels after insertion of the Lippes Loop or a progesterone-releasing IUD but a decrease was found after 8 months' use of a dydrogesterone-releasing IUD (52). Methodological limitations make the data from all these studies difficult to interpret.

While there is some evidence to indicate that copper can influence the synthesis and metabolism of prostaglandins in the endometrium in favour of a lower $\text{PGF}_2/\text{PGE}_2$ ratio (53, 54), there is nothing to suggest that such changes are associated with the antifertility action of a copper-releasing device. Increased uterine activity and/or altered tubal motility, which might be mediated by increased prostaglandin production, have been suggested as possible mechanisms of action of IUDs, but these theories are not supported by any consistent data in the human.

3.5 Biological changes

The most commonly accepted mechanism of action of IUDs involves the alteration in the uterine environment as a result of a pronounced foreign-body reaction. Such a biological response could induce an antifertility effect by interfering with several of the steps leading to successful implantation. In this context, a key question is whether or not the fertilized ovum reaches the endometrial cavity in IUD users at the same rate as in non-users.

3.6 Embryo-specific substances

There would seem to be little controversy as to the definition of fertilization but a biochemical marker has remained elusive. The pregnancy-related protein, early pregnancy factor (EPF), has been detected in serum as early as 24 h after conception, i.e., while the zygote is still in the fallopian tube (55). Positive results have been reported in IUD users tested for EPF (56) but the conclusions have been challenged (57). As EPF has not yet been purified and no antiserum directed against it has yet been produced, the quantification of this protein is based on its ability to reduce or inhibit the spontaneous *in vitro* formation of rosettes between lymphocytes and heterologous red blood cells in the presence of complement. The assay system is said to be tedious, time-consuming, cumbersome and fraught with many pitfalls (58), and some workers have failed to confirm the early production of EPF (59, 60).

Human chorionic gonadotrophin (hCG) can be detected in the circulation as early as 9–11 days post-ovulation (61). In 1976, Beling et al. (62) reported a positive hCG urinary assay in 32 of 73 IUD users in the luteal phase of the cycle; positive results have also been reported by Landesman et al. (63). However, other workers, using a variety of different types of assay for hCG, have failed to confirm these findings (64–67). Even where hCG was detected, its level was considered to be consistent with, or even lower than, that associated with “normal” implantation (68–70). More recently, an immunoradiometric assay specific to the carboxy-terminal peptide of the hCG β -chain has been developed and has been shown to be more sensitive and more specific than two radioimmunoassays for hCG (71). A study in IUD users did not show any transient increase in levels, which suggests that IUDs do not act by interfering with the implanted ovum. Further studies using this new methodology are required. The fact that this assay can be conducted on small

quantities of early morning urine makes it a potentially useful tool for more extensive studies.

3.7 Sperm migration

Attempts have been made in several studies to compare the recovery of spermatozoa from the peritoneal cavity and/or the different segments of the female genital tract after natural or artificial insemination during the fertile period in IUD users and non-users (43, 72-77). In studies of this type it is difficult to satisfy all the criteria for an adequate experimental design. Nevertheless, spermatozoa have frequently been found to be absent or fewer in number in the upper female genital tract, particularly in the presence of copper-bearing devices. However, spermatozoa can migrate to the fallopian tubes in some cases but are less likely to reach the normal site of fertilization in the same numbers as in control women (43, 73, 74, 76-78). The fertilizing capacity of these spermatozoa has not been determined.

3.8 Transport and development of ova

Ova have been recovered from different segments of the genital tract and at different times after ovulation both in users of copper-bearing IUDs and in women not using any type of IUD. In IUD users, these studies indicate a virtual absence of ova in the uterine cavity (79) and a lower rate of recovery from the fallopian tube as compared with non-users (80). The microscopic examination of the ova recovered from the fallopian tube in IUD-using women who had had intercourse during the fertile period indicated that the majority showed no signs of development, while at least 50% of the ova recovered from the fallopian tube in the control group exhibited features compatible with those of a normal healthy developed embryo (80).

It is unlikely that the contraceptive efficacy of IUDs results, mainly or exclusively, from their capacity to interfere with implantation; it is more probable that they exert their antifertility effects beyond the uterus and interfere with steps in the reproductive process that take place before the ova reach the uterine cavity. It is likely that the uterine and tubal fluids that are altered in the presence of an IUD impair the viability of the gametes, thus reducing their

chances of union and impeding fertilization. Copper ions released by an IUD probably potentiate these effects.

4. CLINICAL STUDIES OF EFFECTIVENESS

The development of IUDs was briefly reviewed in section 2.2 and a number of devices were described. They may be divided into two broad groups, medicated and non-medicated, each of which in turn, may be divided into two principal sub-classes. *Non-medicated devices* are either ring devices, most often made of stainless steel and used principally in China, or "open" plastic devices, the most widely used of which have been the Lippes Loop and the Saf-T-Coil. *Medicated devices* release either copper or a progestational steroid. Each of the four sub-groups include a number of different products and devices still undergoing clinical evaluation, but only those in widespread use and for which data from randomized trials are available will be considered here. The non-medicated and copper-bearing devices reviewed have all been approved, either by the appropriate regulatory agency or *de facto* in the country of manufacture. Because interest in long-acting hormone-releasing devices is growing, steroid devices for which published data from multicentre or single-centre trials are available will also be reviewed.

4.1 Sources of data

Published reports of randomized clinical trials are reviewed here. Multicentre trials usually include more subjects than do single-centre trials and therefore have smaller sampling errors. Data from single-centre randomized trials may differ markedly from those from other trials of the same device or devices because of differences in several factors including, but not limited to, the following: (i) subject selection; (ii) timing of IUD insertion; (iii) frequency and timing of return visits and physical and gynaecological examinations; (iv) definitions of loss to follow-up; (v) the training, experience and skill of the investigators; (vi) attitudes and reactions of paramedical and medical staff toward conditions possibly related to IUD use; and (vii) the age and parity of the women included and (viii) the cultural, local and clinic milieu. Accordingly, while randomized single-centre trials provide useful information on failure rates and other aspects of performance associated with particular models of IUD, the small

sample size and the other sources of variability indicated above limit their usefulness in comparison with multicentre randomized trials.

Firstly, the diversity of the investigators decreases the sampling error and reduces some sources of bias. In a single-centre study, an investigator's greater experience or facility with one of the devices may be reflected in its "superior" performance with respect to expulsion, pregnancy and continuation rates. When a new device is compared with a familiar or standard IUD, however, even multicentre trials do little to decrease this experiential bias. Secondly, the diversity of sites and centres, as well as of investigators, reduces the sampling errors attributable to the well known "clinic effect". Thirdly, even modest sample sizes at each centre produce a large total study population. Large studies are necessary to ensure the precision of the overall results and to provide some assurance that important differences in events between two devices will be detected: large studies also improve the possibilities of statistical analysis. A large total study size also permits precise analysis of important sub-groups of subjects, e.g., women under the age of 25 or primiparous women. The results based on sub-groups from single-centre studies generally have large standard errors and are imprecise because of the small size of the group.

For the purposes of this report, a multicentre, randomized trial is defined as one involving at least three clinics—approximately equal numbers of women being included in the study group at each clinic. A large, multicentre, randomized trial is defined as one which includes data from 300 or more insertions of each device. Data from randomized trials with less than 300 women per device are presented together with those from randomized single-centre trials.

Multicentre randomized studies have generally been sponsored by international organizations and/or those engaged in contraceptive development, or carried out by a number of universities in collaboration. Follow-up in these studies has ranged from adequate in the earliest multicentre studies to virtually complete follow-up in a recent Chinese study (81).

4.2 Methods of analysis

Published data from randomized clinical trials are customarily and correctly summarized by using life-table estimates of pregnancy rates, including both intrauterine and extrauterine pregnancies. In order to provide summary statistics of pregnancy rates from

published data, the data from each study have been converted from the life-table estimate into the "Pearl index". For a given period, this is computed by dividing the number of pregnancies in that period by the number of woman-years of use over the same period and multiplying by 100. Within each year of use, the Pearl index is very similar to the life-table net probability of pregnancy. A summary Pearl index of pregnancy rates is obtained by dividing the number of pregnancies in the first year of use in all multicentre studies by the number of woman-years in these studies. The homogeneity of the results from the various studies has been tested by a chi-squared analysis. In several of the multicentre trials and overall for several devices in this report, the Pearl index in the first year was not significantly different from that in the second year.

4.3 Results of multicentre randomized trials

4.3.1 Large multicentre randomized trials

Table 2 shows the Pearl indices for each type of device for the first year and first two years of use, as determined in large multicentre randomized trials. The various devices are considered separately below.

Steel rings. Mahua double, stainless steel rings have been studied in only one large multicentre trial in China. The first year's Pearl pregnancy rate was significantly above 2 per 100 women. In this trial, the Mahua steel ring had pregnancy rates significantly greater than those of the TCU-220 C and the TCU-380 Ag (81, 82).

Lippes Loop D. The Lippes Loop D studied in 4 multicentre randomized trials had first-year failure rates significantly greater than 2 per 100 women. In these trials, the Lippes Loop D was found to have pregnancy rates similar to those of the TCU-200 and Copper-7, but in 2 of these trials the Lippes Loop had pregnancy rates significantly higher than those of the TCU-220 C (17, 83-85).

Copper-7. The Copper-7 and the TCU-200 have each been studied in 5 large multicentre trials. In one study, the 2 IUDs were compared and were not found to be significantly different with regard to pregnancy rates (86). In 3 studies, the Copper-7 had significantly higher pregnancy rates than the TCU-220 C (7, 84, 87-89). In a trial

Table 2. Values of the Pearl pregnancy index in large, multicentre, randomized trials by type and specific device

Type and device	No. of studies	Pearl index \pm S.E.		No. of woman-years		References
		First year	First 2 years	First year	First 2 years	
Non-medicated						
<i>Steel ring</i> Mahua	1	3.3 \pm 0.6	2.7 \pm 0.4	874	1 345	(81, 82)
<i>Plastic</i> Lippes Loop D	4	2.8 \pm 0.4	2.4 \pm 0.3	2 178	2 787	(17, 83-85)
Medicated						
<i>Copper-bearing</i>						
Copper-7	5	2.9 \pm 0.3	2.7 \pm 0.2	3 077	5 043	(17, 84-96)
TCu-200	5	2.5 \pm 0.2	3.0 \pm 0.2	4 592	6 045	(83, 86, 90, 91)
TCu-220C	10	0.9 \pm 0.1	0.9 \pm 0.1	6 247	14 184	(17, 81, 82, 84, 85, 87-90)
TCu-380A or Ag	5	0.5 \pm 0.1	0.4 \pm 0.1	5 013	7 289	(81, 82, 90, 92-96)
Nova T	3	1.2 \pm 0.3	1.3 \pm 0.2	1 124	3 671	(91, 97-99)
MLCu-250	2	1.7 \pm 0.7	1.2 \pm 0.2	356	2 568	(87-100)
MLCu-375	2	0.6 \pm 0.2	0.5 \pm 0.3	989	653	(92, 93, 98, 99)
<i>Progesterone-releasing</i>						
IPCS (25 μ g)	2	1.6 \pm 0.3	1.7 \pm 0.2	2 030	3 300	(24)
<i>Levonorgestrel-releasing</i>						
Levonorgestrel (2 μ g/day)	1	2.3 \pm 0.5	2.1 \pm 0.4	1 030	1 422	(97)
Levonorgestrel (20 μ g/day)	1	0.2 \pm 0.1	0.1 \pm 0.1	966	1 584	(95, 96)

in South-East Asia, which also included the TCu-220 C, the Copper-7 was found to have significantly higher failure rates than the Multiload-250 (87-89). The Copper-7 was compared with the Lippes Loop D in 3 of the trials and in none had a pregnancy rate significantly different from that of the latter (17, 84, 85). The summary Pearl index at 1 year was 2.9 per 100, significantly above 2 per 100 woman-years.

TCu-200. In 5 trials, the TCu-200 has been compared with the Lippes Loop D, the TCu-380 A, the Copper-7, the TCu-220 C and the Nova T (83, 86, 90, 91). No statistically significant differences in pregnancy rates were found in the comparisons of the TCu-200 with the Lippes Loop D or with the Copper-7 (83, 86). The TCu-200 was found to have significantly higher failure rates than the TCu-380 A, the TCu-220 C and the Nova T (90, 91). The summary Pearl rate for the first year of use was 2.5 per 100, which is significantly greater than 2 per 100 woman-years.

Nova T. To date, there have been 3 large multicentre, randomized studies of the Nova T (91, 97-99). This device has been compared with the TCU-200 Ag, the Multiload-375 and the TCU-220 C; comparison with the last of these, however, is based on data for 2 years only, the 1-year pregnancy rates not having been published (97). The Nova T was found to have a significantly lower failure rate than the TCU-200 Ag in the first and following year (91). At 2 years, the failure rate of the Nova T in a WHO trial was significantly higher than that of the TCU-220 C (97). In the first year of use, the Pearl index for the Nova T in the 2 studies for which 1-year data are available was 1.2 per 100, with an upper 95% confidence limit below 2.0 per 100 woman-years.

MLCu-250. There have been only 2 large multicentre, randomized trials of the Multiload-250 (MLCu-250) which meet the criteria for inclusion in this section of the report (87-89, 100). In one, the MLCu-250 had a significantly lower failure rate than the Copper-7 (87-89). In 2 trials, considered separately, pregnancy rates for the MLCu-250 did not differ from those for the TCU-220 C (87-89, 100), but the 1-year data base for the MLCu-250 comprises only 356 woman-years, yielding a Pearl index of 1.7 per 100. In the 2-year data base, 2568 woman-years of experience were accumulated. The Pearl index for 2 years was 1.2 per 100, which is significantly below 2 per 100 woman-years.

MLCu-375. In the 2 multicentre studies of the Multiload-375 (MLCu-375), the device was compared with the Nova T (98, 99) and with the TCU-380 Ag (92, 93). In neither study was a significant difference found between the devices. The total number of woman-years during the first year was just less than 1000. The summary Pearl index for the MLCu-375 was 0.6 per 100, a rate whose upper limit is approximately 1.0 per 100 woman-years.

TCu-220 C. Like the MLCu-375, the two copper-collared T devices, the TCU-220 C and the TCU-380 A or Ag, have Pearl indices below 1.0 per 100 (see Table 2). The pregnancy rate for the TCU-220 C at 1 year is based on 6247 woman-years of use, and yields a Pearl index of 0.9, a value which is significantly below 1.5 per 100. In the various studies, the TCU-220 C has proved to have significantly lower failure rates than the TCU-200 in 1 trial, the Copper-7 in 3 trials, the Lippes Loop D in 2 trials, a device releasing

25 µg of progesterone per day in 3 trials, the Nova T in 1 multicentre trial, and the Tianjin Mahua steel ring (17, 24, 81, 82, 84, 85, 90, 97, 100). In 2 separate trials in which the MLCu-250 was compared with the TCu-220 C, the point estimate of the pregnancy rate of the TCu-220 C was lower in each study but the difference in rates was not statistically significant (87–89, 100). In the 2 multicentre trials in which the TCu-220 C was compared with the TCu-380 Ag, the former had a higher Pearl index in each study, and in the WHO study the failure rate of the TCu-220 C was significantly greater than that of the TCu-380 A (81, 82, 94).

TCu-380 A or Ag. Large, multicentre, randomized studies of the TCu-380 A or TCu-380 Ag have accumulated 5013 woman-years of use in trials yielding first-year results. In the WHO study, the TCu-380 A proved to have a significantly lower pregnancy rate than the TCu-220 C (94). In the other studies, the TCu-380 proved to have significantly lower pregnancy rates than the Mahua steel ring (81, 82) and the TCu-200 (90). In one study of the TCu-380, a point estimate of the failure rate was lower than that of the MLCu-375, but the difference was not significant (92, 93). In another study in the first year, the TCu-380 Ag had a Pearl index equivalent to that of the IUD releasing 20 µg/day of levonorgestrel (95, 96). At 2 years, the levonorgestrel-releasing device had a failure rate that was below that of the TCu-380 Ag, but not significantly so when summarized over all multicentre, randomized trials (96).

TCu-380 devices have had pregnancy rates significantly below 1 per 100 per year (Table 2), except among women who were less than 25 years old on admission.

Steroid-releasing devices. There have been no published reports of multicentre randomized comparative trials of the Progestasert IUD, which releases 65 µg/day of progesterone, and none of the levonorgestrel-releasing devices studied in multicentre comparative trials has as yet been approved by the governmental regulatory agency in the country of manufacture. However, it appears probable that at least one such device will be approved in the near future.

The failure rate of the device releasing 25 µg/day of progesterone was 1.6 per 100 at 1 year, based on 2030 years of experience (24). The relatively high rates of ectopic pregnancy associated with this device may preclude its further development (24).

A similarly high risk of ectopic pregnancy was found in the multicentre study of a device releasing 2 µg/day of levonorgestrel, which had a first-year failure rate of 2.3 per 100 and a second-year pregnancy index of 2.1 per 100 (97). This IUD's pregnancy rate was not found to differ significantly from that of the Nova T device but it did have significantly higher pregnancy rates than the TCu-220 C, with which it was also compared.

A levonorgestrel-releasing device rated at 20 µg/day had a failure rate of 0.1–0.2 per 100 in one large, multicentre, randomized trial (Table 2). The device had a Pearl pregnancy rate significantly below 1 per 100 at one year (95, 96).

Summary. The results of these large multicentre studies may be summarized as follows. Steel rings and plastic devices have had failure rates significantly above 2.0 per 100 at 1 year. The first two copper devices (Copper-7 and TCu-200) also have first-year failure rates at or above 2.0 per 100. The Nova T and the Multiload-250 have had failure rates between 1.0 and 2.0 per 100 at 1 year. Copper-bearing devices (TCu-220 C and TCu-380), when summarized for all the large, multicentre, randomized studies, gave point estimates below 1.0 per 100 at 1 year. For the TCu-380, this value was significantly below 1.0 per 100, based on 5103 woman-years of experience. Experience with the MLCu-375 is more limited, but the upper 95% confidence limit is more than 1.0 per 100 at 1 year.

Of the steroid-releasing devices, the one that releases 20 µg/day of levonorgestrel has exhibited failure rates significantly lower than 2 per 100. Indeed, the data suggest a failure rate significantly below 1 per 100 for this device (95, 96). In four published multicentre randomized comparative trials (see Table 3), the Progestasert has had a Pearl index of 2.9 per 100 (101–104).

4.3.2 *Small, randomized trials*

The 1-year data from small, single-centre, randomized trials and the small multicentre trials shown in Table 3 support the conclusions of the large multicentre randomized studies.

4.4 Long-term effectiveness

Comparative data on pregnancy rates during the fourth or the fifth year of use are available from only one large multicentre study (119). Data from two small randomized multicentre studies are also

Table 3. Pearl index in first year of use in small, multicentre, randomized trials or in single-centre randomized trials, by type and device

Type and device	Pearl index	Standard error	No. of woman-years	References
Non-medicated				
Stainless steel ring	6.0	1.8	182	(105)
Lippes Loop	2.9	0.7	510	(16)
Medicated				
<i>Copper-bearing</i>				
Copper-7	2.3	0.7	514	(16, 101)
TCu-200	1.9	0.3	1816	(16, 102, 106-110)
TCu-220C	1.0	0.3	945	(105, 111)
TCu-380A	0.5	0.3	442	(111, 112)
Nova T	1.7	0.3	1718	(103, 107, 109, 113-116)
Shanghai VCu-200	1.5	0.8	206	(105)
MLCu-250	0.6	0.2	1266	(106, 108, 115, 117, 118)
MLCu-375	0.8	0.3	834	(116, 118)
<i>Hormone-releasing</i>				
Progestasert	2.9	0.7	514	(101-104)
Levonorgestrel (20 µg/day)	0.7	0.4	138	(113, 114)

Table 4. Annual Pearl index (or gross pregnancy rates) after 4 or 5 years in selected studies

Type and device	Location of study	Annual Pearl index			References
		1 year	4 years	5 years	
Non-medicated					
<i>Plastic</i>					
Lippes Loop D	USA	2.9	1.0	0.3	(119)
Medicated					
<i>Copper-bearing</i>					
TCu 200	USA	3.1	1.1	NA	(90)
TCu 200	China	1.7	1.3	1.3	(122)
TCu 200Ag	Scandinavia	2.1	0.6	1.8	(91)
TCu 200 ^a	Chile	2.5	2.0	3.7	(123)
Cu 7	Chile	2.6	1.0	NA	(124)
Cu 7	USA	1.8	0	(6.9) ^b	(125)
Nova T	Scandinavia	0.8	0.3	0.5	(91)
Nova T ^a	Finland	3.2	1.4	0.0	(120)
TCu 380A	USA	1.1	0.5	NA	(126)
TCu 220C ^a	Belgium	1.3	0.8	0.9	(127)
MLCu 375 ^a	Belgium	0.4	0.6	0.4	(128)
<i>Hormone-releasing</i>					
Levonorgestrel (20 µg/day)	Finland	0.8	0	0	(120)

^aEstimated annual gross pregnancy rates.

^bEstimated. Value for year 5 estimated and based on 20 women only.

available for 5 years (91, 120). The available data from the fourth year of use are summarized in Table 4, in which they are presented in the form of a Pearl index equivalent to the net probability of pregnancy.

None of the studies show significantly higher failure rates in the fourth year of use than in the first. Because the women still using an IUD after 4 years tend to be older than those starting the study, these findings are not remarkable. However, they do show continuing effectiveness at the end of 4 years of use. Available data on the Lippes Loop D, the TCU-200, the TCU-220 C and the MLCu-375 all show pregnancy rates in the fifth year of use that are not significantly higher than those reported in the first year.

There appears to be no reduction in the effectiveness of most kinds of copper-bearing device for a period of at least 5 years. The collared copper-bearing devices (TCu-380 A, TCU-380 Ag and TCU-220 C) probably all have effective lifetimes well beyond 5 years, and the same applies to copper-bearing devices with a silver core wire (Nova T, TCU-380 Ag). Age selection of continuing users should permit these devices to remain effective for longer than 5 years, but reliable data are sparse for copper-releasing devices. Data have been published indicating that TCU-220 C remains effective for at least 10 years (121).

5. TIMING OF IUD INSERTION

The conventional time of IUD insertion—either during or immediately after menstruation—has been chosen because the cervical canal is slightly dilated during menses and this facilitates insertion; the practice also reduces the risk of insertion in early pregnancy. However, it may not be necessary. White et al. (129) reviewed 9094 insertions of the Copper T IUD in the Population Council's clinical trials and found that expulsion rates were lower the later in the menstrual cycle the IUD was inserted. On the other hand, rates of IUD removal for pain and bleeding and rates of accidental pregnancy were higher the later in the cycle insertion took place, particularly after the seventeenth day. Other studies have not demonstrated any significant changes in pertinent event rates in relation to the day of the cycle on which IUDs were inserted (130).

In some cases, IUD insertion at different times, e.g., postplacental, postpartum or postabortum, may be more

convenient, both to the health personnel and the patient. Indeed, immediately following delivery or abortion the subject may be more strongly motivated towards accepting an IUD rather than later, when menstruation has been re-established, and she then has to return to have the IUD inserted.

5.1 Postpartum insertion

It is important to distinguish between postpartum and so-called "postplacental" insertion, when the device is inserted immediately following delivery of the placenta. In the review by Rosenfield & Castadot (131) of postpartum insertion, it was shown that subsequent complications were no higher when the device was inserted within 48 h of delivery than when it was inserted 6 weeks or later post partum; in fact, the uterine perforation rate was lower (0.2% compared with 0.4%).

The incidence of uterine perforation was higher when the IUD was inserted 4-8 weeks post partum; but the removal rate for bleeding, pain, or pelvic inflammatory disease was not increased after such early post-partum insertion. However, the expulsion rate following insertion before 8 weeks post partum was about double that when the device was inserted after that time (5). Recent research has suggested that lactating women may be at greater risk of uterine perforation than non-lactating women, regardless of the time of the insertion (132, 133), but these results have yet to be independently confirmed. The risk of expulsion of the device would not appear to be greater in lactating IUD-users (134). As the IUD does not interfere with lactation, it is the most suitable contraceptive method for lactating women.

5.2 Postplacental insertion

Insertion of an IUD immediately following delivery of the placenta has certain advantages as compared with the more conventional timing of insertion at the first follow-up visit. The woman does not have to return for the IUD to be inserted, since this is done at the time of delivery. This is particularly useful in those areas where contact with potential family planning acceptors is infrequent and where supervised puerperal care is of short duration. However, as against these programmatic advantages, the disadvantages of postplacental IUD insertion might include a high

expulsion rate, an unacceptable incidence of pelvic inflammatory disease, or an increased frequency of uterine perforation.

In the WHO-sponsored, randomized, multicentre, clinical trial of 3 devices—the postpartum TCu-200, the Lippes Loop D, and the Copper-7—3.5, 8, and 1.8% of women, respectively, expelled the devices within 48 h of postplacental insertion. The expulsion rate with the Copper-7 was significantly lower than that for the Lippes Loop D at 6 and 12 months post-insertion (31.1 and 34.8 per 100 women as compared with 41.3 and 44.1 per 100 women, respectively). There was an excessively high expulsion rate with all 3 devices and the study was stopped prematurely. At both 6 and 12 months post-insertion, the pregnancy rate for the Lippes Loop D was very much greater than those for the other two devices. The Lippes Loop D rates were 7.3 and 12.1 per 100 women as compared with 1.6 and 5.6 for the postpartum TCu-200 and 7.2 per 100 women for the Copper-7. Despite some reports of acceptable expulsion rates in other studies, this study showed that the immediate postplacental insertion of any of these devices results in unacceptably high pregnancy and expulsion rates (135).

Thiery and colleagues (136) reported on a total of 2646 postplacental insertions of the Lippes Loop and 4 different copper-bearing devices (TCu-200, TCu-220 C, MLCu-250 and MLCu-375). The pregnancy rate at 1 year was 2.9 for the Lippes Loop, while for the copper-bearing devices values ranged from 0.2 for the TCu-220 C to 1.4 for the MLCu-250, the difference being statistically significant. The expulsion rate for the Lippes Loop was significantly higher (23.7) than that for the copper-bearing devices (range: 7.2–11.3). The ML-375 had a significantly higher expulsion rate than the ML-250.

In general terms, it is clear that the experience of the clinician inserting the device is important in relation to expulsion, pregnancy and perforation rates (136, 137). The addition of chromic catgut sutures to either the Lippes Loop or TCu-200 IUDs to prevent expulsion had no effect (137, 138).

5.3 Insertion at the time of Caesarean section

Nine studies have been reported and summarized on IUD insertion at the time of Caesarean section (139–141); all were undertaken in China, and involved 3116 insertions. The vast majority of the devices used were of the ring type to which chromic

catgut knots were attached. The expulsion rates at 12 months were low (3.9–7.5) but the pregnancy rates were high (1.7–8.9 per 100 women). The authors of a smaller study in Belgium, involving 82 insertions of the TCU-220 C device at the time of Caesarean section, reported a zero pregnancy rate and an expulsion rate of 7.7 at 12 months of use (142). Further evaluation of the procedure as applied to the newer copper-bearing and steroid-releasing devices is necessary before it can be recommended for widespread use. Furthermore, the merits of IUD insertion at the time of Caesarean section compared to insertion later in the puerperium need to be considered. The insertion of an IUD should be discouraged when Caesarean section follows prolonged labour and/or ruptured membrane because of the potential risk of pelvic sepsis resulting from chorioamnionitis in such cases.

5.4 Postabortum insertion

IUD insertion at the time of induced abortion must be distinguished from insertion following evacuation of retained products of conception resulting from a spontaneous abortion. In the latter case, it might reasonably be expected that the women concerned would include a certain number who had not spontaneously aborted but had induced the abortion illegally and therefore would be at special risk of infection.

The published studies on IUD insertion following first-trimester induced abortion provide no evidence of a consequent higher rate of pregnancy, expulsion, infection, or removal for pain or bleeding (83, 143–150). The WHO study, however, indicates a higher expulsion rate when insertion followed second-trimester, as opposed to first-trimester, induced abortion (84). Similar results have been found in the studies on IUD insertion following spontaneous abortion (85, 151, 152). In particular, neither the removal rates for pelvic inflammatory disease nor the uterine perforation rates were higher after insertion following spontaneous abortion than following menstrual or postmenstrual insertion.

In the WHO study on insertion following termination of pregnancy (84), the Lippes Loop had significantly higher use-related discontinuation rates than the TCU-220 C.

6. ECTOPIC PREGNANCY

Ectopic pregnancy is defined as any pregnancy that occurs outside the uterine cavity. If a patient becomes pregnant with an IUD in place, the chance of her having an ectopic pregnancy has been reported to range from 2.9 to 8.9% (153), which is the result of the IUD providing more protection against an intrauterine pregnancy than against an extrauterine (ectopic) pregnancy. Although about 95% of all ectopic pregnancies among IUD users occur in the fallopian tubes, there have been occasional reports of ectopic pregnancies in other locations. Ectopic pregnancy is a dangerous condition; even in developed countries, where women have immediate access to surgical and blood transfusion facilities, it accounts for about 10% of maternal deaths (155). These risks are almost certainly greater in developing countries.

It is now well established that the incidence of ectopic pregnancy in several industrialized countries has increased (155, 156). Previous pelvic inflammatory disease, prior ectopic pregnancy, and tubal surgery are some of the risk factors associated with an increased risk of ectopic pregnancy. Factors that should be considered in the evaluation of any association between IUD use and ectopic pregnancy include:

- (i) appropriate measures of the overall risk of the condition;
- (ii) its frequency independent of IUD use;
- (iii) the special characteristics of IUD users;
- (iv) the type of IUD;
- (v) effects of duration of IUD use and past IUD use; and
- (vi) errors in the diagnosis.

6.1 Measures of risk

Two appropriate measures of the risk of ectopic pregnancy are: (i) the number of ectopic pregnancies per 1000 women aged 15–44 per year; and (ii) the percentage of pregnancies that are ectopic. The first permits an absolute comparison of the incidence of ectopic pregnancy as between different groups of women, classified, *inter alia*, by type of IUD or contraceptive method used. The second is of clinical importance but cannot be used to make comparisons of the risk to women belonging to different groups, e.g., women using different types of IUDs, and depends on the timing of the diagnosis of pregnancy.

6.2 Frequency

In Finland, Sweden, the United Kingdom, and the United States of America, the frequency of ectopic pregnancy has risen over the past 2 decades (156–159). For example, the incidence of ectopic pregnancy in the United States in 1982 was 1.2/1000 women-years, which corresponds at least to a doubling of the 1965 rate (159).

A decade ago, these increases in ectopic pregnancy numbers and rates were attributed by some investigators to the then increasing use of IUDs (156, 160). However, re-analysis and re-interpretation of some of the data relating the increases in ectopic pregnancy to IUD usage have suggested the possibility that this increase was due to other factors, such as the increasing prevalence of sexually transmitted diseases.

Only limited data have been published on the incidence of ectopic pregnancy among IUD users and users of other contraceptive methods. The Oxford Family Planning Association study (161) reported a rate of 1.2 per 1000 woman-years for IUD users, 0.01 per 1000 woman-years for oral contraceptive users and 0.1 per 1000 woman-years for barrier contraceptive users. This study was conducted on a highly selected group of women (married, Caucasian, belonging to the upper social classes, at least 25 years of age, and using their current method of contraception for at least 5 months) and its results may therefore not be applicable to other populations. However, the rates were the same as those found among users of plastic IUDs in the USA in the 1960s and among users of the copper T devices in the 1970s (see Table 5). Other studies, such as the Women's Health Study conducted in the United States (162) and those carried out by WHO (163), have shown that current IUD users are not at any higher risk of ectopic pregnancy than non-contraceptors.

6.3 Special characteristics of IUD users

It is probable that IUD users constitute selected groups of women having a lower prevalence of risk factors for ectopic pregnancy. For example, a recent history of either pelvic infection or prior ectopic pregnancy is considered to be a contraindication to the use of IUDs. In view of this, the *lower risk* of ectopic pregnancy in IUD users as compared to non-users demonstrated in the study and the Women's Health Study (162, 163), both of which were case-control studies,

Table 5. IUD ectopic pregnancy rates 1974–1983, by type of device

Drug and device	Number of studies	No. of woman-years	Rate per 1000 woman-years
Non-medicated			
<i>Plastic</i>			
Lippes Loop C and D	4	12 621	1.1
Saf-T-Coil	1	4 712	0.8
Medicated			
<i>Copper-bearing</i>			
Copper-7	6	5 490	0.9
TCu-200	5	4 836	1.4
TCu-220C	7	11 931	0.8
TCu-380A/Ag	3	1 929	0.0
Nova T	3	2 668	0.7
MLCu-250	4	8 207	0.2
MLCu-375	1	637	0.0
<i>Hormone-releasing</i>			
Progestasert	1	10 128	5.2
Levonorgestrel (20 µg/day)	2	893	1.1

Source: Sivin (159).

does not necessarily imply that the protective effect of IUD usage is as large as indicated by the results of these studies.

The multinational, multicentre case-control study conducted by WHO (163) in both developed and developing countries showed that the relative risk was less than 1.0. It also indicated some major differences between the risks of ectopic pregnancy to IUD users in developed and developing countries (see Table 6).

All the published data on the risks of ectopic pregnancy, with the exception of those published by WHO (163), have been derived from studies conducted in developed countries. Whether the results of, and inferences based on, these studies are applicable to all developing countries, which account for the majority of world-wide IUD usage, must await the outcome of further investigations.

6.4 Type of IUD

Ectopic pregnancy rates among non-users of IUDs vary with the age of the population, the prevalence of sexually transmitted diseases in the population, and other factors. Among IUD users, these factors also will influence the ectopic pregnancy rate. An additional factor complicating the interpretation of ectopic pregnancy rates in studies of IUD users is that incompleteness of the follow-up of

Table 6. Relative risk and 95% confidence limits of ectopic pregnancy for IUD users as compared with non-contraceptors¹

Controls	Developing countries		Developed countries	
	Relative risk	95% confidence limits	Relative risk	95% confidence limits
Non-pregnant	0.4	(0.2-0.6)	0.6	(0.3-1.3)
Pregnant	5.7	(2.7-12.1)	12.2	(3.0-49.7)

¹ Source: Gray (164).

patients may tend to overestimate the calculated ectopic pregnancy rates (165).

Ectopic pregnancy rates based on the results of numerous clinical studies on users of different types of IUDs, have been summarized in Table 5. Although there is considerable variation in the rates for different types of IUD, the data suggest that progesterone-releasing IUDs have a substantially higher ectopic pregnancy rate as compared with either the non-medicated IUDs or the copper-releasing IUDs, and probably do not provide any protection against ectopic pregnancy. The data further suggest that, among the copper-releasing IUDs those with the larger surface areas of copper are associated with lower ectopic pregnancy rates. Confirmation of this finding will have to await the results of the large-scale multicentre clinical trials of IUDs currently being conducted. Limited data on the levonorgestrel-releasing (20 µg/day) IUD indicate that it is associated with an ectopic pregnancy rate similar to that of the copper-bearing IUDs (see Table 5).

6.5 Effects of duration of IUD use and past use of IUDs

Some investigators (166, 167) found a relationship between the duration of IUD use and the ectopic pregnancy rate and suggested a cause-and-effect relationship between the two. Re-evaluation of these studies and the addition of data from other studies (165, 168) has failed to confirm this relationship.

Data from the Oxford Family Planning Association study (167) show that the incidence of intrauterine pregnancy declined over time whereas the incidence of ectopic pregnancy did not change.

Analyses of data from the large case-control Women's Health Study conducted in the United States, show that the relative risk of ectopic pregnancy in IUD users as compared to non-users changes

only slightly with the duration of IUD use and time since last IUD use (see Table 7) (162), and that current short-term IUD users have a reduced risk of ectopic pregnancy.

6.6 Diagnosis

The criteria for the diagnosis of ectopic pregnancy—abdominal pain, amenorrhoea or bleeding irregularities, and pelvic tenderness—are also common to other pelvic disorders, such as pelvic inflammatory disease, urinary tract infection, and complications associated with ovarian cysts, etc. As many ectopic pregnancies present early in gestation, the patient may not have become concerned by a short period of amenorrhoea. The picture is further complicated when an IUD is *in utero* and the patient has had irregular menses, intermenstrual bleeding, or lower abdominal pain. Hallatt (169), in a study of 70 cases of ectopic pregnancy among IUD users, reported that the symptoms were attributed to the use of the IUD in 85% of cases and that 28 of these women had their IUDs removed because of pain and bleeding, prior to the diagnosis of ectopic pregnancy.

In a study of 552 cases of ectopic pregnancy, pain (97%) and menstrual disorders (93%) were the most common symptoms, adnexal tenderness was present in 90% and an adnexal mass in 63% of the cases. Cervical movement was painful in 51% and vaginal bleeding present in 71%. The definitive diagnosis of ectopic pregnancy by laparoscopy was obtained in 97%, and a sensitive pregnancy test was positive in 90% (170).

A positive pregnancy test may distinguish between pregnancy and other conditions but in ectopic pregnancy it may still be negative as a consequence of insufficient hCG production. A negative pregnancy test may therefore not exclude ectopic pregnancy, though this will depend on the sensitivity of the assay. In many cases it is necessary to resort to direct inspection of the fallopian tubes by laparotomy or laparoscopy. The use of very much more sensitive assays for hCG has increased the detection rate to more than 90% in cases of ectopic pregnancy and, in combination with pelvic ultrasonography, can be used to detect ectopic pregnancy prior to tubal rupture (171).

The clinical diagnosis of ectopic pregnancy should be confirmed histologically wherever possible. All material removed from the abdominal cavity should be examined, and the embryonic and fetal parts and trophoblast should be identified microscopically. The

Table 7. Relative risk of ectopic pregnancy for IUD users as compared with non-users, by duration of IUD use and years since last use

Time of last use of IUD	Duration of IUD use (years)							
	Less than 2 years		2-4 years		More than 4 years		All ^a	
	Relative risk	95% confidence limits	Relative risk	95% confidence limits	Relative risk	95% confidence limits		
Used at last menstrual period	0.49	(0.30-0.79)	1.0	(0.57-1.8)	1.7	(1.3-2.2)	1.2	(0.91-1.5)
Used in last year but not at last menstrual period	0.97	(0.56-1.6)	1.9	(0.81-4.4)	2.2	(1.3-3.8)	1.4	(0.98-2.0)
Used more than one year previously	1.2	(0.83-1.8)	1.8	(0.78-4.2)	0.72	(0.25-2.0)	1.2	(0.86-1.7)

^a Mantel-Haenszel estimate adjusted for duration of IUD use. Source: Ory and Women's Health Study (1982).

presence of blood in the tube and a decidual reaction are insufficient to establish the diagnosis. This definition does not preclude a presumptive diagnosis for clinical purposes, based on tubal disruption, decidual change in the fallopian tube or endometrium, and gross blood in the peritoneal cavity.

7. PELVIC INFLAMMATORY DISEASE

7.1 Diagnosis

Because the diagnostic facilities available to the majority of physicians are limited—especially for those working in developing countries—the diagnosis of pelvic inflammatory disease is based on a series of signs and symptoms; in the absence of direct visualization of the fallopian tubes, however, it can only be an assumption.

Table 8 shows the probability of acute pelvic inflammatory disease in Swedish women presenting with different symptoms and

Table 8. Probability of acute pelvic inflammatory disease in Swedish women presenting with different symptoms and signs¹

Symptom or sign	Probability of pelvic inflammatory disease (%)
A. Minimum (if all 3 are present) Low abdominal/pelvic pain of 3 weeks' duration Motion tenderness of the uterus Purulent vaginal discharge	
B. Other Temperature of 38° C or more reported, or at examination Palpable, painful adnexal swelling Intermenstrual bleeding	
Symptom or sign	Probability of pelvic inflammatory disease (%)
All 3 of Group A	50
All 3 of Group A + 1 of Group B	70
All 3 of Group A + 2 of Group B	80
All 3 of Group A + all 3 of Group B	96

¹ Source: Westrom (172).

signs or combinations thereof (172). In addition, the probability of the disease increases if:

- (a) the erythrocyte sedimentation rate is more than 15 mm/h;

- (b) the white blood cell count is more than 10 000/mm³ blood;
- (c) C-reactive protein is positive; and
- (d) a cervical culture is positive for *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*.

In any given case, the doctor has to decide whether to treat the patient or not. However, in view of the serious consequences of pelvic inflammatory disease, including infertility, it is better to treat a suspected pelvic infection than not to treat at all, especially in the young nulliparous woman. Pelvic inflammatory disease should be suspected in all non-pregnant women of reproductive age who consult because of acute abdominal/pelvic pain. It is generally considered to be prudent clinical practice to remove the IUD in women with pelvic inflammatory disease who require hospitalization and/or antibiotic therapy.

Because of the clinical similarities between pelvic inflammatory disease and ectopic pregnancy, it is important to exclude the latter. Tests for hCG in urine that have a sensitivity of 40 IU per litre or less can be used for this purpose.

Women in whom a surgical emergency such as appendicitis or ectopic pregnancy cannot be excluded, should be admitted to hospital. Laparoscopy, if available, should be used to make the diagnosis and should be standard practice in clinical research studies on pelvic inflammatory disease.

7.2 Microbial etiology

The microorganisms causing ascending infection of the endometrium and fallopian tubes can be divided into two main groups, exogenous and endogenous. These are considered below.

7.2.1 Exogenous microorganisms

The majority of these species are transmitted sexually and include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma hominis*.

7.2.2 Endogenous microorganisms in the lower female genital tract

The endogenous microbial flora of the lower female genital tract normally contains a variety of bacterial species, many of them of potential pathogenic capacity. The majority of these species are strictly anaerobic or micro-aerophilic (173–175).

In cases of pelvic inflammatory disease, bacterial isolation from the fallopian tubes and serological studies has revealed that agents of sexually transmitted disease currently account for up to 80% of the tubal infections in women below the age of 25 (174, 176). In patients with pelvic inflammatory disease associated with sexually transmitted disease, in addition, species belonging to the endogenous vaginal flora have been isolated from the upper genital tract or the cul-de-sac; this is the so-called "poly-microbial" pelvic inflammatory disease (174, 175, 177). As in other mixed infections, anaerobic bacteria are favoured by the local conditions. This often gives rise to abscess formation (tubo-ovarian abscess) (178, 179).

Clinically, early pelvic inflammatory disease associated with sexually transmitted disease tends to be mild and in some cases asymptomatic (180, 181). The general condition of the patient is good. Febrile illness is seen in only half the cases (182). Intermenstrual vaginal bleeding, which is probably a symptom of a concomittant endometritis, and dysuria are common complaints. Early and mild pelvic inflammatory disease is most often seen by doctors or at clinics outside hospitals, but the "poly-microbial" form is seen most often in hospitals. The latter is clinically more severe; febrile illness is seen in two-thirds to three-quarters of such cases, the ESR is elevated in 75% of all patients, and adnexal masses may be palpated in half the cases (182). Patients with tubo-ovarian abscesses are most often critically ill. Their general condition is poor and pyrexia, elevated ESR, and palpable adnexal swellings are the rule (178). Poly-microbial pelvic inflammatory disease and tubo-ovarian abscesses are proportionally more often seen in somewhat older patients (over 25 years of age) (174). The diverse aetiological spectrum of pelvic inflammatory disease should be borne in mind when deciding on anti-microbial treatment.

7.3 IUD threads

The use of threads made of nylon or other material attached to the IUD in such a way that they pass through the cervical canal and into the vagina has led to speculation that they may be the vehicle for ascending infection.

In one study (183), in which devices with and without tails were compared, a lower rate of infection was found in women using tailless devices, but another study failed to confirm these results

(184–186). Bacteria were found more often in the uterine cavity of women using devices with both mono- and multifilament tails (187).

Some studies indicate that the risk of pelvic inflammatory disease is highest in the first few months after insertion but decreases dramatically thereafter to become probably no greater than in women not using an IUD (90, 119, 188). The bacterial contamination that is introduced into the endometrial cavity at the time of IUD insertion can no longer be found some 30 days later (189).

7.4 Epidemiological studies

Since 1980, when 16 reports were reviewed by Senanayake & Kramer (190), 9 additional reports of significantly increased risk of pelvic inflammatory disease or tubal infertility among IUD users have been published. These 25 studies, conducted in many different countries by different investigators, albeit with different diagnostic criteria, have all found an increased risk of the disease or its sequelae among IUD users, which argues strongly for a causal relationship. The strength of this association in the most objective studies, expressed as the relative risk, is in the range 1.5–2.6; these figures may, however, be overestimates, owing to selection bias and confounding factors.

The association between IUD use and pelvic inflammatory disease is difficult to clarify because of formidable methodological problems. Thus, many early studies included users of barrier or oral contraceptives in the reference group, but the use of such contraceptives confers significant protection against upper genital tract infection in women (191). Since IUD users were compared with women using these contraceptives in the early investigations, the relative risk of pelvic inflammatory disease associated with IUD use was artificially elevated. This effect can be seen in some recent studies as well, e.g., in the high relative risk observed by Vessey and associates (192, 193) as compared with that found in others in which women not using contraception were taken as the reference group (see Tables 9 and 10).

Ascertainment bias is another important methodological problem, since pelvic inflammatory disease is notoriously difficult to diagnose. Thus the predictive value of a positive clinical diagnosis of pelvic inflammatory disease has been reported to be 0.65 (199). If diagnostic imprecision causes random misclassification, this would tend to obscure any relationship between IUD use and pelvic

Table 9. Summary of data from recent case-control studies on IUDs and pelvic inflammatory disease

Location	No. of cases	Relative risk	95% confidence interval	Remarks	Reference
Helsinki, Finland	144	2.1	1.2- 3.5	Standardized for effect of parity. Reference group: women not using IUDs or oral contraceptives	(194)
16 USA hospitals	1447	1.6	1.2- 2.0	Adjusted for effect of age, race, parity, number of partners, frequency of coitus. Reference group: women not using contraception	(195)
USA and Canadian hospitals	155	8.6	5.3-13.8	Standardized for effect of age. Reference group: women using contraception, but no prior IUD use	(193)
16 USA hospitals	657	1.9	1.5- 2.4	Adjusted for effect of education. Reference group: women not using contraception	(188)
12 centres world-wide	608	11.5	3.6-36.2	Nulliparous women in developed country. Reference group: women not using contraception; no prior IUD use Parous women in developed country Parous women in developing country	(196)
		4.1	1.2-15.1		
		2.3	1.4- 3.9		
7 USA and Canadian centres	283	2.0	1.5- 2.6	Primary tubal infertility as outcome, adjusted for multiple factors. Reference group: women not using contraception	(197)
King County, Washington, USA	159	2.6	1.3- 5.2	Primary tubal infertility as outcome, adjusted or matched for multiple factors. Reference group: women with no prior IUD use	(198)

inflammatory disease. In one study (200), when more rigorous diagnostic criteria for the disease were used, the relative risk increased; in another, the opposite occurred (201).

The main concern, however, is the strong possibility of diagnostic bias introduced by the knowledge of IUD use. Physicians may be more likely to diagnose pelvic inflammatory disease in IUD wearers than in women presenting with similar complaints but not using an

Table 10. Summary of data from recent cohort studies on IUDs and pelvic inflammatory disease

Location	No. of cases	Relative risk	95% confidence interval	Remarks	Reference
Lund, Sweden	571	1.5	1.2- 1.9	Reference group: sexually active women not using contraception	(172)
17 clinics in England and Scotland	42	10.5	5.4-32	Standardized for effect of age. Reference group: women using contraception other than IUDs	(192)

IUD. Over-diagnosis in IUD users would spuriously increase the relative risk of the disease among them.

In two studies on tubal infertility and IUD use (197, 198), the diagnosis of tubal occlusion had to be based on objective evidence obtained by laparoscopy, laparotomy or hysterosal pingography. The unique contribution of these studies is that they avoided the problems of the over-diagnosis of pelvic inflammatory disease among IUD users and the omission of patients with asymptomatic or "silent" forms of the disease, particularly since the latter were probably included.

Use of any IUD in the past increased the risk of primary tubal infertility to 2.6 (95% confidence limits 1.3-5.2), but the use of a copper IUD alone had a relative risk of 1.3 (0.6-3.0), which was not significantly greater than that for the control group in one study (198) and only just greater (1.6, 1.1-2.4) than that in another one (197). The lower relative risk with copper devices was significantly different from that associated with certain non-medicated devices (Dalkon Shield, Lippes Loop, or Saf-T-Coil). Too few subjects had used hormone-releasing devices to permit their evaluation. No increased risk of tubal infertility was found among women who used an IUD and who reported having only one sexual partner but the risk was increased among women with more than one partner whether or not an IUD had been used.

The use of a copper IUD after the first pregnancy was not associated with secondary infertility due to tubal disease (197).

In three of the studies mentioned in Tables 9 and 10, bias was reduced by relying on objective evidence as regards the outcome. In the cohort study of Weström (172), each patient thought to have pelvic inflammatory disease underwent a diagnostic laparoscopy to

confirm the diagnosis. Although "silent" pelvic inflammatory disease with few or no symptoms was not covered, this population-based investigation found a relative risk of symptomatic disease among IUD users of only 1.5.

Finally, women who choose an IUD for contraception may differ from other women in important, yet unmeasured ways. These differences in personal life styles or sexual behaviour may influence their risk of acquiring pelvic inflammatory disease; factors such as previous pelvic inflammatory disease, socioeconomic status, number of sexual partners, coital frequency, and the presence of sexually transmitted diseases have received the most attention. Although the role of parity remains unclear (202), the contribution of sexually transmitted pathogens appears important. In stable, monogamous relationships, IUD use carries little risk of pelvic inflammatory disease (197).

Most IUD-related pelvic inflammatory disease can be attributed to contamination of the endometrium during insertion of the device. Mishell et al. (189) demonstrated that microorganisms could be isolated from the uterine cavity up to 12 h after IUD insertion. During the following weeks, the number of organisms decreased, and after 1 month the cavity was sterile. Except in users of the Dalkon Shield, pelvic inflammatory disease that develops more than 4 months after insertion appears to be due to other factors, such as acquisition of a sexually transmitted disease (188) and may be clinically more severe.

Epidemiological data (195) can identify appropriate candidates for IUDs and thus minimize the risk of pelvic inflammatory disease. For example, in the USA, white women age 25 years or older who have only one sexual partner and who have coitus 5 or fewer times a week can be expected to have a low risk of the disease. Data from the United Kingdom (192) confirm that married women aged 25 years or older and of upper socioeconomic status who use IUDs have rates of pelvic inflammatory disease less than 2.0 per 1000 woman-years of use.

7.5 Effect of type of IUD

The risk of pelvic inflammatory disease appears higher with the Dalkon Shield than with other devices. Six reports published since mid-1980 have been concerned with device-specific risk of the disease or tubal infertility (see Table 11). Most published studies lack the

Table 11. Summary of data from recent studies on specific types of IUDs and pelvic inflammatory disease

Location	Type of study	No. of cases	Rank ordering of risk	Remarks	Reference
17 clinics in England and Scotland	Cohort	42	Dalkon Shield Saf-T-Coil Other/unknown Lippes Loop Copper device	Acute definite pelvic inflammatory disease. Significance testing not reported	(192)
Hospitals in USA and Canada	Case-control	155	Dalkon Shield Saf-T-Coil Lippes Loop Other Copper device	Risk with Dalkon Shield significantly higher than with copper device	(193)
16 hospitals in USA	Case-control	657	Dalkon Shield Progestasert Copper-7 Saf-T-Coil Lippes Loop	Risk with Dalkon Shield significantly higher than with other IUDs	(188)
17 clinics in England, Scotland and Wales	Cohort	Not stated, but at least 79	Dalkon Shield Lippes Loop 2D Lippes Loop 3C	Differences not significant	(203)
7 centres in USA and Canada	Case-control	283	Dalkon Shield only Lippes Loop or Saf-T-Coil only Non-copper IUD Other combination of IUDs Copper device only	Primary tubal infertility as outcome. Risk with Dalkon Shield, Lippes Loop, and Saf-T-Coil significantly higher than with copper device	(197)
King County, Washington, USA	Case-control	159	Dalkon Shield Lippes Loop or Saf-T-Coil Copper IUD	Primary tubal infertility as outcome. Significance testing not reported	(198)

power to identify clinically important differences in the risk of pelvic inflammatory disease or of infertility associated with various IUDs. Table 11 therefore provides an assessment of those risks in decreasing order of magnitude.

7.6 Effect on infertility

The results of prospective studies (204–209) of the reproductive events in women treated for laparoscopically verified pelvic inflammatory disease are summarized in Table 12.

Table 12. Tubal infertility caused by pelvic inflammatory disease

History of pelvic inflammatory disease	Proportion with tubal infertility (%)
One episode	11.4
Two episodes	23.1
Three or more episodes	54.3
Women aged 15–24 years, one episode	9.4
Women aged 25–34 years, one episode	19.2
Mild disease, one episode	6.1
Moderately severe disease, one episode	13.4
Severe disease, one episode	30.0
Total (all episodes)	17.4

The risk of an ectopic pregnancy after pelvic inflammatory disease is increased by a factor of 7–10 as compared with women who have never had the disease.

7.7 Choice of antimicrobial therapy

Since it is known that 75% of cases of pelvic inflammatory disease are due to sexually transmitted disease, of which *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common causative organisms (175), rational management calls for treatment with broad-spectrum antibiotics.

Because no single antibiotic is effective against the known pathogens in pelvic inflammatory disease a two-drug regime is recommended. The usual precautions against drug sensitivity should be taken.

Appropriate therapeutic regimes are listed below, but the choice of drugs will depend on availability and cost and the results of antibiotic-sensitivity tests may dictate certain changes. In any case, the regimes listed below are to be regarded only as guidelines. Each consists of an initial or “loading” dose followed by further (“follow-on”) therapy, either as an inpatient or outpatient:

Loading dose

This consists of one of the following:

(i) benzylpenicillin potassium (penicillin G), 4.8 mega units, intramuscular injection;¹

¹ 600 mg of benzylpenicillin potassium is approximately equal to 1 million units (1 mega unit).

- (ii) ampicillin, 3.5 g orally;
- (iii) amoxicillin, 3 g orally;
- (iv) cefoxitin 2.0 g, intramuscular injection.

Each of the above should be supplemented with probenecid, 1.0 g orally.

Follow-on therapy

(a) *Outpatient regime*: tetracycline, 500 mg 4 times a day, orally, for 14 days, or doxycycline, 100 mg twice a day for 14 days plus metronidazole, 400 mg 3 times a day for 14 days.

(b) *Inpatient regime*

The alternatives are:

- (1) Doxycycline, 100 mg intravenously twice a day plus cefoxitin, 2 g intravenously 4 times a day. This regime should be continued for at least 4 days and at least 48 h after the patient demonstrates clinical improvement. Doxycycline should, however, be continued orally at 100 mg twice a day for a total of 14 days.
- (2) Clindamycin, 600 mg intravenously 4 times a day plus gentamicin 2.0 mg/kg intravenously followed by 1.5 mg/kg 3 times a day in patients with normal renal function. This regime should be continued for at least 4 days and 48 h after demonstrable clinical improvement. An additional course of clindamycin, 450 mg orally 4 times a day for 14 days, should be given. It should be noted, however, that this therapy might not give the best results with *Chlamydia trachomatis* infection.

After 24 h of antibiotic therapy, the IUD should be removed, but this may be done earlier if intravenous antibiotic therapy has been commenced.

All male partners of patients with pelvic inflammatory disease should be examined and investigated for sexually transmitted disease and treated when appropriate.

When acute pelvic inflammatory disease is diagnosed on clinical grounds, patients with moderate to severe disease should be hospitalized. Other indications for hospitalization are:

- doubtful diagnosis;
- suspected ectopic pregnancy or appendicitis;
- suspected pelvic abscess;

- failure to improve despite outpatient therapy;
- poor compliance with drug regimes;
- young or adolescent patient.

8. OTHER PROBLEMS

8.1 Expulsion of the IUD

Reported expulsion rates for IUDs vary considerably as between different trials and centres, and for different devices (see Table 13), ranging from 13.0 per 100 women for the Lippes Loop D (83) to 1.0

Table 13. Expulsion rates at one year of use in selected comparative trials

Device	Range of reported expulsion rates per 100 women	References
Non-medicated		
Mahua ring	6.3 ^a	(82)
Stainless steel ring	12.6 ^b	(105)
Lippes Loop D	7.8–13.0	(17, 83)
Medicated		
<i>Copper-bearing</i>		
Copper-7	5.3–15.5	(17, 86)
TCu-200	1.4– 8.8	(108, 86)
TCu-220C	3.1– 8.0	(89, 90)
TCu-380A/Ag	3.3– 7.1	(96, 90)
Nova T	2.5– 9.2	(94, 103)
Shanghai VCu-200	1.0 ^a	(105)
MLCu-250	2.4–11.4	(89, 117)
MLCu-375	4.1– 9.4	(93, 98)
<i>Hormone-releasing</i>		
Progestasert (progesterone 65 µg)	1.2– 4.2	(103, 101)
IPCS-52 (progesterone 25 µg)	6.9	(24)
Levonorgestrel (2 µg/day)	9.2	(97)
Levonorgestrel (20 µg/day)	6.4	(95)

^a18 month data.

^bSingle-centre study.

per 100 women for the Shanghai VCu-200 (105). In general terms, non-medicated devices have higher expulsion rates. Other factors which influence the rates include the age and parity of the women, the timing of the insertion—postpartum insertion having the highest rates—and the skill of the person inserting the device. Nulliparous women or women who have never been pregnant have a higher expulsion rate than multiparous women, and this is particularly so for the larger devices, such as the Lippes Loop. Multiparous women

over the age of 30 have nearly half the expulsion rate of women under 30.

Most expulsions take place within 3 months of IUD insertion and frequently occur during menstruation (86, 119); with most devices, more than two-thirds of the expulsions occur within the first year of use.

8.2 Uterine perforation

Uterine perforation is a rare but potentially serious complication of IUD use. Perforations are associated almost exclusively with the insertion procedure.

8.2.1 Frequency

When subjects in whom a device was inserted less than 6 weeks postpartum or postabortum are excluded, the net perforation rates per 1000 insertions are as given in Table 14.

Table 14. Reported uterine perforation rates for IUDs

Device type	Number of perforations	Number of insertions	Rate per 1000 insertions	Reference
Non-medicated				
<i>Plastic</i>				
Mahua ring	0	983	—	(82)
Lippes Loop	89	76 631	1.2	(210)
Medicated				
<i>Copper-bearing</i>				
Copper-7	14	22 914	0.6	(210)
TCu-200	7*	9 838	0.7	(90)
TCu-220C	8	9 175	0.9	(17, 24, 89, 90, 94, 97, 105)
TCu-380A	2*	3 536	0.6	(90)
Nova T	2	3 181	0.6	(97, 99, 109, 211)
MLCu-250	0	2 553	—	(97, 108, 212)
MLCu-375	0	1 772	—	(93, 99)
<i>Hormone-releasing</i>				
Progestasert	13	11 356	1.1	(21, 101)
Levonorgestrel (20 µg/day)	1	755	1.3	(95)

*Specifically excludes cervical perforations.

8.2.2 Factors affecting perforation

The device. There is little difference in perforation rates as between the various devices, values ranging from 1.1 to 0.4 per 1000 insertions in the larger studies reported; however, those devices with a straight vertical stem appear to have a higher incidence of cervical, rather than uterine perforation. The addition of a thickened or bulbous end to the vertical stem has been advocated as a means of reducing the risk of cervical perforation, as has enlarging the internal diameter of the inserter tube to avoid friction.

Insertion technique. The two principal techniques of IUD insertion are (1) the "push" method, in which the inserter tube and device are introduced into the uterine fundus and the device expelled by pushing in a plunger; and (2) the "withdrawal" technique, which also requires fundal placement, but with the difference that the inserter tube is then withdrawn from the device, leaving it placed at the fundus. With the types of IUD currently in use, no significant differences have been observed in perforation rates as between the two methods. The design of the inserter tube may affect the incidence. For example, 12 uterine perforations were reported in 6525 insertions of the Progestasert but when the inserter tube was made more flexible, and a uterine sound incorporated into it, only 1 perforation in 4685 insertions was reported (21).

It is important, before inserting an IUD, to sound the uterine cavity to determine its length and, in particular, its position.

Timing of insertion. The postpartum interval is an opportune time to initiate intrauterine contraception, and this is a popular practice in many parts of the world. However, extra caution during insertion at this time appears warranted. Several early studies (213–215) documented a higher rate of uterine perforation with postpartum insertion as compared with insertion at other times. A recent study (132) found a 10-fold increased risk of perforation among lactating women as compared with parous women not lactating. This finding needs to be confirmed by other studies because of its potential clinical importance.

Although IUDs are commonly inserted during menstruation, insertion at other times during the menstrual cycle is both safe and effective (129, 130).

The individual inserting the IUD. Account has been taken in a number of studies of the skill and training of the persons inserting the IUD, and these have shown that there is a higher perforation rate when the device is inserted by a less experienced operator (215–217). The use of paramedical personnel adequately trained in IUD insertion is not associated with higher perforation rates than those found when gynaecologists insert the device (218–222).

8.2.3 *Consequences of uterine perforation*

An intra-abdominal IUD can lead to serious consequences, such as bowel obstruction or perforation. When a uterine perforation has occurred, therefore, the device should be removed as soon as possible after the diagnosis has been made. Laparoscopy can often be used. Copper devices are known to elicit a greater tissue reaction than non-medicated devices, with the formation of adhesions in the peritoneal cavity, and may have to be removed by laparotomy.

8.3 Management of the missing IUD

Unnoticed expulsion or uterine perforation should be suspected whenever the threads attached to the IUD are not visible on vaginal inspection. Abdominal radiography may be used to locate the device only if it lies outside the pelvic cavity. Anteroposterior and lateral pelvic radiography cannot distinguish between the extra- and the intrauterine device, unless the uterine cavity is made visible by radio-opaque material or a uterine sound. Before any radiographic technique is used pregnancy should be excluded.

Ultrasound has been used to localize IUDs with success rates of between 80 and 100% (223, 224).

8.4 Restoration of fertility following IUD removal

There is no evidence of impairment in the resumption of fertility in women who discontinue the use of an IUD in order to become pregnant, apart from one report in which the proportion of women over the age of 35 who failed to conceive within 36 months of IUD removal was 3 times higher than in women who had had an IUD in place for less than 1 year (225). Other reports have shown conception rates of 88.3% after 12 months following the removal of the Lippes Loop, Margulies Spiral, Birnberg Bow, Steel ring, and

Saf-T-Coil devices (226). Other authors have found no impairment in the restoration of fertility in prior users of the Nova T, TCu-200, levonorgestrel (20 µg/day) or Copper-7 devices) 90, 227–229). As expected, there were lower conception rates at 6 and 12 months following discontinuation of IUD use in women aged more than 30 years (230). The fertility rates found in various studies in these patients who have had a device removed in order to become pregnant are shown in Table 15, together with data for some other methods of contraception for purposes of comparison.

8.5 Pregnancy with an IUD in place

It is important to remember that 3–9% of pregnancies that occur with an IUD in place are ectopic (153). Therefore if a patient with an IUD develops symptoms of pregnancy, ectopic gestation should always be borne in mind. If intrauterine pregnancy occurs with an IUD in place, there is a risk of spontaneous abortion, especially in the second trimester (235–237); if the pregnancy continues beyond 28 weeks, obstetric complications may be increased as well (235, 238).

In the largest multicentre study of this association (239) in women with an IUD in place at conception and left *in situ* during the first trimester, the risk of second trimester fetal loss was increased 10-fold as compared with the risk among women not having an IUD at conception. This risk was much greater for septic second trimester spontaneous abortion (26-fold) than for nonseptic fetal loss (3-fold). However, if the IUD was removed during the first trimester, the risk of second trimester spontaneous abortion was not increased.

Septic spontaneous abortion in IUD users can result in maternal and fetal death, the clinical features of the syndrome differing from those of chorioamnionitis (240). Because of the risks to the pregnancy as well as to the woman's health, the IUD should be removed as soon as pregnancy is diagnosed, whether or not the woman plans to continue the pregnancy. Adoption of this practice in the USA in the mid-1970s has virtually eliminated deaths from sepsis in cases of IUD-related spontaneous abortion (241).

If the IUD cannot be removed because the tail is not visible, the woman should be carefully counselled about the risks of continuing the pregnancy. If she elects to do so, she must be alert for the onset of an influenza-like syndrome, which may be a prodrome of septic spontaneous abortion (240). If a woman continues her pregnancy

Table 15. Restoration of fertility (% of women) in those planning pregnancy after removal of an IUD or cessation of another method of contraception: life table rates of conception

Device or method of contraception	Number of cases	Age (years)	Years after removal or cessation			Reference
			1	2	3	
Various IUDs	397		51.2 ± 2.4 ^a	89.4 ± 1.6 ^a	93.3 ± 1.4	(237)
Diaphragm	865		63.2 ± 1.5 ^a	91.8 ± 0.9 ^a	95.4 ± 0.8	
Other (other than oral contraceptives)	837		60.6 ± 1.5 ^a	89.4 ± 1.1 ^a	93.8 ± 0.9	
Various IUDs	125		75.8 ± 4.2	93.3 ± 2.8	96.8 ± 2.0	(232)
DMPA	796		76.2 ± 1.5	91.5 ± 1.0	93.6 ± 0.9	
TCu-380A	293		78.4 ± 2.7	-	-	(90)
TCu-220C	127		77.4 ± 4.2	-	-	
Nova T	82		72.0 ± 5.5	85.5 ± 4.6	91.5 ± 4.7	(228)
TCu-200	62		83.8 ± 5.3	96.8 ± 4.5	-	
Levonorgestrel (20 µg/day)	60		96.4 ± 3.5	-	-	(229)
TCu-380A	50		91.1 ± 7.6	-	-	
Levonorgestrel (12, 25, 30, 50 µg/day)	21		81.0 ± 8.6	-	-	(233)
Various IUDs	437	<30	88.6	93.6 ± 1.2	-	(229)
	139	>30	78.4	86.0 ± 2.9	-	
Various IUDs	70	>35	-	78% ± 5.0	-	(234)
		25-34	-	90% ± 1.5	-	
		17-24	-	92% ± 3.1	-	

^a Because of the design of the study these figures represent the percentages of women remaining undelivered of a live birth or a still birth rather than pregnancy rates.

with an IUD in place, special obstetric care is necessary because of an increased risk of premature birth and a decreased likelihood of a live birth (236–238).

8.6 Carcinogenicity

8.6.1 *Animal studies*

Most of the IUDs used at present that do not release either copper or hormonal steroids have not been studied in long-term conventional carcinogenicity tests in appropriate animal species. It is well known that the implantation of a foreign body subcutaneously in rats results in a high frequency of sarcoma formation (the Oppenheimer effect) (242). It has been shown that the introduction of either a plastic or stainless steel implant in the uteri of Wistar rats results in a higher frequency of epidermoid carcinomata and sarcomata than that found in the control group of animals (243).

The relevance of these findings to women is not yet known, although it should be pointed out that there have been few studies of the long-term effects of IUDs on the human endometrium and that both the endometrial cycle and the hormonal secretory pattern and metabolism in the rodent are different from those in women; thus the presence of an intrauterine foreign body may not have the same effect in both. The most appropriate experimental animal for these studies is probably the subhuman primate, of which, despite a worldwide shortage, the rhesus monkey (*Macaca mulatta*) is the most popular. The long-term carcinogenicity studies on the Copper T undertaken by the Population Council in the rhesus monkey have shown no evidence of uterine malignancy after 7 years (244).

8.6.2 *Human studies*

For obvious reasons, attention in human studies has been concentrated on cervical rather than uterine malignancy, and there have been very few studies of malignant uterine cancer with an IUD in place (245–247); in none of these studies was there a control or comparison group. Furthermore, no epidemiological studies have been undertaken on this subject.

The addition of copper or steroids to an IUD might raise some doubts as to its carcinogenic potential. In the report summarizing

the clinical experience with the Copper T IUD (90), carcinoma of the cervix was detected in 8 women out of 8632 acceptors, 6 cases being detected within 6 months of insertion. The rates are comparable to those quoted by Ferenczy (248) for women using either oral contraceptives or other methods.

8.7 Teratogenicity

8.7.1 *Animal studies*

There have been no formal publications on teratological studies of plain plastic devices. However, there was no evidence of teratogenicity in the control groups used in the studies on copper-releasing IUDs, nor was any found in the group using medicated devices (249, 250). Chang & Tatum (250) failed to observe any abnormalities in rat blastocysts transferred from a copper-IUD-bearing uterine horn to a normal horn, and in another study (251), there was no significant increase in the incidence of either congenital malformations or growth retardation in fetal rats. In the teratogenicity trials on rats and rabbits reported by the Alza Corporation (21), no evidence was found that the intrauterine release of progesterone caused or was associated with congenital abnormalities.

8.7.2 *Human studies*

In two studies on Copper-7, there were 20 684 insertions and 714 pregnancies with the device *in utero*, of which 167 reached viability, and 8% were lost to follow-up. Normal infants were recorded in 159 pregnancies, no details were available on 3 and, of the remaining 5, 3 had minor abnormalities and 2 major abnormalities, namely congenital dislocation of the hip, and lumbosacral meningo-myelocele with bilateral talipes (252).

Tatum et al. (253) reviewed the outcome of 918 pregnancies in women who conceived with a Copper T in place. Only 157 pregnancies resulted in a viable birth and there was only 1 congenital abnormality—a benign fibroma of the vocal cord. In another series, which included 196 pregnancies with the Lippes Loop *in situ*, 102 devices were left in the uterus and 94 IUDs were removed. In the first group, 42 infants reached viability, as compared with 66 in the second. There was only one abnormality, namely a case of microphthalmos in the first group (254).

In the only case-control study on the relation between limb-reduction defects and IUDs, that reported by Layde et al. (255), 96 infants with limb defects were compared with appropriately selected controls; no significant increase in the incidence of limb defects in the IUD group was found. There was only one congenital abnormality—bilateral inguinal hernia—in 15 infants exposed *in utero* to progesterone released from the Progestasert IUD (21).

Studies on morphological abnormalities in spontaneous abortion have shown no evidence of an increased incidence of abnormalities in such abortions with an IUD *in utero* as compared with a group of spontaneous abortions not associated with an IUD (256, 257). There is thus no evidence from the clinical use of IUDs that they have an adverse effect on infants conceived with the device *in situ*.

9. PATIENT SELECTION AND CHOICE OF METHOD¹

9.1 History and physical examination

A case history must be obtained from the woman, with special reference to any pregnancies, the menstrual cycle, and past or present genital tract infections. A careful abdominopelvic examination must follow: the size, shape, and position of the uterus must be defined and conditions such as gynaecological infections excluded. It is useful to have a check-list for both the history and the physical examination so that no contraindications are overlooked; this is especially important where personnel other than doctors provide the service. Laboratory tests are not essential before an IUD is inserted, but the service to the patient is improved if haemoglobin estimation, pregnancy test, microscopy of vaginal discharge and cervical cytology are available. A clinical assessment for the possible presence of severe anaemia should always be carried out if laboratory tests for haemoglobin levels are not available.

Absolute contraindications for the insertion of an IUD include:

- malignant disease of the corpus uteri or cervix, or vaginal bleeding of undiagnosed etiology;
- suspected pregnancy;
- active pelvic inflammatory disease.

¹ This section is a modified version of that in: WORLD HEALTH ORGANIZATION. *Intrauterine devices: their role in family planning care*. Geneva, 1983 (Offset Publication No. 75), pp. 21–22.

Relative contraindications to IUD use include:

- nulliparity;
- previous ectopic pregnancy;
- anaemia;
- menorrhagia;
- a history of pelvic inflammatory disease since last pregnancy;
- congenital uterine malformation or cavity distortion (fibromas, etc.);
- current or recurrent lower genital tract infection;
- multiple sexual partners;
- rheumatic heart disease;
- immunosuppressive therapy;
- Wilson's disease (applies to copper IUDs only).

The age of the woman is not *per se* a contraindication for IUD use, but there are special problems for certain age-groups, namely the very young and those near the menopause, that must be taken into account.

Nulliparity is not an absolute contraindication, but previous pelvic inflammatory disease, previous ectopic pregnancy, sexually transmitted disease, and multiple sexual partners may all make the choice of an IUD inappropriate.

The absolute and relative contraindications are summarized in Table 16.

9.2 Choice of method

A woman's choice of contraceptive method from the variety available, should be an informed one. Medical considerations may suggest that a particular method is more suitable, but for the method to be successful the woman must feel that she makes the final decision and that the method chosen is the best for her.

10. MENSTRUAL BLOOD LOSS

10.1 Menstrual bleeding in IUD users

The most common reason for the premature removal of an IUD is bleeding and pain. Removal rates with the copper devices vary from 13.1 per 100 women at 1 year of use with TCu-380 A (90) to

Table 16. Contraindications to IUD insertion and/or use

Event	Type of contraindication		Remarks
	Nulliparous women	Parous women	
Pregnancy	Absolute	Absolute	Suspected or confirmed
Genital infection	Absolute	Absolute	Active, with the exception of candidiasis
Sexually transmitted disease during the past 12 months	Absolute	Absolute	Does not apply to bacterial vaginosis, candidiasis, recurrent herpesvirus infection, hepatitis B or cytomegalovirus infection
Serious pregnancy-related pelvic infection during the past 12 months	Absolute	Relative	–
Previous ectopic pregnancy	Absolute	Relative	–
Previous pelvic inflammatory disease	Absolute	Relative	–
Multiple sexual partners	Relative	Relative	Absolute for nullipara in areas of high known or suspected prevalence of sexually transmitted disease
Anaemia	Relative	Relative	–
Pathology of the uterine corpus	Relative	Relative	–
Immunosuppressive therapy	Relative	Relative	–
Wilson's disease	Relative	Relative	Copper IUDs

4.4 per 100 women with the Nova T (93). Generally speaking, removal rates are higher with the non-medicated devices such as the Lippes Loop and Saf-T-Coil.

Increases in blood loss can take a number of forms. Thus the menses can be prolonged and/or heavy, or there can, in addition, be intermenstrual bleeding or spotting. The increase in menstrual blood loss associated with the use of an IUD may not compromise the iron stores of healthy, well-nourished women but, as will be shown later, can sometimes result in significant reductions in iron stores to below the levels normally associated with iron-deficiency anaemia. This is particularly important in women in developing countries, where the dietary intake of iron and protein is low, intestinal hookworm infestation may be widespread, and iron stores may already be depleted by repeated pregnancies and lactation.

10.2 Normal values of menstrual blood loss

According to reports from many countries, the normal volume of blood lost during menstruation in women not using any form of contraception (see Table 17) is generally in the range of 31–39 ml,

Table 17. Normal menstrual blood loss

Country	No. of women	Mean menstrual blood loss \pm standard error	Reference
Sweden	476	38.5 \pm 1.9	(258)
United Kingdom	280	34.6 \pm 24.2	(259)
Egypt	145	37.0 \pm 2.0	(260)
Mexico	140	35.1 ^a	(261)
Brazil	127	32.9 ^a	(262)
Republic of Korea	114	30.7 \pm 2.2	(263)
China			
Beijing	421	54.2 \pm 2.8	(264)
Shanghai	NS ^b	46.9 \pm 5.6	(264)
Japan	120	52.3 \pm 24.7	(265)

^aStandard error not specified.

^bNot specified.

independent of parity or prior oral contraceptive use, but studies in China have shown normal values of 47–54 ml for healthy women (264), while in Japan values in the range of 50–56 ml have been observed (265). The reasons for these differences are not clear.

Menstrual blood loss is usually less in nulliparous than in multiparous women but is independent of age and parity after the age of 25 years (266). It has been estimated that an average increase in blood loss of 31 ml will result in a 15% increase in the number of women with menorrhagia (more than 80 ml blood loss) and an increase of 41 ml will result in a 25% increase (267). These estimates are derived from studies on healthy, well-nourished Swedish women.

10.3 Menstrual blood loss with IUDs

The use of non-medicated and copper devices is known to increase menstrual blood loss, while the progestogen-releasing IUDs cause a reduction in the volume of blood lost. The non-medicated devices, such as the Lippes Loop, Saf-T-Coil and other plastic IUDs, have been shown to at least double the blood flow levels measured before insertion (262, 267–272). Recent WHO studies have confirmed these findings for the Lippes Loop and showed that, after 24 months of use, the increase in menstrual blood loss was still significantly greater than the pre-insertion values (273). The

interpretation of data on menstrual blood loss following IUD insertion is made difficult by the probability that those women who experienced excessive blood loss may have discontinued IUD use in the first few months of the study; the inclusion of their data in the computation of mean values might thus give erroneous results.

With TCu-200 and Copper-7, several studies have reported an average increase in menstrual blood loss over 6–12 months of use of about 40–50% as compared with pre-insertion levels (18, 274–277). In the WHO studies in South America, there was a moderate increase (10.6–12.7%) up to 6 months of use, followed by a progressive return to normal levels by 24 months (273).

Said et al. (269) found that 101 users of the MLCu-250 IUD had a mean 116% increase in the first month of use, falling to a mean 26% increase over pre-insertion values at 12 months post-insertion. A higher proportion of nulliparous women experienced increased bleeding when using this IUD (278). The menstrual blood loss observed with MLCu-375 was significantly increased up to 12 months of use but declined thereafter (272).

Gao et al. (264) found a significant increase in menstrual blood loss after 12 months with the VCu-200 IUD, namely from 56.7 ml pre-insertion to 80.3 ml (a 41.6% increase), and with the TCu-220 C IUD, a mean increase of 61.3%. In the second year of observation, losses had still not returned to pre-insertion levels, and the differences were still statistically significant.

Progestagen-releasing devices have been found to reduce the volume of bleeding to about 40–50% of pre-insertion values (273, 279–281), and this reduction was sustained for up to at least 12 months of use. Menstrual blood loss was significantly reduced with levonorgestrel devices releasing either 20 or 30 µg per day, which resulted in a high incidence of oligomenorrhoea or amenorrhoea, and was reduced even if women who had amenorrhoea were excluded from the analysis (282).

10.4 Intermenstrual bleeding or spotting

Most IUDs are associated either with intermenstrual bleeding or spotting in the first 3 months or so of use. The frequency of spotting is higher with Progestasert than with other devices (283–286). However, intermenstrual bleeding is greater in volume in patients with a Copper-7 than a Progestasert (101). In a study in which intermenstrual bleeding was measured quantitatively, 90% of

women using a Lippes Loop C had intermenstrual bleeding in the first cycle following insertion as compared with 84% of those using the TCU-200 (262).

10.5 Sequelae of increased menstrual blood loss

It has been shown that the incidence of iron-deficiency anaemia is doubled if menstrual blood loss is between 60 and 80 ml and trebled when the loss exceeds 80 ml (258). Most, if not all of the currently available non-medicated and copper IUDs increase the menstrual blood loss, so that subsequent iron-deficiency anaemia is a potential risk.

Guillebaud et al. (269) found that the haemoglobin level fell significantly in British women having an average menstrual blood loss of 66 ml 1 year following insertion of each of three different IUDs (Lippes Loop D, Copper-7 and Dalkon Shield). As many as 50% of women with IUDs may become iron-deficient if dietary iron is not supplemented (275).

Studies in Brazil, India and Mexico, on the other hand, have failed to show significant changes in haemoglobin values following IUD insertion (273, 287, 288). Shaw (289) has speculated that, although IUDs increase menstrual blood loss, the prevention of pregnancy in the multiparous woman is more important in protecting her from the hazard of iron deficiency. Pregnancy itself results in a loss of 750 mg of iron, equivalent to a blood loss of 1500 ml which, over a period of 9 months, is equivalent to an average menstrual blood loss of about 170 ml. The haemoglobin level is probably the last indicator of iron stores to fall in iron-deficiency anaemia, and plasma iron and total iron-binding capacity levels do not adequately measure iron stores. A good correlation between serum ferritin and iron depletion has been reported (290, 291) and, in a number of studies of menstrual blood loss with IUDs, serum ferritin has been measured by direct radioimmunoassay (287, 292).

Guillebaud et al. (292) studied 47 women before, and for 1 year following, IUD insertion. Of these, 9 subjects (19%) were considered to be iron-deficient prior to insertion (serum ferritin less than 16 µg), whereas after 1 year, 45% of subjects had serum ferritin values of less than 16 µg/l. Those patients with a menstrual blood loss exceeding 80 ml showed the greatest fall in serum ferritin. In other studies in Chile, Malaysia and Mexico, falls in serum ferritin and transferrin saturation, haemoglobin and haematocrit were reported

6 and 12 months after insertion of non-medicated and copper IUDs (101, 288, 293–295). Falls in serum ferritin in subjects with a Lippes Loop D or Copper-7 but a rise in subjects with a Progestasert IUD have been reported (23). Similar increases in ferritin values have been reported from Mexico (288). This finding correlates well with the reduction in menstrual blood loss found with this device and is evidence that iron stores are actually increasing in women following insertion of the Progestasert.

It is clear that the short-term consequences of increased menstrual blood loss do not include iron-deficiency anaemia but, in many of the studies, the subjects had haemoglobin levels greater than 110 g/l prior to IUD insertion; in many developing countries, however, the so-called “normal” haemoglobin level is 100 g/l or less. There is a need for longer-term studies on menstrual blood loss and iron-deficiency anaemia because the duration of use of the smaller copper-bearing devices is being extended beyond the 2 years originally approved by drug regulatory agencies.

10.6 Etiology of increased menstrual blood loss

A foreign body within the uterine cavity leads to trauma of varying degrees to the endometrium; this may be increased by the uterine contractions that take place throughout the menstrual cycle.

Studies of uteri and endometrial tissue that have been exposed to intrauterine devices have demonstrated that there may be one or both of two basic lesions. Superficial endometrial microscopic ulceration may be caused by either abrasion or pressure necrosis (35, 296, 297). The endometrial capillaries are eroded, leading to interstitial haemorrhage. Areas of the endometrium remote from the IUD and not in contact with it, have shown increased vascularity and interstitial red cell extravasation (298, 299). A striking paucity of platelet/fibrin thrombi was observed in vessels in which they would have been expected (300). There was some epithelial erosion but not enough for simple mechanical erosion to account, by itself, for all IUD-induced haemorrhage.

It would appear, therefore, that the IUD causes a vascular reaction which is most pronounced in the endometrium adjacent to it and includes increased vascularity, congestion and increased vascular permeability, endothelial cell degeneration, and vessel wall defect formation. What is not clear is how this reaction is produced.

When an IUD has been removed because of excessive bleeding, a high level of plasminogen activator has been found in the tissue surrounding the device (301). Increased fibrinolytic activity in the endometrium of women with a Copper-7 *in situ* has been reported (302), as has increased endometrial plasminogen activator concentration in 80% of women after IUD insertion (303). The cells adhering to an IUD are predominantly macrophages, which produce plasminogen activator as well as prostaglandins E₂ and F₂ (48). It has been shown that: (1) these macrophages also produce fibrinolytic enzymes; (2) there were more macrophages on the Lippes Loop and Saf-T-Coil than on the Copper-7; and (3) there were significantly higher counts on the devices from patients with menorrhagia or intermenstrual bleeding (304).

Several studies have shown that mast cells are increased in numbers in IUD-exposed endometrium (305, 306). Mast-cell secretion is stimulated by prostaglandins and the C3a and C5a components of complement produce histamine, which could result in vascular dilatation and increased permeability. These cells also liberate serotonin, another vasoactive substance. However, anti-histamine therapy had no beneficial effect on IUD-induced bleeding. Mast cells also produce heparin, and large quantities of heparin-like material have been found in human endometrial fluid; greater quantities still may be present in women with IUDs, possibly causing impaired vascular haemostasis (304).

10.7 Role of prostaglandins and related compounds

Prostaglandins are produced by the uteri of many species (307), and the presence of an IUD increases production of PGE₂ in the IUD-influenced secretory endometrium (51). Such increased release of prostaglandins in users of a large, non-medicated IUD, the Lippes Loop D, seems to be mainly restricted to the first few menstrual cycles following insertion, i.e., in the phase in which excessive and irregular bleeding is commonly reported (308). The large IUDs are associated with greater menstrual blood loss, which may in part be due to mechanical distension of the uterus; this is known to cause increased prostaglandin production in sub-primates (309). An IUD causes an inflammatory or foreign-body reaction in the endometrium, and this could theoretically be associated with increased prostaglandin production. Prostacyclin appears to be increased in the endo- and myometrium in women with menorrhagia

(310, 311); it is known to be a potent vasodilator and inhibitor of platelet aggregation (312) and its production in excess may thus contribute to the haemostatic defect. Another aspect which has yet to be explored is that of the range of arachidonic acid derivatives formed along the lipoxygenase enzyme pathway.

10.8 Role of platelets

Formation of haemostatic plugs is an essential step in normal haemostasis, and platelets play a crucial role in this process. Endometrial haemostatic plugs, while present in the endometrium during menstruation, are fewer in numbers than those observed in skin wounds (313). This difference may be attributable to local production by the uterus of prostacyclin, which inhibits haemostasis and probably potentiates the anticoagulant effect of heparin released from mast cells, through its effect as an inhibitor of platelet aggregation. The complex interrelationship of the events associated with IUD-induced increased menstrual bleeding is shown diagrammatically in Fig. 2.

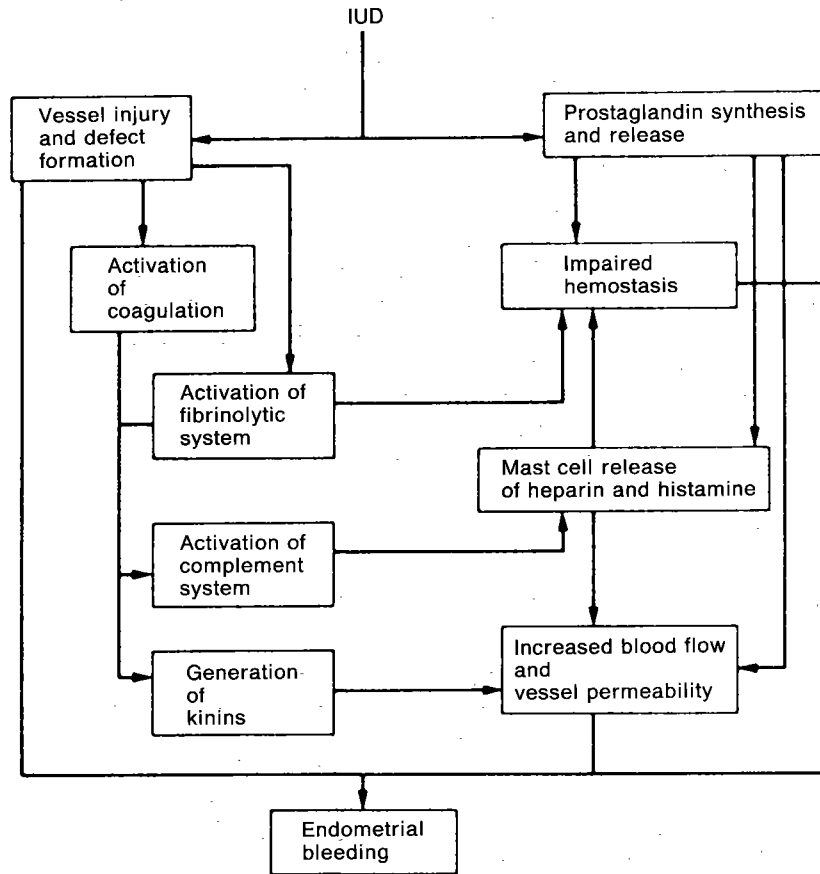
10.9 Treatment of increased menstrual blood loss

The main emphasis in efforts to control abnormal bleeding due to IUDs has been on mechanical and pharmacological approaches. The use of special instruments to measure the dimensions of the uterine cavity has been advocated (314, 315) but their cost and inconvenience probably limit their usefulness. These methods may reduce bleeding problems but will by no means eliminate them.

Pharmacological approaches to the control of abnormal bleeding are aimed either at the local release (medicated IUDs) or systemic administration of various compounds. In the first generation of medicated IUDs, copper was added, which reduced menstrual blood loss, though not to normal values. This was probably the consequence partly of the smaller size of the device, and partly of the effect of copper, which causes less fibrinolytic activity than inert devices, and modifies prostaglandin synthesis and metabolism (316, 317).

Hormone-releasing IUDs (Progestasert and those releasing levonorgestrel) reduce menstrual blood loss but are associated with a significant increase in the number of bleeding days, particularly in the first 3 months of use (283, 318). The levonorgestrel IUD releasing

Fig. 2. Simplified diagram showing the events that may occur in an IUD-exposed endometrium and that may lead to excessive bleeding



Source: Rowe (252).

20 µg/day has a longer effective life-time (at least 7 years) than Progestasert, which has a life-time of only 1 year. The levonorgestrel device is associated, however, with a higher incidence of removals for amenorrhoea than other hormone-releasing devices (96), and this may increase the rate of removal in the first 12 months of use. Devices releasing progestogens are associated with histological suppression of the endometrium but cause less endometrial erosion

and vascularity compared with inert and copper-bearing IUDs (319). Moreover, inhibition of prostaglandin production and reduced fibrinolytic activity as well as a quiescent myometrium are additional factors that contribute to the reduced menstrual blood loss with these hormone-releasing IUDs (319, 320).

IUDs which release antifibrinolytic agents in the uterine cavity have also been tested. Aprotinin, a pancreatic trypsin inhibitor which is inactive orally, successfully reduced menstrual blood loss when instilled into the uterine cavity (321, 322). When this compound was evaluated in a sustained release system, it proved to be chemically unstable and rapidly lost its potency (323).

ϵ -Aminocaproic acid and tranexamic acid have also been tested both by local instillation and by the use of Multiload devices, and gave an improved menstrual blood loss in the first post-insertion cycle; later, when the drug reserve in the device was exhausted, this beneficial response was lost (324).

The finding of increased fibrinolytic activity in the endometrium of IUD users and its production by the macrophages adhering to IUDs, has led to the trial of systemically administered antifibrinolytic agents (325–327). Weström & Bengtsson administered tranexamic acid for the treatment of IUD-induced menorrhagia. The placebo-treated groups experienced an 83% increase in menstrual blood loss, whereas the drug-treated groups had a mean increase of only 11.5% (327).

Oral intake of tranexamic acid during menstruation in women using the Lippes Loop D resulted in a highly significant reduction in menstrual blood loss (303). The treatment also reduced the duration of bleeding and the incidence of intermenstrual spotting or bleeding. However, side-effects such as dizziness, nausea and headache were reported by 77.8% of the subjects.

There have been 3 reports on the use of ethamsylate in the treatment of IUD-induced menorrhagia (303, 328, 329). It is claimed that this substance enhances platelet aggregation, increases capillary resistance, and reduces menorrhagia by counteracting the fall in capillary resistance that occurs in the premenstrual phase of the cycle. In the first of these trials (303), women complaining of excessive menstrual blood loss while using IUDs were studied during 6 consecutive periods. The devices used were the Saf-T-Coil, Dalkon Shield, Copper-7, and Lippes Loop. Women were randomly allocated to treatment with either tranexamic acid or ethamsylate, the latter being found to have no beneficial effect on menstrual blood

loss. In the second study (328), a 19% decrease in menstrual blood loss was found and in the third study (329) a subjective decrease was reported.

The hypothesis that excessive prostaglandin production by the endometrium may play a part in the increase in menstrual blood loss has been supported by a number of studies in which patients with menorrhagia have been treated with prostaglandin synthetase inhibitors (otherwise known as non-steroidal anti-inflammatory agents) with significant reduction in blood loss (330, 331). Thus IUD-induced menorrhagia has been treated with agents such as indomethacin (332, 333), mefenamic acid and flufenamic acid (331-334), naproxen (335-336), diclofenac sodium (337) and ibuprofen (338, 339).

It should be noted that these compounds are relatively expensive and have some serious side-effects; prolonged administration or chronic intrauterine release, if feasible, may thus be undesirable and there is a risk of teratogenicity if pregnancy occurs with a device *in situ*.

The effect of non-steroidal anti-inflammatory agents on the duration of menstrual blood loss remains controversial but, in most studies, it was concluded that they do control and prevent IUD-induced pain. The best member of this family of drugs to use and the optimal schedule of administration in the management of intermenstrual bleeding are still unsettled.

11. IUDs VERSUS OTHER METHODS OF CONTRACEPTION

All drugs and devices, including all methods of fertility regulation, are associated with a certain risk. The risk-benefit ratios of the various methods of contraception vary from country to country. In developing countries, the high mortality and morbidity rates associated with pregnancy, whether planned or unplanned, indicate that any method of contraception is a valuable component of reproductive health care. The rates of specific complications vary according to the type of contraceptive method employed, including the use of IUDs.

For oral contraceptive users there is an increased risk of cardiovascular disease, cerebral haemorrhage, and benign liver tumours (340, 341). Although the use of barrier methods of

contraception, such as the condom and diaphragm, have a very low risk of complications, these methods have relatively high failure rates and hence expose women to a higher risk of morbidity and mortality associated with unwanted pregnancy.

The use of IUDs provides effective protection against pregnancy. When compared with women who use other reversible methods of contraception, those who use IUDs have the lowest mortality resulting from deaths directly attributable to those methods and to the consequences of unwanted pregnancy.

Fig. 3 shows the maternal mortality associated with pregnancy and reversible contraception in both developed and developing countries. In both settings, the use of IUDs significantly reduces the maternal mortality resulting from unwanted pregnancy.

It should be noted that the death rate in women not using any method of fertility regulation rises with age and that, in oral contraceptive users, there is a large increase in the death rate between the age-groups 35–39 and 40–44, which is especially marked in those users who smoke (see Table 19).

Table 19. Death rates per 100 000 per annum in women using various methods of contraception¹

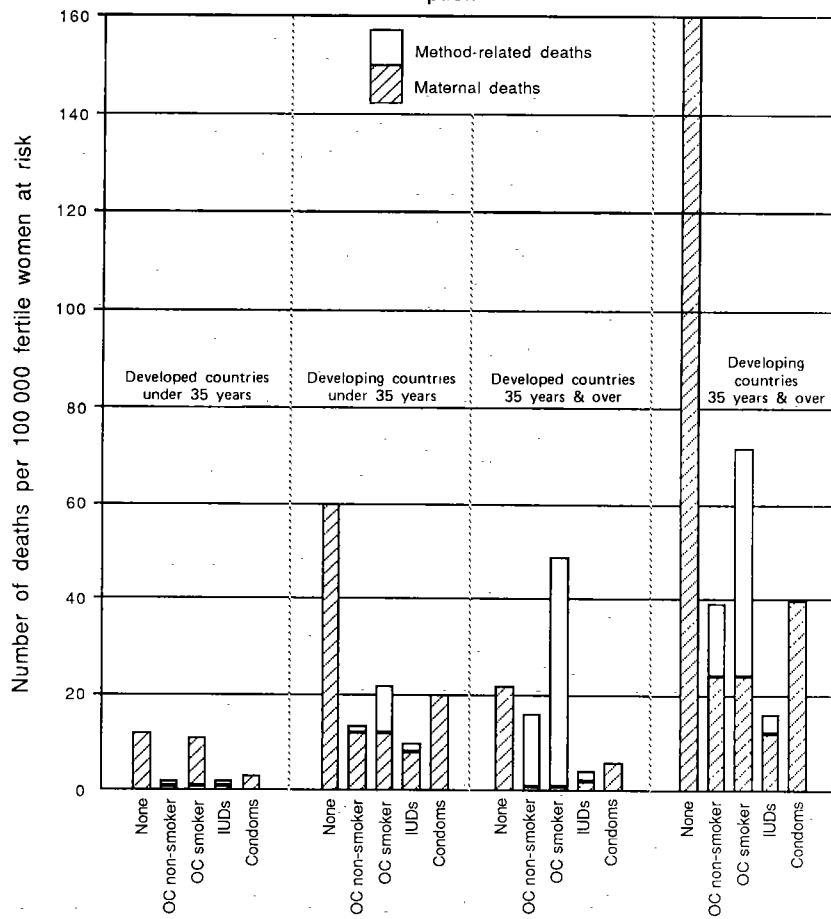
Method	Age (years)					
	15–19	20–24	25–29	30–34	35–39	40–44
None	5.6	6.1	7.4	13.9	20.8	22.6
Oral contraceptives						
Non-smokers	1.3	1.4	1.4	2.2	4.5	7.1
Smokers	1.5	1.6	1.6	10.6	13.4	58.9
IUDs	0.9	1.0	1.2	1.4	2.0	1.9
Barrier methods	1.1	1.6	2.0	3.6	5.0	4.2

¹ Source: Tietze (343).

Special risks that have been associated with IUD usage include uterine perforation, pelvic inflammatory disease, and tubal infertility, the first two of which have been fully discussed in other sections of this report.

The question of tubal infertility among IUD users is complex and has not been adequately studied. In two case-control studies (197, 198) conducted in the USA, higher relative risks of infertility were found among IUD users than in users of other contraceptive methods. The risk was lowest among women using copper-bearing IUDs. Other factors, e.g., multiple sexual partners, were also identified that were associated with significantly elevated risks of infertility.

Fig. 3. Maternal mortality associated with pregnancy and reversible contraception^{a, b}



^aAdapted from Kols et al. (342).
^bOC = oral contraceptives.

In contrast to these findings, other studies have shown that fertility is immediately restored in women who stop using IUDs, whereas this is not the case with other methods of contraception. Thus, when all the evidence is considered, IUDs are shown to be a safe and effective method of fertility regulation.

12. THE LEGAL SITUATION IN THE UNITED STATES OF AMERICA

In 1974, the manufacturers of the Dalkon Shield IUD withdrew it from the market; the company was subsequently the defendant in a large number of law suits, and was forced into bankruptcy. In 1983, the manufacturers of the Saf-T-Coil withdrew this device from the American market and, in September 1985, the manufacturers of the Lippes Loop announced their decision to stop sales because of "economic considerations".

On 31 January 1986, it was announced that the manufacture and distribution of the TCu-200 and Copper-7 devices in the USA would be discontinued because of "mounting unjustified litigation in the U.S. that has made future product liability insurance virtually unobtainable" (4).

Following this latest withdrawal from the IUD market, an Expert Panel convened by the Planned Parenthood Federation of America stated that "the IUD is one of the most effective forms of reversible contraception that has yet been approved by the FDA", and that "the IUDs approved by the FDA continue to be a safe method of contraception for many women" (344). The Population Council (345), which developed the T-shaped copper IUDs, and the American College of Obstetricians and Gynecologists, emphasized that the withdrawal of the two IUDs was not related to, and did not alter the approved regulatory status of any copper IUD in the USA (345, 346) and this view was also endorsed by the International Planned Parenthood Federation (3). At the XII World Congress on Fertility and Sterility (1986) the International Federation of Fertility Societies stated that "IUDs are important methods of fertility control, have relatively low side effects, low failure rates and good patient acceptability. The XII Congress fully endorses their continued use in appropriately selected and informed women throughout the world...".

The Scientific Group noted the particular legal situation in the United States of America and that the decisions to withdraw the Lippes Loop, Copper-7 and TCu-200 from the American market were based on commercial and financial considerations rather than on questions of safety. The Group re-emphasized that the currently available copper and hormone-releasing IUDs, when properly used, are probably the most effective and reliable reversible method of fertility regulation.

13. CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

Based on the foregoing review of the mechanism of action, safety and efficacy of IUDs, the Scientific Group reached the conclusions described below and formulated a series of practical recommendations for further research.

13.1 Conclusions

All IUDs stimulate a foreign-body reaction in the endometrium that is potentiated by the addition of copper; progestogen-releasing IUDs produce endometrial suppression similar to that seen when the drug is administered by other routes, e.g., orally or by injection.

It is unlikely that any single mechanism of action accounts for the antifertility effect of IUDs. The mechanisms whereby this effect is exerted remain ill-defined but probably include alteration or inhibition of (a) sperm migration in the upper female genital tract, (b) fertilization and (c) ovum transport. These factors probably play a more important role than does the prevention of implantation resulting from biochemical and histological changes in the endometrium.

The IUD is both a highly effective method of contraception and one for which the continuation rates are as high, if not higher, than those for other reversible methods of fertility regulation. After 1 or 2 years of use, the newer copper devices are significantly better in preventing pregnancy than the early copper devices (Copper-7, TCu-200) and the inert devices (Lippes Loop, Saf-T-Coil). These newer devices include the variants of the T device (TCu-220 C, TCu-380 A or Ag), Nova T, and the Multiload devices. The effective life of these newer copper devices is at least 5 years and they can therefore be left in place for at least that length of time, provided that there are no medical or personal reasons for their removal. The levonorgestrel IUD releasing 20 µg/day promises to be as effective as the newer copper IUDs.

Insertion of an IUD after induced or non-febrile spontaneous abortion does not increase the risk either of pelvic infection or uterine perforation and is a safe and effective procedure. The expulsion rate of IUDs after insertion immediately following spontaneous or induced first trimester abortion is similar to that following intermenstrual insertion.

In general terms, for non-medicated inert devices, the larger the device, the higher the expulsion rate; lower rates are seen with the copper devices, and especially the newer ones. Expulsion is, however, also influenced by the following factors:

- age—the expulsion rate decreases with increase in age;
- parity—nulliparous women have higher expulsion rates;
- timing of insertion—early postpartum insertion is associated with a higher expulsion rate than insertion at other times.

The expulsion rate of IUDs inserted immediately following spontaneous or induced first trimester abortion is similar to that following conventional intermenstrual insertion, but is higher after insertion immediately following second trimester abortion.

Insertion immediately following delivery of the placenta is associated with a higher expulsion rate than intermenstrual insertion. In China, IUD insertion at the time of elective Caesarian section appears to be safe, with acceptably low expulsion and perforation rates. Insertion more than 1 week after delivery is safe and effective and is associated with an acceptable expulsion rate in women who are not lactating. However, in lactating women, the incidence of uterine perforation may be increased.

There is no convincing evidence of a cause-and-effect relationship between IUD use and ectopic pregnancy. The newer copper IUDs have the lowest rates of ectopic pregnancy.

The uterine perforation rate is usually less than 1 for every 2000 insertions. The rates vary, however, and are influenced by factors such as experience in IUD insertion, the type of technique used to insert a particular device, and the timing of the insertion.

Fertility returns promptly in women discontinuing use of an IUD and at 2 years following removal of the device for planned pregnancy the proportion of women who remain infertile is not different from that of women who discontinue other methods of fertility regulation in order to become pregnant.

Ectopic pregnancy should be excluded in women who become pregnant with an IUD *in situ*, and every effort should be made to remove the device as soon as possible in order to minimize the risk of septic abortion and other complications of pregnancy. If the device cannot be removed, induced abortion should be offered where national legislation permits. If induced abortion is illegal or unacceptable to the woman, her pregnancy should be carefully followed.

The majority of cases of pelvic inflammatory disease, whether the woman has an IUD in place or not, are caused by bacterial agents of sexually transmitted disease, and most infections are caused by more than one organism. Drug therapy is indicated for all cases of pelvic inflammatory disease; nevertheless, one episode of the disease, even if treated, will cause approximately 10% of the women concerned to be infertile. If pelvic inflammatory disease occurs with an IUD in place, it should be removed once adequate antibiotic therapy has been instituted. The disease increases the risk of an ectopic pregnancy by a factor of 7–10 as compared with that of women who have not had it. The incidence of pelvic inflammatory disease would appear to be higher in the first three months or so following insertion, but the use of prophylactic antibiotic therapy at the time of insertion has so far given inconclusive results.

The IUD-associated risk of pelvic inflammatory disease is much lower than was previously thought, as methodological problems relating to decreased risk in control groups, choice of comparison groups, over-diagnosis and confounding factors have all caused it to be overestimated. The increased risk with IUDs appears to be limited to the first four months of use. Data from the USA suggest that the use of any IUD in the past increases the risk of primary tubal infertility but that this does not apply if a copper IUD alone has been used. No increased risk of tubal infertility has been found among women who used an IUD and had a stable monogamous sexual relationship. The use of a copper IUD after the first pregnancy is not associated with secondary infertility due to tubal disease.

Menstrual blood loss is increased in users of non-medicated and copper IUDs, but the increase with copper IUDs is smaller. Hormone-releasing devices reduce menstrual blood loss, as compared with pre-insertion values. Intermenstrual bleeding or spotting is most frequent during the first 3 months of use but, whilst it may be a nuisance to the patient, is not clinically important.

The use of serum ferritin is both less time-consuming and just as informative as quantitative estimates of the volume of menstrual blood loss in monitoring the long-term effects of IUDs on body iron stores.

There is no standard treatment at present for IUD-associated increased menstrual blood loss but, in some cases, the use of non-steroidal anti-inflammatory drugs and antifibrinolytic agents, given during the menses, may reduce such loss to acceptable levels. The

routine or frequent use of these drugs is not recommended until possible adverse effects on the local uterine and systemic haemostatic mechanism have been clarified.

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.

In view of the findings regarding pregnancy rates and since the newer copper-releasing devices also tend to have lower expulsion rates than the plastic and steel ring devices, and as a result, have higher overall continuation rates, the Scientific Group recommends that as supplies or current stocks of the latter devices are exhausted, they should be replaced by the more effective copper-releasing IUDs.

13.2 Recommendations for further research

The following recommendations for further research were made by the Scientific Group:

1. In order to elucidate further the mechanism of both the IUD's antifertility effect and the side-effects such as increased menstrual blood loss, studies should be undertaken on arachidonic acid metabolism and should include both the cyclo-oxygenase and lipoxygenase pathways in leukocytes and other cells that accumulate in the endometrium and the uterine fluid and on IUDs.

2. Research on the effect of IUDs on sperm physiology, migration and survival in the female genital tract, and on sperm-ovum fertilizing capacity, should be continued.

3. In order to better understand the physiological events occurring between fertilization and the establishment of pregnancy, the tests and methodology for the detection of embryo- and blastocyst-specific substances require further validation and evaluation.

4. Studies should be undertaken to determine the rate of fertilization in both IUD users and non-users.

5. The cytology and morphology of the fallopian tubes in both IUD users and non-users should be studied further in relation to

endometrial changes and ovarian activity in both short- and long-term users of IUDs.

6. As good clinical data are still needed, large multicentre studies on the newer copper-releasing devices and the progestagen-releasing IUDs should be continued in order to collect information on their clinical efficacy and acceptability after more than five years of use.

7. Life-table analysis should be used in all studies, which should be randomized and multicentre character, and good follow-up should be encouraged. This would make valid comparisons between different studies possible.

8. Further research should be carried out to determine the factors associated with IUD expulsion following immediate postplacental insertion.

9. Further research on the insertion, at the time of elective Caesarian section, of the newer models of copper and progestogen-releasing IUDs is needed to confirm the safety and efficacy of this procedure.

10. Steps should be taken to encourage the development of specific, simple, inexpensive, and robust kits for the diagnosis of current and prior infection by the organisms of sexually transmitted disease, and particularly *Chlamydia* and *Neisseria*.

11. Multicentre studies should be conducted in both developed and developing countries on the epidemiology of sexually transmitted diseases in order to identify groups at high risk of contracting such a disease and thus at risk of pelvic inflammatory disease if an IUD is used.

12. Further studies should be undertaken on the relationship between lower and upper genital tract infection and the mechanism of spread of organisms.

13. Studies should be carried out to determine the optimal treatment of pelvic inflammatory disease and thus minimize the sequelae of the disease.

14. Studies should be carried out on the use of prophylactic antibiotics given at the time of insertion, to determine whether this will result in a lower incidence of infection in the first few months following insertion.

15. The micro-organisms, including *Chlamydia* and *Mycoplasma*, present during the normal cycle and in IUD-users in the endometrium immediately following IUD insertion should be identified.

16. Prospective studies should be conducted to determine whether the threads on an IUD influence the incidence of pelvic infection.

17. Epidemiological studies on primary and secondary tubal infertility and previous IUD use should be repeated in areas where sexually transmitted disease is highly prevalent, and in particular in developing countries.

18. Formal studies on the restoration of fertility and the outcome of pregnancy should be conducted with the newer copper and progestogen-releasing IUDs.

19. Studies on fertility and pregnancy outcome in women who have stopped using the IUD for reasons other than planned pregnancy should be carried out.

20. Comparative studies should be undertaken on the future reproductive prospects of women treated for ectopic pregnancy with, and without, an IUD in place.

21. Because of the suggestion that the use of low-dose progestogens is associated with an increased risk of ectopic pregnancy, all current and future studies on progestogen-releasing devices should be monitored closely for this.

22. Research should be undertaken to elucidate the reasons for the differences between the normal menstrual blood loss in Chinese and Japanese women and other population groups.

23. The effect on the peripheral and local uterine haemostatic systems of antifibrinolytic and non-steroidal anti-inflammatory drugs used for the treatment of excessive menstrual blood loss in IUD users should be investigated, and the development of systems for delivering low doses of these drugs from IUDs should be encouraged.

24. Long-term studies should be carried out on menstrual blood loss and ferritin when levonorgestrel-releasing and the newer copper IUDs are used.

25. A comparative study of complication rates after IUD insertion in lactating and non-lactating women should be undertaken.

REFERENCES

1. WHO Technical Report Series, No. 332, 1966 (*Basic clinical aspects of intrauterine devices: report of a WHO Scientific Group*).

2. WHO Technical Report Series, No. 397, 1968 (*Intrauterine devices: physiological and clinical aspects: report of a WHO Scientific Group*).
3. Concerns in the USA about IUDs—IMAP's comments. *International Planned Parenthood Federation Medical Bulletin*, **20**: 1 (1986).
4. *FDC Reports*, **48**: T and G, 6–7 (1986).
5. LISKIN, L. & FOX, G. IUDs: an appropriate contraceptive for many women. *Population reports*, Series B, No. 4, Washington, DC, 1982.
6. RICHTER, R. Ein Mittel zur Verhütung der Konzeption [A means of preventing pregnancy]. *Deutsche Medizinische Wochenschrift*, **35**: 1525–1527 (1909).
7. GRAEFENBERG, E. An intrauterine contraceptive method. In: Sanger, M. & Stone, H.M., ed. *The practice of contraception. Proceedings of the 7th International Birth Control Conference. Zürich, Switzerland, September 1930*. Baltimore, Williams & Wilkins, 1930, pp. 33–47.
8. OTA, T. A study on birth control with an intrauterine instrument. *Japanese journal of obstetrics and gynecology*, **17**: 210–214 (1934).
9. OPPENHEIMER, W. Prevention of pregnancy by the Graefenberg ring method: a re-evaluation after 28 years' experience. *American journal of obstetrics and gynecology*, **78**: 446–454 (1959).
10. ISHIHAMA, A. Clinical studies on intrauterine rings, especially the present state of contraception in Japan and experiences in the use of intrauterine rings. *Yokohama medical bulletin*, **10**: 89–105 (1959).
11. GUTTMACHER, A.F. Intrauterine contraceptive devices. (The 8th Oliver Bird Lecture presented at the London School of Hygiene and Tropical Medicine.) *Journal of reproduction and fertility*, **10**: 115–128 (1965).
12. LIPPES, J. A study of intrauterine contraception: development of a plastic loop. In: Tietze, C. & Lewit, S., ed. *Intrauterine contraceptive devices*. Amsterdam, Excerpta Medica Foundation, 1962, pp. 69–75 (International Congress Series No. 54).
13. ZIPPER, J. ET AL. Suppression of fertility by intrauterine copper and zinc in rabbits: A new approach to intrauterine contraception. *American journal of obstetrics and gynecology*, **105**: 529–534 (1969).
14. ZIPPER, J. ET AL. Contraception through the use of intrauterine metals. I. Copper as an adjunct to the "T" device. *American journal of obstetrics and gynecology*, **109**: 771–776 (1974).
15. SIVIN, I. A comparison of the Copper T-200 and the Lippes Loop in four countries. *Studies in family planning*, **15**: 115–123 (1976).
16. COLE, L.P. & EDELMAN, D.A. A comparison of the Lippes Loop and two copper-bearing intrauterine devices. *International journal of gynaecology and obstetrics*, **18**: 35–39 (1980).
17. WORLD HEALTH ORGANIZATION. A randomized multicentre comparative trial of the Lippes Loop D, TCu220C and Copper 7. *Contraception*, **26**: 1–22 (1982).
18. MALMQVIST, R. ET AL. Menstrual bleeding with copper covered intrauterine contraceptive devices. *Contraception*, **9**: 627–633 (1974).
19. SHAW, S.T. ET AL. Quantitative menstrual and intermenstrual blood loss in women using Lippes Loop and Copper T intrauterine devices. *Contraception*, **21**: 343–352 (1980).
20. SCOMMEGNA, A. ET AL. Intrauterine administration of progesterone by a slow release device. *Fertility and sterility*, **21**: 201–210 (1970).

21. Alza Pharmaceuticals. *The Progestasert: intrauterine progesterone contraceptive system: release rated 65 ug/day progesterone for one year: a new contraceptive*. Palo Alto, CA, Alza Corporation, 1976.
22. ROWE, P.J. ET AL. Comparative bleeding patterns of a progesterone-releasing IUD. In: Hefnawi, F. & Segal S.J., ed. *Analysis of intrauterine contraception*, Amsterdam, North-Holland, 1975, pp. 185-198.
23. WHO SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION. *Ninth annual report*. Geneva, World Health Organization, 1980.
24. WHO TASK FORCE ON INTRAUTERINE DEVICES FOR FERTILITY REGULATION. The Alza T IPCS52, a longer acting progesterone IUD: safety and efficacy compared to the TCu 220C and Multiload 250 in two randomized multicentre trials. *Clinical reproduction and fertility*, **2**: 113-128 (1983).
25. SIVIN, I. ET AL. Intrauterine contraception with copper and with levonorgestrel: A randomized study of the TCu 380Ag and levonorgestrel 20 mg/day devices. *Contraception*, **30**: 443-456 (1984).
26. NILSSON, C.G. ET AL. Clinical performance of a new levonorgestrel-releasing intrauterine device. A randomized comparison with a Nova-T copper device. *Contraception*, **25**: 345-356 (1982).
27. NILSSON, C.G. Comparative quantitation of menstrual blood loss with a d-norgestrel-releasing IUD and a Nova-T-copper device. *Contraception*, **15**: 379-387 (1977).
28. NILSSON, C.G. ET AL. Endometrial morphology of women using a D-norgestrel-releasing intrauterine device. *Fertility and sterility*, **29**: 397-401 (1978).
29. NILSSON, C.G. ET AL. Serum lipids and high-density-lipoprotein cholesterol in women on long-term sustained low-dose IUD treatment with levonorgestrel. *International journal of fertility*, **26**: 135-137 (1981).
30. HEIKKILA, M. & LUUKKAINEN, T. Duration of breast feeding and development of children after insertion of a levonorgestrel-releasing intrauterine contraceptive device. *Contraception*, **25**: 279-292 (1982).
31. SHAW, S.T. ET AL. Morphologic studies on IUD-induced metrorrhagia. I. Endometrial changes and clinical correlations. *Contraception*, **19**: 47-61 (1979).
32. SHAW, S.T. & MACAULAY, L.K. Morphologic studies on IUD-induced metrorrhagia. II. Surface changes of the endometrium and microscopic localization of bleeding sites. *Contraception*, **19**: 63-80 (1979).
33. BARTELMEZ, G.W. The human uterine mucus membrane during menstruation. *American journal of obstetrics and gynecology*, **21**: 623-643 (1931).
34. MISHELL, D.R. JR. ET AL. The intrauterine device: a bacteriologic study of the endometrial cavity. *American journal of obstetrics and gynecology*, **96**: 119-126 (1966).
35. MOYER, D.L. & MISHELL, D.R. JR. Reactions of human endometrium to the intrauterine foreign body. II. Long-term effects on the endometrial histology and cytology. *American journal of obstetrics and gynecology*, **111**: 66-80 (1971).
36. EL SAHWI, S. & MOYER, D.L. Antifertility effects of the intrauterine foreign body. *Contraception*, **2**: 1-28 (1970).
37. SEDLIS, A. & REYNIAC, J.V. Endometrial leukocytes in patients using intrauterine contraceptive devices. *American journal of obstetrics and gynecology*, **108**: 1209-1212 (1970).

38. SAGIROGLU, N. & SAGIROGLU, E. Biologic mode of action of Lippes-loop in intrauterine contraception. *American journal of obstetrics and gynecology*, **106**: 505-515 (1970).
39. KAR, A.B. ET AL. Effect of an intrauterine contraceptive device on biochemical composition of uterine fluid. *American journal of obstetrics and gynecology*, **101**: 966-970 (1968).
40. SHEPPARD, B.L. & BONNAR, J. The response of endometrial blood vessels to intrauterine contraceptive devices: an electron microscopic study. *British journal of obstetrics and gynaecology*, **87**: 143-154 (1980).
41. CUADROS, A. & HIRSCH, J.G. Copper on intrauterine devices stimulates leukocyte exudation. *Science*, **175**: 175-176 (1972).
42. HAGENFELDT, K. Intrauterine contraception with the copper-T device. 4. Influence on protein and copper concentrations and enzyme activities in uterine washings. *Contraception*, **6**: 219-230 (1972).
43. CROXATTO, H. B. ET AL. Studies on sperm migration in the human female genital tract. In: Thibault, C. & Hafez, E. S. E., ed. *Transport, survie et pouvoir fécondant des spermatozoïdes chez les vertébrés*. Paris, INSERM, 1973, pp. 165-182.
44. HAGENFELDT, K. ET AL. Biochemical and morphological changes in the human endometrium by the Progestasert device. *Contraception*, **16**: 183-197 (1977).
45. MARTINEZ-MANAUTOU, J. ET AL. Endometrial morphology in women exposed to uterine systems releasing progesterone. *American journal of obstetrics and gynecology*, **121**: 175-179 (1975).
46. JOHANNISSON, E. ET AL. The effect of intrauterine progesterone on the DNA-content in isolated human endometrial cells. *Acta cytologica*, **21**: 441-446 (1977).
47. SPILLMAN, C.H. & DUBY, R.T. Prostaglandin mediated luteolytic effect of an intrauterine device in sheep. *Prostaglandins*, **2**: 159-165 (1972).
48. MYATT, L. ET AL. Macrophages on intrauterine contraceptive devices produce prostaglandins. *Nature*, **257**: 227-228 (1975).
49. SAMUELSSON, B. Leukotrienes and related compounds. *Advances in prostaglandin thromboxane leukotriene research*, **15**: 1-9 (1985).
50. GREEN, K. & HAGENFELDT, K. Prostaglandins in the human endometrium. *American journal of obstetrics and gynecology*, **122**: 611-614 (1975).
51. HILLIER, K. & KASONDE, J.M. Prostaglandin E and F concentrations in human endometrium after insertion of intrauterine contraceptive devices. *Lancet*, **1**: 15-16 (1976).
52. SCOMMEGNA, A. ET AL. Endometrial prostaglandin F content in women wearing non-medicated or progestin-releasing intrauterine devices. *Fertility and sterility*, **29**: 500-504 (1978).
53. KELLY, R.W. & ABEL, M.H. Copper and zinc inhibit the metabolism of prostaglandin by the human uterus. *Biology of reproduction*, **28**: 883-889 (1983).
54. PEPLOV, R.V. & HURST, P.R. Prostaglandin synthesis by rat uterine homogenate in the presence of copper ions, and the effects of indomethacin and salicylic acid. *Prostaglandin and leukotriene medicine*, **21**: 15-22 (1986).
55. MORTON, H. ET AL. Early pregnancy factor: biology and clinical significance. In: Grudzinkas, J., Teisner, B. & Seppala, M., ed. *Pregnancy proteins: biology, chemistry and clinical application*. Sydney, Academic Press, 1982, pp. 391-395.
56. SMART, Y.C. ET AL. Early pregnancy factor as a monitor for fertilization in women wearing intrauterine devices. *Fertility and sterility*, **37**: 201-204 (1982).
57. CROXATTO, H. A mode of action of IUDs. *Fertility and sterility*, **39**: 114 (1983).

58. SINOSICH, M.J. ET AL. Placental proteins in the diagnosis and evaluation of the "elusive" early pregnancy. *Obstetrical and gynecological survey*, **40**: 273-282 (1985).
59. THOMSON, A.W. ET AL. Rosette inhibition levels during early human gestation. *Journal of reproductive immunology*, **2**: 263-268 (1980).
60. COOPER, D.W. & AITKEN, R.J. Failure to detect altered rosette inhibition titres in human pregnancy serum. *Journal of reproduction and fertility*, **61**: 241-245 (1981).
61. KOSAKA, T. ET AL. Early detection of implantation using a radio-immunoassay specific for human chorionic gonadotrophin. *Journal of clinical endocrinology and metabolism*, **36**: 622-624 (1973).
62. BELING, C.G. ET AL. Demonstration of gonadotrophin during the second half of the cycle in women using intrauterine contraception. *American journal of obstetrics and gynecology*, **125**: 855-858 (1976).
63. LANDESMAN, R. ET AL. Detection of human chorionic gonadotropin in blood of regularly bleeding women using copper intrauterine contraceptive devices. *Fertility and sterility*, **27**: 1062-1066 (1976).
64. SHARPE, R.M. ET AL. Absence of hCG-like activity in the blood of women fitted with intrauterine contraceptive devices. *Journal of clinical endocrinology and metabolism*, **45**: 496-499 (1977).
65. KLEIN, T.A. & MISHELL, D.R. JR. Absence of circulating gonadotropin in wearers of intrauterine contraceptive devices. *American journal of obstetrics and gynecology*, **129**: 626-628 (1977).
66. AUBERT, J.M. ET AL. Assessment of human chorionic gonadotropin (hCG) levels during luteal phase in women using intrauterine contraception. *Contraception*, **26**: 557-560 (1977).
67. SEGAL, S.J. ET AL. Absence of chorionic gonadotropin in sera of women who use intrauterine devices. *Fertility and sterility*, **44**: 214-218 (1985).
68. NILSSON, C.G. & LÄHTEENMÄKI, P. Fertilization in women with intrauterine devices. *Lancet*, **2**: 1126 (1977).
69. SHALIT, A. ET AL. Human chorionic gonadotropin in intrauterine device users. *International journal of fertility*, **25**: 134-136 (1980).
70. NILSSON, C.G. ET AL. Detection of beta subunit hCG in plasma of IUD users as an indication of frequency of conception. *International journal of fertility*, **24**: 134-137 (1979).
71. WILCOX, A.J. ET AL. Measuring early pregnancy loss: laboratory and field methods. *Fertility and sterility*, **44**: 366-374 (1985).
72. MOYER, D.L. ET AL. Sperm distribution and degradation in the human female reproductive tract. *Obstetrics and gynecology*, **35**: 831-840 (1970).
73. SAGIROGLU, N. Phagocytosis of spermatozoa in the uterine cavity of women using intrauterine device. *International journal of fertility*, **16**: 1-14 (1971).
74. SETTLAGE, D.S. ET AL. Sperm transport from the external cervical os to the Fallopian tubes in women: a time and quantitation study. *Fertility and sterility*, **24**: 655-661 (1973).
75. TREDWAY, D.R. ET AL. Effect of intrauterine devices on sperm transport in the human being: Preliminary report. *American journal of obstetrics and gynecology*, **123**: 734-735 (1975).
76. EL-HABASHI, M. ET AL. Effect of Lippes loop on sperm recovery from human Fallopian tubes. *Contraception*, **22**: 549-555 (1980).

77. KOCH, U.J. Sperm migration in the human female genital tract with and without intrauterine devices. *Acta Europea fertilitatis*, **2**: 33–60 (1980).
78. MORGENSTERN, L.L. ET AL. Observations on spermatozoa in the human uterus and oviducts in the chronic presence of intrauterine devices. *American journal of obstetrics and gynecology*, **96**: 114–118 (1966).
79. CROXATTO, H.B. The duration of egg transport and its regulation in mammals. In: Coutinho, E.M. & Fuchs, F., ed. *Physiology and genetics of reproduction*, Part B. New York, Plenum Publishing Corporation, 1974, pp. 159–166.
80. ORTIZ, M.E. & CROXATTO, H.B. The mode of action of IUDs. *Contraception* (in press, 1987).
81. SUNG, S. ET AL. Comparative clinical experience with 3 IUDs, TCu 380 Ag, TCu 220 C and Mahua ring in Tianjin, People's Republic of China. *Contraception*, **29**: 229–239 (1984).
82. SUNG, S. ET AL. Two-year comparative clinical experience with three IUDs in China. In: Zatuchni, G.I. et al. ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 109–114.
83. TIETZE, C. & LEWIT, S. Comparison of the Copper-T and Loop D: A research report. *Studies in family planning*, **3**: 277–278 (1972).
84. WHO TASK FORCE ON INTRAUTERINE DEVICES FOR FERTILITY REGULATION. IUD insertion following termination of pregnancy: A clinical trial of the TCu 220 C, Lippes Loop D and Copper 7. *Studies in family planning*, **14**: 99–108 (1983).
85. WHO TASK FORCE ON INTRAUTERINE DEVICES FOR FERTILITY REGULATION. IUD insertion following spontaneous abortion. A clinical trial of the TCu 220 C, Lippes Loop D, and Copper 7. *Studies in family planning*, **14**: 109–114 (1983).
86. JAIN, A.K. Comparative performance of three types of IUDs in the United States. In: Hefnawi, E.F. & Segal, S.J., ed. *Analysis of intrauterine contraception*. Amsterdam/New York, North-Holland/American Elsevier, 1975, pp. 3–16.
87. HUTAPEA, H. ET AL. The acceptability of the Copper 7, Multiload 250 and Copper T 220 C intrauterine devices *Contraceptive delivery systems*, **5**: 11–16 (1984).
88. GOH, T.H. ET AL. A multicenter randomized comparative investigation of ML Cu 250, TCu 220 C and Cu 7 IUDs. *Advances in contraceptive delivery systems*, Monograph I: 126–129 (1985).
89. GOH, T.H. ET AL. A randomized comparative evaluation of the Copper 7, Multiload Copper 250 and T Copper 220 C IUDs. *Contraception*, **27**: 75–84 (1983).
90. SIVIN, I. & STERN, J. Long-acting, more effective Copper T IUDs: A summary of U.S. experience, 1970–1975. *Studies in family planning*, **10**: 263–281 (1979).
91. LUUKKAINEN, T. ET AL. Five years' experience of intrauterine contraception with the Nova-T and the Copper-T-200. *American journal of obstetrics and gynecology*, **147**: 885–892 (1983).
92. COLE, L.P. ET AL. Comparative copper IUD trials. In: Zatuchni, G.I., Goldsmith, A. & Sciarra, J.J. ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 95–100.
93. COLE, L.P. ET AL. An evaluation of the TCu 380 Ag and the Multiload Cu 375. *Fertility and sterility*, **43**: 214–217 (1985).
94. WHO SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION. *Intrauterine devices*. 13th Annual Report, Geneva, World Health Organization, 1984, pp. 40–44.

95. SIVIN, I. ET AL. Intrauterine contraception with copper and with levonorgestrel: A randomized study of the TCU 380 Ag and levonorgestrel 20 mcg/day devices. *Contraception*, **30**: 443-456 (1984).
96. SIVIN, I. ET AL. Two years of intrauterine contraception with Copper or with Levonorgestrel: A randomized comparison of the TCU 380 Ag and Levonorgestrel 20 mcg/day devices (in press, 1987).
97. WORLD HEALTH ORGANIZATION TASK FORCE ON INTRAUTERINE DEVICES FOR FERTILITY REGULATION: Microdose intrauterine levonorgestrel for contraception. *Contraception* (in press).
98. HIRVONEN, E. & KAIVOLA, S. Fincoid-350 IUD. In: Zatuchni, G.I., Goldsmith, A. & Sciarra, J.J., ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 251-262.
99. SAURE, A. ET AL. Comparative performance of Fincoid, Nova-T and ML 375 IUDs. In: Zatuchni, G.I., Goldsmith, A. & Sciarra, J.J., ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 104-108.
100. WHO SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION. *Intrauterine devices*. 12th Annual Report, Geneva, World Health Organization, 1983, pp. 40-45.
101. PIZARRO, E. ET AL. Comparative study of the progesterone T (65 µg daily) and Copper 7 IUD. *Contraception*, **16**: 313-323 (1977).
102. LARSEN, S. ET AL. Comparison between two IUDs: Progestasert and TCU 200. *Contraceptive delivery systems*, **2**: 281-286 (1981).
103. FYLLING, P. & FAGERHOL, M. Experience with two different medicated intrauterine devices: a comparative study of the Progestasert and Nova-T. *Fertility and sterility*, **31**: 138-141 (1979).
104. BRENNER, P.F. ET AL. Clinical study of a progesterone-releasing intrauterine contraceptive device. *American journal of obstetrics and gynecology*, **121**: 704-706 (1975).
105. GAO, J. ET AL. A randomized comparative clinical evaluation of the steel ring, the VCU 200 and TCU 220 C IUDs. *Contraception*, **33**: 443-454 (1986).
106. LADEHOFF, P. ET AL. A comparison of two IUDs Multiload Cu 250 and Copper T 200. *Contraceptive delivery systems*, **4**: 9-13 (1983).
107. BATAR, I. ET AL. Randomized use-effectiveness comparison of Nova T and Copper T 200—Preliminary report. *Contraceptive delivery systems*, **4**: 49 (1983).
108. THIERY, M. ET AL. Comparative performance of two copper-wired IUDs (ML Cu 250 and T Cu 200). Immediate postpartum and interval insertion. *Contraceptive delivery systems*, **1**: 27-35 (1980).
109. KOZUH, M. ET AL. A randomized comparative trial of Nova-T and TCU 200 Ag in Yugoslavia. *Advances in contraception*, **2**: 31-36 (1986).
110. ANDOLSEK, L. ET AL. A comparative study of the Nylon T and Copper T 200. *Contraceptive delivery systems*, **4**: 297-300 (1983).
111. ROY, S. ET AL. Comparison of three different models of the Copper T intrauterine contraceptive device. *American journal of obstetrics and gynecology*, **134**: 568-574 (1979).
112. DIAZ, J. ET AL. Randomized clinical study of the T Cu-380 A and the Lippes Loop C, in Campinas, Brazil. *Contraception*, **26**: 221-228 (1982).
113. NILSSON, C.G. ET AL. Intrauterine contraception with levonorgestrel: A comparative randomised clinical performance study. *Lancet*, **1**: 577-580 (1981).

114. NILSSON, C.G. ET AL. Two years' experience with two levonorgestrel-releasing intrauterine devices and one copper-releasing intrauterine device. A randomized comparative performance study. *Fertility and sterility*, **39**: 187-192 (1983).
115. MCCARTHY, T. ET AL. Comparative studies of IUDs in Singapore. *Contraceptive delivery systems*, **4**: 219-225 (1983).
116. DE CASTRO, A. & ANGUIANO, J.M. Comparative performance of two copper IUDs: Nova-T and MLCu 375. *Advances in contraception*, **2**: 155-159 (1986).
117. KIVIJARVI, A. Randomized comparison of multiloop standard short devices. *Contraceptive delivery systems*, **4**: 289-292 (1983).
118. LIM, L.S. ET AL. Post-abortion insertion of MLCu 250 and MLCu 375—A comparative trial. *Contraception*, **31**: 471-477 (1985).
119. TIETZE, C. & LEWIT, S. Evaluation of intrauterine devices: ninth progress report of the Cooperative Statistical Program. *Studies in family planning*, **1**: 1-40 (1970).
120. LUUKKAINEN, T. ET AL. Five years' experience with levonorgestrel-releasing IUDs. *Contraception*, **33**: 139-148 (1986).
121. THIERY, M. ET AL. A decade of experience with the TCu 220 C. *Advances in contraception*, **1**: 313-318 (1985).
122. PEI-ZHU, Z. Five years experience with the Copper T 200 in Shanghai. *Contraception*, **22**: 561-571 (1980).
123. ZIPPER, J. ET AL. Six-year continuation rates for Cu-T-200 users. *Journal of reproductive medicine*, **18**: 95-97 (1977).
124. ZIPPER, J. ET AL. Four years' experience with the Cu 7 200 device—endouterine copper in fertility control. *Contraception*, **13**: 7-15 (1976).
125. GOBEAUX-CASTADOT, M.-J. ET AL. Five years' clinical experience with the Copper 7 intrauterine device. *International journal of gynaecology and obstetrics*, **19**: 181-192 (1981).
126. SIVIN, I. & TATUM, H.J. Four years of experience with the TCu 380 A intrauterine contraceptive device. *Fertility and sterility*, **36**: 159-163 (1981).
127. VAN DER PAS, H. ET AL. Six years' experience with the TCu 220 C intrauterine contraceptive device. *Contraceptive delivery systems*, **1**: 1-10 (1980).
128. THIERY, M. ET AL. The MLCu 375 intrauterine contraceptive device. *Advances in contraception*, **1**: 37-44 (1985).
129. WHITE, M.K. ET AL. Intrauterine device termination rates and the menstrual cycle day of insertion. *Obstetrics and gynecology*, **55**: 220-224 (1980).
130. EDELMAN, D. ET AL. Timing of the IUD insertion. *Contraception*, **19**: 449-454 (1979).
131. ROSENFELD, A.G. & CASTADOT, R.G. Early postpartum and immediate postabortion intrauterine contraceptive device insertion. *American journal of obstetrics and gynecology*, **118**: 1104-1114 (1974).
132. HEARTWELL, S.F. & SCHLESSELMAN, S. Risk of uterine perforation among users of intrauterine devices. *Obstetrics and gynecology*, **61**: 31-36 (1983).
133. CHI, I.-C. & KELLY, E. Is lactation a risk factor of IUD- and sterilisation-related uterine perforations?—A hypothesis. *International journal of gynaecology and obstetrics*, **22**: 315-317 (1984).
134. COLE, L.P. ET AL. Effects of breast feeding on IUD performance. *American journal of public health*, **73**: 384-388 (1983).
135. WORLD HEALTH ORGANIZATION SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION.

- Comparative multicentre trial of three IUDs inserted immediately following delivery of the placenta. *Contraception*, **22**: 9–18 (1980).
136. THIERY, M. ET AL. Immediate postplacental IUD insertion: the expulsion problem. *Contraception*, **31**: 331–349 (1985).
 137. CHI, I.-C. ET AL. Expulsions in immediate postpartum insertions of Lippes Loop D and Copper T IUDs and their counterpart Delta devices—An epidemiological analysis. *Contraception*, **32**: 119–134 (1985).
 138. THIERY, M. ET AL. Immediate postplacental IUD insertion: a randomized trial of sutured (Lippes Loop and TCu 220 C) and non-sutured (TCu 220 C) models. *Contraception*, **28**: 299–313 (1983).
 139. LIU, B.H. ET AL. Intrauterine contraceptive device insertion with suture fixation at Cesarean section. *Chinese medical journal*, **96**: 141–144 (1983).
 140. CHI, L.-C. ET AL. Post-Cesarean section insertion of intrauterine devices. *American journal of public health*, **74**: 1281–1282 (1984).
 141. CHI, L.-C. ET AL. IUD insertion at Cesarean section—the Chinese experience. *Advances in contraception*, **2**: 145–153 (1986).
 142. VAN KETS, H. ET AL. IUD insertion during Cesarean section. *Advances in contraception*, **1**: 337–340 (1985).
 143. ANDOLSEK, L. Experiences with immediate post-abortion insertion of the IUD. In: Lewit, S., ed. *Abortion techniques and services*. International Congress Series No. 225. Amsterdam, Excerpta Medica, 1972, pp. 63–67.
 144. LARSSON, B. & HAMBERGER, L. Insertion of copper-7 IUDs in connection with induced abortion during first trimester. *Contraception*, **12**: 69–76 (1975).
 145. NYGREN, K.-G. & JOHANSSON, E.D.B. Postabortion insertion of the intrauterine copper T (TCu 200). In: Hefnawi, F. & Segal, S.J., ed. *Analysis of intrauterine contraception*. Amsterdam, North-Holland, 1975, pp. 115–118.
 146. ROSS, J.A. & KWON, H.Y. Post-abortal immediate IUD insertion: further experience and a controlled comparison of three devices. *Contraception*, **17**: 237–246 (1978).
 147. TIMONEN, H. & LUUKKAINEN, T. The use-effectiveness of the Copper-T-200 in a simulated field trial. *Contraception*, **9**: 1–13 (1974).
 148. NEWTON, J.R. ET AL. Immediate post-termination insertion of Copper 7 and Dalkon Shield intrauterine contraceptive devices. *Journal of obstetrics and gynaecology of the British Commonwealth*, **81**: 389–392 (1974).
 149. NIELSEN, N.C. ET AL. Three years of experience after post-abortal insertion of NOVA-T and Copper-T-200. *Acta obstetrica et gynecologica Scandinavica*, **63**: 261–264 (1984).
 150. QUERIDO, L. ET AL. IUD insertion following induced abortion. *Contraception*, **31**: 603–610 (1985).
 151. VIEL, B. & LUCERO, S. An analysis of three years' experience with intrauterine devices among women in the western area of the city of Santiago, July 1 1964 to June 30 1967. *American journal of obstetrics and gynecology*, **106**: 765–775 (1970).
 152. FAUNDES, A. ET AL. Post-abortion insertion of the copper T-200 and Lippes Loop—a comparative study. *Contraception*, **8**: 583–588 (1973).
 153. MISHALL, D.R. Pregnancy related complications and bleeding problems with IUDs. In: Sciarra, J. et al., ed. *Risks, benefits and controversies in fertility control*. Hagerstown, Harper & Row, 1978, pp. 428–434.
 154. LEHFELDT, H.J. ET AL. Ovarian pregnancy and the intrauterine device. *American journal of obstetrics and gynecology*, **108**: 1005–1009 (1970).

155. RUBIN, G.L. ET AL. Ectopic pregnancy in the United States: 1970 through 1978. *Journal of the American Medical Association*, **249**: 1725–1729 (1983).
156. BERAL, V. An epidemiological study of recent trends in ectopic pregnancy. *British journal of obstetrics and gynaecology*, **82**: 775–782 (1975).
157. ERKKOLA, R. & LINKKO, P. Intrauterine device and ectopic pregnancy. *Contraception*, **16**: 569–574 (1977).
158. MEIRIK, O. Ectopic pregnancy during 1961–78 in Uppsala County, Sweden. *Acta obstetrica gynecologica Scandinavica*, **60**: 545–548 (1981).
159. SIVIN, I. IUD-associated ectopic pregnancies, 1974 to 1984. In: Zatuchni, G.I. et al. ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 340–353.
160. TATUM, H.J. & SCHMIDT, F.K. Contraceptive and sterilization practices and extrauterine pregnancy. A relative perspective. *Fertility and sterility*, **28**: 407–421 (1977).
161. VESSEY, M. ET AL. A long-term follow-up study of women using different methods of contraception: an interim report. *Journal of biosocial science*, **8**: 373–427 (1976).
162. ORY, H.W. & WOMEN'S HEALTH STUDY. Ectopic pregnancy and intrauterine contraceptive devices: new perspectives. *Obstetrics and gynecology*, **57**: 137–144 (1981).
163. WORLD HEALTH ORGANIZATION'S SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION. A multinational case-control study of ectopic pregnancy. *Clinical reproductive fertility*, **3**: 131–143 (1985).
164. GRAY, R.H. A case-control study of ectopic pregnancy in developed and developing countries. In: Zatuchni, G.I. et al., ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 354–364.
165. SIVIN, I. IUDs and ectopic pregnancy. *Studies in family planning*, **14**: 57–63 (1983).
166. JAIN, A.K. Non-medicated intrauterine devices: review and assessment. In: Diczfalusy, E., ed. *WHO Symposium on Advances in Fertility Regulation*. Copenhagen, Scriptor, 1977, pp. 361–379.
167. VESSEY, M.P. ET AL. Risk of ectopic pregnancy and duration of use of an intrauterine device. *Lancet*, **2**: 501–503 (1979).
168. EDELMAN, D.A. & PORTER, C.W. The intrauterine device and ectopic pregnancy. *Advances in contraception*, **2**: 55–63 (1986).
169. HALLATT, J.C.G. Ectopic pregnancy associated with the intrauterine device: a study of seventy cases. *American journal of obstetrics and gynecology*, **125**: 754–758 (1976).
170. TUOMIVAARA, L. ET AL. Ectopic pregnancy—an analysis of the etiology, diagnosis and treatment in 552 cases. *Archives of gynecology*, **237**: 135–139 (1986).
171. WECKSTEIN, L.N. Current perspectives on ectopic pregnancy. *Obstetrical and gynecological survey*, **40**: 259–272 (1985).
172. WESTRÖM, L. Incidence, prevalence, and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. *American journal of obstetrics and gynecology*, **138**: 880–92 (1980).
173. MARDH, P.-A. An overview of infectious agents of salpingitis, their biology and recent advances in methods of detection. *American journal of obstetrics and gynecology*, **138**: 933–951 (1980).

174. SWEET, R.L. & GIBBS, R.S. Pelvic inflammatory disease. In: Sweet, R.L. & Gibbs, R.S., ed. *Infectious disease of the female genital tract*. Baltimore, Williams & Wilkins, 1985, pp. 53–77.
175. LEDGER, W. Micro-organisms that cause infection. In: Ledger, W., ed. *Infection in the female*. Philadelphia, Lea & Febiger, 1986, pp. 9–34.
176. MARDH, P.-A. ET AL. Antibodies to *Chlamydia trachomatis*, *Mycoplasma hominis* and *Neisseria gonorrhoeae* in sera of patients with acute salpingitis. *British journal of venereal diseases*, **57**: 125–129 (1981).
177. ESCHENBACH, D. ET AL. Polymicrobial etiology of acute pelvic inflammatory disease. *New England journal of medicine*, **293**: 166–171 (1975).
178. SWEET, R.L. & GIBBS, R.S. Pelvic abscess. In: Sweet, R.L. & Gibbs, R.S., ed. *Infectious disease of the female genital tract*. Baltimore, Williams & Wilkins, 1985, pp. 161–180.
179. BIELUCH, V.M. & TALLY, F.P. Pathology of abscess formation. In: Charles, D., ed. *Clinics in obstetrics and gynaecology*, Vol 10. London, W.B. Saunders Company Ltd, 1982, pp. 93–104.
180. TUNNONEN, R. ET AL. Chlamydial serology in infertile women by immunofluorescence. *Fertility and sterility*, **31**: 656–659 (1979).
181. GUMP, D.W. ET AL. Evidence of prior pelvic inflammatory disease and its relationship to *Chlamydia trachomatis* antibody and intrauterine device use in infertile women. *American journal of obstetrics and gynecology*, **146**: 153–159 (1983).
182. WESTRÖM, L. & MARDH, P.-A. Chlamydial salpingitis. *British medical bulletin*, **39**: 145–150 (1983).
183. ELSTEIN, M. Pelvic inflammation and intrauterine contraceptive devices. *Proceedings of the Royal Society of Medicine*, **60**: 397 (1967).
184. BUCHMAN, M.J. A study of the intrauterine contraceptive device with and without an extracervical appendage or tail. *Fertility and sterility*, **21**: 348–355 (1979).
185. LEHFELDT, H. Comparative study of two intra-uterine contraceptive devices (abstract). In: Segal, S.J. et al., ed. *Intra-uterine contraception*, International Congress Series No. 86. Excerpta Medica, Amsterdam, 1965, p. 237.
186. WILLSON, J.R. ET AL. The Margulies intrauterine contraceptive device. *American journal of obstetrics and gynecology*, **92**: 62–70 (1965).
187. SPARKS, R.A. ET AL. Bacteriological colonisation of uterine cavity: role of tailed intrauterine contraceptive device. *British medical journal*, **282**: 1189–1191 (1981).
188. LEE, N.C. ET AL. Type of intrauterine device and the risk of pelvic inflammatory disease. *Obstetrics and gynecology*, **62**: 1–6 (1983).
189. MISHILL, D.R. ET AL. The intrauterine device: a bacteriological study of the endometrial cavity. *American journal of obstetrics and gynecology*, **96**: 119–126 (1966).
190. SENANAYAKE, P. & KRAMER, D.G. Contraception and the etiology of pelvic inflammatory disease: new perspectives. *American journal of obstetrics and gynecology*, **138**: 852–860 (1980).
191. STONE, K.M. ET AL. Personal protection against sexually transmitted diseases. *American journal of obstetrics and gynecology*, **155**: 180–188 (1986).
192. VESSEY, M.P. ET AL. Pelvic inflammatory disease and the intrauterine device: findings in a large cohort study. *British medical journal*, **282**: 855–857 (1981).

193. KAUFMAN, D.W. ET AL. The effect of different types of intrauterine devices on the risk of pelvic inflammatory disease. *Journal of the American Medical Association*, **250**: 759–762 (1983).
194. PAAVONEN, J. & VESTERINEN, E. Intrauterine contraceptive device use in patients with acute salpingitis. *Contraception*, **22**: 107–114 (1980).
195. BURKMAN, R. T. & WOMEN'S HEALTH STUDY. Association between intrauterine device and pelvic inflammatory disease. *Obstetrics and gynecology*, **57**: 269–276 (1981).
196. WITTOONPANICH, P. ET AL. PID associated with fertility regulating agents. *Contraception*, **30**: 1–21 (1984).
197. CRAMER, D.W. ET AL. Tubal infertility and the intrauterine device. *New England journal of medicine*, **312**: 937–941 (1985).
198. DALING, J.R. ET AL. Primary tubal infertility in relation to the use of an intrauterine device. *New England journal of medicine*, **312**: 937–941 (1985).
199. JACOBSON, L. & WESTRÖM, L. Objectivized diagnosis of acute pelvic inflammatory disease. *American journal of obstetrics and gynecology*, **105**: 1088–1098 (1969).
200. FAULKNER, W.L. & ORY, H.W. Intrauterine devices and acute pelvic inflammatory disease. *Journal of the American Medical Association*, **235**: 1851–1853 (1976).
201. BURKMAN, R.T. Intrauterine device use and the risk of pelvic inflammatory disease. *American journal of obstetrics and gynecology*, **138**: 861–863 (1980).
202. STRUTHERS, B.J. Pelvic inflammatory disease, intrauterine contraception, and the conduct of epidemiologic studies. *Advances in contraception*, **1**: 63–76 (1985).
203. SNOWDEN, R. & PEARSON, B. Pelvic infection: a comparison of the Dalkon Shield and three other intrauterine devices. *British medical journal*, **88**: 1570–1573 (1984).
204. WESTRÖM, L. Effect of acute pelvic inflammatory disease on fertility. *American journal of obstetrics and gynecology*, **121**: 707–713 (1975).
205. WESTRÖM, L. ET AL. Infertility after acute salpingitis: Results of treatment with different antibiotics. *Current therapeutic research*, **26**: 752–759 (1979).
206. WESTRÖM, L. Reproductive events after acute salpingitis. In: *Sexually transmitted diseases, status report*. NIAID STD Study Group. Washington, DC, NIH Publications No. 81–2213, 1980, pp. 43–54.
207. WESTRÖM, L. Reproductive events after acute salpingitis. *British journal of clinical practice*, Suppl. **17**: 17–20 (1982).
208. SVENSSON, L. ET AL. Infertility after acute salpingitis with special reference to *Chlamydia trachomatis*. *Fertility and sterility*, **40**: 322–329 (1983).
209. WESTRÖM, L. Influence of sexually transmitted diseases on sterility and ectopic pregnancy. *Acta Europaea fertilitatis*, **16**: 21–24 (1985).
210. EDELMAN, D.A. ET AL. *Intrauterine devices and their complications*. Boston, Hall, 1979.
211. LUUKKAINEN, T. ET AL. Combined and national experience of postmenstrual IUD insertions of Nova-T and Copper-T in a randomized study. *Contraception*, **19**: 11–20 (1979).
212. MYLOTTE, N.J. & LOUDON, N. Interim insertion of Multiload Cu 250 IUCD. *British journal of obstetrics and gynaecology*, Suppl. **4**, 41–42 (1982).
213. TIETZE, C. Contraception with intrauterine devices, 1959–1966. *American journal of obstetrics and gynecology*, **96**: 1043–1054 (1966).

214. LEAN, T.-H. Optimum insertion time for the IUD after delivery. In: *Proceedings of the 8th International Conference, 9-15 April 1967, Santiago, Chile*. International Planned Parenthood Federation, London, 1967, pp. 47-54.
215. RATNAM, S.S. & TOW, S.H. Translocation of the loop. In: Zatzuchni, G.I., ed. *Postpartum family planning. A report on the International Program*, New York, McGraw-Hill, 1970, pp. 63-70.
216. HALL, R.E. A reappraisal of intrauterine contraceptive devices. Prompted by the delayed discovery of uterine perforations. *American journal of obstetrics and gynecology*, **99**: 808-813 (1967).
217. SCUTCHFIELD, F.D. & LONG, W.N. Perforation of the uterus with the Lippes Loop. *Journal of the American Medical Association*, **208**: 2335-2336 (1969).
218. BEASLEY, W.B. The nurse-midwife as a mediator of contraception. *American journal of obstetrics and gynecology*, **98**: 201-207 (1967).
219. OSTERGARD, D.R. & BROEN, E.M. The insertion of intrauterine devices by physicians and paramedical personnel. *Obstetrics and gynecology of New York*, **41**: 257-258 (1973).
220. PASTENE, L. ET AL. IUD insertions by midwives: five years experience in Santiago, Chile. *International journal of gynaecology and obstetrics*, **15**: 84-87 (1977).
221. NEWTON, J.R. ET AL. Nurse specialists in family planning. *British medical journal*, **1**: 950-952 (1976).
222. VAILLANT, H.W. ET AL. Insertion of Lippes Loop by nurse-midwives and doctors. *British medical journal*, **3**: 671-673 (1968).
223. SZOKE, B. & KISS, D. The localization of intrauterine contraceptive devices with B-scan ultrasonic echo technique. *International journal of fertility*, **20**: 220-225 (1975).
224. VAN EYCK, J. ET AL. Grey-scale sonography and the IUD. *Contraception*, **13**: 489-496 (1976).
225. JAIN, A.K. & MOOTS, B. Fecundability following the discontinuation of IUD use among Taiwanese women. *Journal of biosocial science*, **9**: 135-151 (1977).
226. TIETZE, C. Fertility after discontinuation of intrauterine and oral contraception. *International journal of fertility*, **13**: 385-389 (1968).
227. NIELSEN, N.C. ET AL. Return of fertility after removal of Nova T/Copper T 200. *Acta obstetrica et gynecologica Scandinavica* (Suppl. 116), Abstract No. 166, 97 (1985).
228. PYOROLA, T. ET AL. Return of fertility after the removal of Nova T or Copper T 200. *Contraception*, **26**: 113-120 (1982).
229. BELHADJI, H. ET AL. Recovery of fertility after use of the levonorgestrel 200 mcg/d or Copper T 380 Ag intrauterine device. *Contraception*, **34**: 261-267 (1986).
230. RANDIC, L. ET AL. Return to fertility after IUD removal for planned pregnancy. *Contraception*, **32**: 253-259 (1985).
231. VESSEY, M.P. ET AL. Fertility after stopping use of intrauterine contraceptive device. *British medical journal*, **286**: 106 (1983).
232. PARDTHAISONG, T. Return of fertility after use of the injectable contraceptive depoprovera: updated data analysis. *Journal of biosocial sciences*, **16**: 23-34 (1984).
233. NILSSON, C.G. Fertility after discontinuation of levonorgestrel-releasing intrauterine devices. *Contraception*, **25**: 273-278 (1982).

234. ANDOLSEK, L. ET AL. Time to conception after IUD removal: Importance of duration of use, IUD type, pelvic inflammatory disease and age. *International journal of gynaecology and obstetrics*, **24**: 217–223 (1986).
235. VESSEY, M.P. ET AL. Outcome of pregnancy in women using an intrauterine device. *Lancet*, **1**: 495–498 (1974).
236. STEVEN, J.D. & FRASER, I.S. The outcome of pregnancy after failure of an intrauterine contraceptive device. *Journal of obstetrics and gynaecology of the British Commonwealth*, **81**: 282–284 (1974).
237. ALVIOR, G.T. JR. Pregnancy outcome with removal of intrauterine device. *Obstetrics and gynecology*, **41**: 894–896 (1973).
238. TATUM, H.J. ET AL. Management and outcome of pregnancies associated with the Copper T intrauterine contraceptive device. *American journal of obstetrics and gynecology*, **126**: 869–874 (1976).
239. FOREMAN, H. ET AL. Intrauterine device usage and fetal loss. *Obstetrics and gynecology*, **58**: 669–677 (1981).
240. CATES, W. ET AL. The intrauterine device and deaths from spontaneous abortion. *New England journal of medicine*, **295**: 1155–1159 (1976).
241. CATES, W. ET AL. Publicity and the public health: the elimination of IUD-related abortion deaths. *Family planning perspectives*, **9**: 138–140 (1977).
242. OPPENHEIMER, D.D. ET AL. Malignant tumours resulting from embedding plastics in rodents. *Science (New York)*, **116**: 305–307 (1953).
243. COREMAN, P.A. & RICHART, R.M. Uterine epidermoid carcinoma induced in rats by plastic and stainless steel intrauterine devices. In: Sobrero, A. & Lewit, S., ed. *Advances in planned parenthood III*. International Congress Series No. 156. Amsterdam, Excerpta Medica, 1968, pp. 89–91.
244. ROWE, P.J. The intrauterine device: a review of recent advances and controversies. In: Finn, C.A., ed. *Oxford reviews of reproductive biology*, Vol. 2. Oxford, Oxford University Press, 1981, pp. 49–94.
245. HSU, C.T. ET AL. Uterine malignancy developing after a long-term use of IUCDs. *Asia-Oceania journal of obstetrics and gynaecology*, **10**: 347–357 (1984).
246. CASTADOT, M. ET AL. Recognizing malignancy in intrauterine contraceptive device users. *American journal of obstetrics and gynecology*, **136**: 966–969 (1980).
247. OBER, W.B. ET AL. Endometrial morphology and polyethylene devices—a study of 200 endometrial biopsies. *Obstetrics and gynecology*, **32**: 782–793 (1968).
248. FERENCZY, A. Steroid contraception and cervical and ovarian neoplasia. In: Sciarra, J.J., Zatzuchi, G.I. & Speidel, J.J., ed. *Risks, benefits and controversies in fertility control*. Hagerstown, MD, Harper & Rowe, 1978, pp. 194–210.
249. NUTTING, E.F. & MUELLER, M. The effect of a copper intrauterine device during the early stages of pregnancy in the rabbit. *Fertility and sterility*, **26**: 838–843 (1975).
250. CHANG, C.C. & TATUM, H.J. Absence of teratogenicity of intrauterine copper wire in rats, hamsters and rabbits. *Contraception*, **7**: 413–414 (1973).
251. BARLOW, S.M. ET AL. Intrauterine exposure to copper IUDs and prenatal development in the rat. *Journal of reproductive fertility*, **62**: 123–130 (1981).
252. GUILLEBAUD, J. The IUD and congenital abnormality. *British medical journal*, **1**: 1016 (1976).
253. TATUM, H.J. ET AL. Management and outcome of pregnancies associated with the Copper T intrauterine contraceptive device. *American journal of obstetrics and gynecology*, **126**: 869–879 (1976).

254. KOETSAWANG, S. ET AL. Outcome of pregnancy in the presence of intrauterine device. *Acta obstetrica et gynecologica Scandinavica*, **56**: 479–482 (1977).
255. LAYDE, P.M. ET AL. Failed intrauterine device contraception and limb reduction deformities: a case control study. *Fertility and sterility*, **31**: 18–20 (1979).
256. HONORÉ, L.H. The effect of the intrauterine contraceptive device on the prevalence of morphologic abnormalities in human spontaneous abortions. *Contraception*, **21**: 47–52 (1980).
257. HONORÉ, L.H. The negative effect of the IUCD on the occurrence of heteroloidy-correlated abnormalities in spontaneous abortions: an update. *Contraception*, **31**: 253–260 (1985).
258. HALLBERG, L. ET AL. Menstrual blood loss—a population study. *Acta obstetrica et gynecologica Scandinavica*, **45**: 320–351 (1966).
259. COLE, S.K. ET AL. Sources of variation in menstrual blood loss. *Journal of obstetrics and gynaecology of the British Commonwealth*, **78**: 933–939 (1971).
260. HEFNAWI, F. ET AL. Menstrual blood loss with copper IUDs. *Contraception*, **9**: 133–139 (1974).
261. PEDRON, N. ET AL. Valoracion de la cantidad del sangrado menstrual en la mujer mexicana. *Ginecología y obstetricia de Mexico*, **45**: 429–437 (1979).
262. SHAW, S.T. ET AL. Quantitative menstrual and intermenstrual blood loss in women using Lippes Loop and Copper T intrauterine devices. *Contraception*, **21**: 343–352 (1980).
263. TCHAI, B.S. ET AL. Studies on menstrual blood loss and iron nutrition in Korean women. *Korean journal of nutrition*, **13**: 82–91 (1980).
264. GAO, J. ET AL. Menstrual blood loss in healthy Chinese women. *Contraception*, **23**: 591–601 (1981).
265. WAGATSUMA, T. IUDs in Japan. In: Zatuchni, G.I., Goldsmith, A. & Sciarra, J.J., ed. *Intrauterine contraception: advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 243–250.
266. RYBO, G. Menstrual blood loss in relation to parity and menstrual pattern. *Acta obstetrica et gynecologica Scandinavica*, **45**: Suppl. 7, 25–45 (1966).
267. RYBO, G. The IUD and endometrial bleeding. *Journal of reproductive medicine*, **20**: 175–182 (1978).
268. GUILLEBAUD, J. & BONNAR, J. Longer though lighter menstrual and intermenstrual bleeding with copper as compared to inert intrauterine devices. *British journal of obstetrics and gynaecology*, **85**: 707–712 (1978).
269. GUILLEBAUD, J. ET AL. Menstrual blood loss with intrauterine devices. *Lancet*, **1**: 387–390 (1976).
270. SAID, F. ET AL. Menstrual blood loss of multiloop “ML Cu 250” intrauterine device. *Population studies*, **4**: 67–77 (1983).
271. GALLEGOS, A. ET AL. Intrauterine devices and menstrual blood loss. A comparative study of eight devices during the first six months of use. *Contraception*, **17**: 153–161 (1978).
272. GUTTORM, E. Menstrual bleeding with IUCD. *Acta obstetrica et gynecologica Scandinavica*, **50**: 9–16 (1971).
273. ANDRADE, A.T.L. ET AL. Quantitative studies on menstrual blood loss in IUD users. *Contraception* (in press, 1987).
274. HEFNAWI, F. ET AL. Medical intrauterine devices to improve bleeding events. *International journal of gynaecology and obstetrics*, **15**: 79–83 (1977).
275. ISRAEL, R. ET AL. Comparative quantitation of MBL with the Lippes Loop, Dalkon Shield and Copper-T IUDs. *Contraception*, **10**: 63–71 (1974).

276. LARSSON, B. ET AL. Influence of copper IUD on the menstrual blood loss. *Acta obstetrica et gynecologica Scandinavica*, **54**: 315-318 (1975).
277. LIEDHOLM, P. ET AL. Copper IUD. Influence on menstrual blood loss and iron deficiency. *Contraception*, **12**: 317-325 (1975).
278. SNOWDEN, R. *Second progress report: evaluation of Multiload Cu 250*. Institute of Population Studies, University of Exeter, England, 1980.
279. RYBO, G. & BERQVIST, A. Comparison of menstrual blood loss with the Progestasert system and the Cu-T-200: preliminary results. In: Mishell, D.R. & Martinez-Manautou, J., ed. *Proceedings of a Symposium on Clinical Experience with the Progesterone Uterine Therapeutic System*. Princetown, Excerpta Medica, 1978, pp. 106-110.
280. ZABOR, G. ET AL. Clinical experience with the uterine progesterone system (Progestasert). *Contraception*, **13**: 559-569 (1976).
281. NILSSON, C.G. & LUUKKAINEN, T. Improvement of a d-norgestrel-releasing IUD. *Contraception*, **15**: 295-306 (1977).
282. LUUKKAINEN, T. ET AL. Five years experience with levonorgestrel-releasing IUDs. *Contraception*, **33**: 139-148 (1986).
283. ROWE, P.J. ET AL. Comparative bleeding patterns of a progesterone-releasing IUD. In: Hefnawi, F. & Segal, S.J., ed. *Analysis of intrauterine contraception*. North-Holland, Amsterdam, 1975, pp. 185-198.
284. WAN, L.S. ET AL. Effects of the Progestasert on the menstrual patterns, ovarian steroids and endometrium. *Contraception*, **16**: 417-420 (1977).
285. NEWTON, J.R. ET AL. A collaborative study of the progesterone intrauterine device (Progestasert). *Contraception*, **19**: 575-579 (1979).
286. PHARRISS, B.B. ET AL. Progestasert: a uterine therapeutic system for long term contraception. In: Philosophy and clinical efficacy. *Fertility and sterility*, **25**: 915-921 (1974).
287. TEJUJA, S. Clinical significance of hemoglobin levels in users of the IUD. A four year study. *American journal of obstetrics and gynecology*, **110**: 735-738 (1971).
288. RIVERA, R. ET AL. Effect of the Lippes IUD on the circulating levels of hemoglobin, hematocrit, serum iron and iron binding capacity in normal women. *Contraception*, **17**: 195-199 (1978).
289. SHAW, S.T. Studies on pathophysiology of IUD-induced endometrial bleeding. In: Hafez, E.S.E. & van Oss, W.A.A., ed. *Medicated IUDs and polymeric delivery systems. Proceedings of an International Symposium*, Amsterdam, Excerpta Medica, 1979, pp. 27-30 (International Congress Series No. 46).
290. JACOBS, A. & WORWOOD, M. Ferritin in serum: clinical and biochemical implications. *New England journal of medicine*, **292**: 951-956 (1975).
291. BARNETT, M.D. ET AL. Measurement of ferritin in serum by radioimmunoassay. *Journal of clinical pathology*, **31**: 742-748 (1978).
292. GUILLEBAUD, J. ET AL. Plasma ferritin levels as an index of iron deficiency in women using intrauterine devices. *British journal of obstetrics and gynaecology*, **86**: 51-55 (1979).
293. GOH, T.H. ET AL. A longitudinal study of serum iron indices and haemoglobin concentration following copper-IUD insertion. *Contraception*, **22**: 389-395 (1980).
294. FERNANDEZ, X.T. ET AL. The IUD and anaemia: a study of haematocrit. *Contraceptive delivery systems*, **1**: 49-53 (1980).

295. RIVERA, R. ET AL. The use of different hormonal contraceptives and IUDs in anemic women: a six-month follow-up. *Advances in planned parenthood*, **15**: 56-63 (1980).
296. KAR, A.B. & CHANDRA, H. Uterine bleeding in Rhesus monkeys after insertion of an intrauterine device. *Indian journal of experimental biology*, **3**: 269-273 (1965).
297. ISRAEL, R. & DAVIS, H.J. Effect of intrauterine contraceptive devices on the endometrium. *Journal of the American Medical Association*, **195**: 764-768 (1966).
298. WILLSON, J.R. ET AL. The effect of an intrauterine contraceptive device on the histologic pattern of the endometrium. *American journal of obstetrics and gynecology*, **93**: 802-806 (1965).
299. ANCLA, M. ET AL. Aneurysmal microthrombosis associated with intrauterine devices in the human endometrium. An electron microscopic study. *Laboratory investigation*, **17**: 61-70 (1967).
300. APARICIO, S.R. ET AL. Effect of intrauterine contraceptive device on uterine haemostasis: a morphological study. *British journal of obstetrics and gynaecology*, **86**: 314-324 (1979).
301. BONNAR, J. ET AL. Fibrinolytic activity *in utero* and bleeding complications with intrauterine contraceptive devices. *British journal of obstetrics and gynaecology*, **83**: 160-164 (1976).
302. LARSSON, B. ET AL. Increased fibrinolytic activity in the endometrium of patients using copper IUD (Gravigard). *International journal of fertility*, **20**: 77-80 (1975).
303. KASONDE, J.M. & BONNAR, J. Aminocaproic acid and menstrual loss in women using intrauterine devices. *British medical journal*, **4**: 17-19 (1976).
304. FOLEY, M.E. ET AL. Heparin-like activity in uterine fluid. *British medical journal*, **2**: 322-324 (1978).
305. MATHUR, V.S. & CHAUDHURY, R.R. The effect of an intra-uterine plastic device on the mast cell count in the rat uterus. *Journal of reproduction and fertility*, **15**: 135-138 (1968).
306. PARR, E. Histamine content of the rat uterus containing an IUCD. *Journal of reproduction and fertility*, **14**: 321-324 (1967).
307. JONES, R.L. ET AL. Production of 6-oxo-prostaglandin F_{1α} by rat, guinea-pig and sheep uteri *in vitro*. *British journal of pharmacology*, **59**: 436-438 (1977).
308. TOPPOZADA, M.K. Prostaglandins and their inhibitors in IUD-induced bleeding. In: Zatuchni, G.I. et al. ed. *Intrauterine contraception: recent advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 319-334.
309. POYSER, N.L. ET AL. Identification of prostaglandin F₂ released by distension of guinea-pig uterus *in vitro*. *Nature (Lond.)*, **230**: 526-528 (1971).
310. SMITH, S.K. ET AL. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *British journal of obstetrics and gynaecology*, **88**: 434-442 (1981).
311. KELLY, R.W. ET AL. The relationship between menstrual blood loss and prostaglandin production in the human: evidence for increased availability of arachidonic acid in women suffering from menorrhagia. *Prostaglandins and leukotriene medicine*, **16**: 69-78 (1984).
312. WILLIS, A.L. ET AL. Release and actions of prostaglandins in inflammation and fever. Inhibition by anti-inflammatory and anti-pyretic drugs. In: Ramwell,

- P.W. & Pharriss, B.B., ed. *Prostaglandins in cellular biology*. Plenum Press, New York, 1972, pp. 227–235.
313. CHRISTIAENS, G.C.M.L. ET AL. Morphological aspects of menstrual bleeding: possible influences of IUD. In: Hafez, E.S.E. & Van Oss, W.A.A., ed. *Medicated IUDs and polymeric delivery systems. Proceedings of an international symposium*. Abstract No. 43, Amsterdam, 1980.
 314. HASSON, H.M. Uterine geometry and IUD performance. In: Hafez, E.S.E. & Van Oss, W.A.A., ed. *Medicated intrauterine devices, physiological and clinical aspects*. Amsterdam, Martinus Nijhoff, 1980, pp. 11–12.
 315. HASSON, H.M. Clinical studies of the Wing Sound II metrology device. In: Zatuchni, G.I. et al., ed. *Intrauterine contraception: recent advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 126–141.
 316. HEFNAWI, F. ET AL. Fibrinolytic activity of menstrual blood in normal and menorrhagic women wearing the Lippes Loop and Cu T 200. *International journal of gynaecology and obstetrics*, **16**: 400–407 (1979).
 317. MADDOX, I.S. The role of copper in prostaglandin synthesis. *Biochimica et biophysica acta*, **306**: 74–81 (1973).
 318. HAUKKAMAA, M. ET AL. Long-term clinical experience with Levonorgestrel-releasing IUD. In: Zatuchni, G.I. et al., ed. *Intrauterine contraception: recent advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 232–237.
 319. SHAW, S.T. Endometrial histopathology and ultrastructural changes with IUD use. In: Zatuchni, G.I. et al., ed. *Intrauterine contraception: recent advances and future prospects*. Philadelphia, Harper & Row, 1985, pp. 276–296.
 320. LIEDHOLM, P. ET AL. No increase in the fibrinolytic activity of the human endometrium by the progesterone releasing IUD (Progestasert). *Contraception*, **17**: 531–540 (1978).
 321. TAUBER, P.F. ET AL. Hemorrhage induced by intrauterine devices: control by local proteinase inhibition. *Fertility and sterility*, **28**: 1375–1377 (1977).
 322. GENICOT, R. Le traitement des saignements due aux stérilets par un inhibiteur de protéinases. *Revue médicale de Liège*, **33**: 183–185 (1978).
 323. BURNS, J.W. ET AL. Development and evaluation of an inhibitor-releasing matrix for intrauterine devices. *Contraception*, **26**: 521–533 (1982).
 324. TAUBER, P.F. ET AL. Reduced menstrual blood loss by release of an antifibrinolytic agent from intrauterine devices. *American journal of obstetrics and gynecology*, **140**: 322–328 (1981).
 325. RAGAB, M.I. & THOMAS, M.N. The use of Tranexamic acid (AMCA) in IUDs as an antibleeding agent. *International journal of gynaecology and obstetrics*, **14**: 137–141 (1976).
 326. RIVERA, R. ET AL. Sustained intrauterine release of AMCA to reduce menstrual blood loss. *Contraceptive delivery systems*, **5**: 109–115 (1984).
 327. WESTRÖM, L. & BENGSSON, L.P. Effect of Tranexamic acid (AMCA) in menorrhagia with intrauterine contraceptive devices. *Journal of reproductive medicine*, **5**: 154–161 (1970).
 328. HARRISON, R.F. & CAMPBELL, S. A double-blind trial of ethamsylate in the treatment of primary and intrauterine-device menorrhagia. *Lancet*, **2**: 283–285 (1976).
 329. KOVACS, L. & ANNUS, J. Effectiveness of Etamsylate in intrauterine device menorrhagia. *Gynecologic and obstetric investigation*, **9**: 161–165 (1978).
 330. ANDERSON, A.B.M. ET AL. Reduction of menstrual blood loss by prostaglandin synthetase inhibitors. *Lancet*, **1**: 744–766 (1976).

331. JAKUBOWICZ, D.L. & WOOD, C. The use of the prostaglandin synthetase inhibitor mefenamic acid in the treatment of menorrhagia. *Australian and New Zealand journal of obstetrics and gynaecology*, **18**: 135–138 (1978).
332. DAMARAWY, H.A. & TOPPOZADA, M.K. Control of bleeding due to IUDs by a prostaglandin synthesis inhibitor. *International research communications series: obstetrics and gynaecology*, **4**: 5–7 (1976).
333. TOPPOZADA, M.K. ET AL. Control of IUD induced bleeding by three non-steroidal anti-inflammatory drugs. *Contraceptive delivery systems*, **3**: 117–125 (1982).
334. GUILLEBAUD, J. ET AL. Reduction by mefenamic acid of increased menstrual blood loss with intrauterine contraception. *British journal of obstetrics and gynaecology*, **85**: 53–62 (1978).
335. DAVIES, A.J. ET AL. Reduction by Naproxen of excessive menstrual bleeding in women using intrauterine devices. *Obstetrics and gynaecology*, **57**: 74–78 (1981).
336. RYBO, G. ET AL. Naproxen in menorrhagia. *Lancet*, **1**: 608–609 (1981).
337. YLIKORKALA, O. & VIINIKKA, L. Comparison between antifibrinolytic and anti-prostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices. *British journal of obstetrics and gynaecology*, **90**: 78–83 (1983).
338. ROY, S. & SHAW, S.T. Role of prostaglandins in IUD associated uterine bleeding—effect of prostaglandin synthetase inhibitor (Ibuprofen). *Obstetrics and gynaecology*, **58**: 101–106 (1981).
339. MAKARAINEN, L. & YLIKORKALA, O. Ibuprofen prevents IUCD-induced increases in menstrual blood loss. *British journal of obstetrics and gynaecology*, **93**: 285–288 (1986).
340. KAY, C.R. Oral contraceptives and health: the Royal College of General Practitioners' study. *American journal of epidemiology*, **102**: 458–466 (1975).
341. WHO Technical Report Series, No. 619, 1978 (*Steroid contraception and the risk of neoplasia: report of a WHO Scientific Group*).
342. KOLS, A. ET AL. Oral Contraceptives in the 1980s. *Population reports*, Series A., No. 6, 1982.
343. TIETZE, C. What price fertility control? Lower than that of unwanted pregnancy. *Contemporary obstetrics and gynecology*, **1**: 32–36 (1978).
344. Anonymous. Copper IUDs no longer available for U.S. women. *Outlook*, **4**: 7–8 (1986).
345. ZEIDENSTEIN, G. Memorandum from the Population Council concerning the international availability of Copper T IUDs. New York, Population Council, 4 February, 1986.
346. AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS. *ACOG's statement on Searle's removal of IUDs*. Washington, DC, ACOG, January 31, 1986.

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