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**INTRA-UTERINE DEVICES :
PHYSIOLOGICAL AND
CLINICAL ASPECTS**

**Report
of a WHO Scientific Group**

WORLD HEALTH ORGANIZATION

GENEVA

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**WHO SCIENTIFIC GROUP ON
PHYSIOLOGICAL AND CLINICAL ASPECTS OF INTRA-UTERINE DEVICES**

Geneva, 5-11 December 1967

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INTRA-UTERINE DEVICES : PHYSIOLOGICAL AND CLINICAL ASPECTS

Report of a WHO Scientific Group

A WHO Scientific Group on Physiological and Clinical Aspects of Intra-Uterine Devices met in Geneva from 5 to 11 December 1967. The meeting was opened by Dr A. M.-M. Payne, Assistant Director-General, on behalf of the Director-General. Dr S. J. Segal was elected Chairman and Dr A. B. Kar Vice-Chairman ; Dr D. L. Moyer and Dr Christopher Tietze were appointed Rapporteurs.

This was the second Scientific Group convened by WHO to advise the Director-General on this subject, the first Group having met in 1966.¹ The WHO Advisory Committee on Medical Research has recommended, however, that the Organization should periodically review developments in the field of contraception. Although the present meeting was concerned primarily with the latest clinical experience with intra-uterine devices and with the most recent results of basic research on their mode of action and biological effects, an attempt was made to cover the subject in its entirety.

1. INTRODUCTION

1.1 Extent of present usage

Since the previous Scientific Group meeting on this subject, intra-uterine devices (IUDs) have been used for contraception by millions of women in all regions of the world. An estimate of the extent to which their use has spread in the past two years is given in Table 1.

The countries listed in the table provide contraceptive services through their national health services and maintain records of their experience with IUDs under these programmes. Accurate figures for the use of IUDs in the private sector of medicine in these countries, and in other countries where the method is used chiefly in the private practice of medicine, are unavailable. In the USA it is known that by the end of 1967, the major manufacturers of IUDs had distributed over 3 000 000 devices, but it is impossible to ascertain how many have actually been used.

¹ The report of this meeting was published in *Wld Hlth Org. techn. Rep. Ser.*, 1966, 332.

The total number of women who have used IUDs for contraception in recent years throughout the world is estimated to be six to eight million.

TABLE 1. USE OF INTRA-UTERINE DEVICES TO DATE

Country	Approximate number of IUD Insertions	
	31 December 1965	31 December 1967
South Korea	350 000	1 100 000
Taiwan	150 000	370 000
Chile	20 000	110 000
Pakistan	50 000	1 200 000
India	320 000	2 000 000

1.2 History

Intra-uterine devices have long been used in the treatment of gynaecological abnormalities and for the regulation of fertility. The nineteenth-century literature on the subject is large. At that time devices were used often for the correction of uterine displacement and occasionally for contraception.

A new chapter was opened in 1929 when Gräfenberg reported a high level of contraceptive effectiveness with the use of intra-uterine rings made of silkworm gut or silver. At that time, other workers demonstrated in experimental animals that the presence of a foreign body in the uterus prevented pregnancy. Despite their promise as contraceptives, the Gräfenberg devices were soon condemned by the medical profession because it was feared that they would cause uterine injury and pelvic infection. No further work in the field was reported for nearly thirty years.

In 1959 Oppenheimer published the results of years of experience with modifications of the Gräfenberg ring. He reported on one thousand five hundred women who had IUDs without serious complications. In the same year Ishihama reviewed the results obtained with the use of the Ota ring by 20 000 Japanese women. Japanese workers, including Ota, were the first to utilize plastic materials for intra-uterine contraceptive devices. These two reports renewed interest and stimulated further research.

Within five years many new devices were designed and tested. The chief innovations were the use of materials such as polyethylene, nylon or stainless steel, with the object of reducing tissue reaction, and the development of insertion techniques that do not require dilatation of the cervix. Some of the new polyethylene devices are linear and can be threaded into a catheter or cervical cannula similar in size and design to those generally used by gynaecologists for diagnostic procedures. The cannula is then

inserted through the cervical canal and the intra-uterine device is pushed into the cavity with a plunger. Other devices are placed within the uterine cavity in a partially collapsed state, either by means of a notched uterine sound or a modified uterine dressing forceps. Some of the devices have extensions or fine attachments that protrude outside the cervical os when the device is *in situ*, thereby permitting confirmation of its presence, and facilitating its removal when necessary or desired.

1.3 Design of IUDS

A variety of rings fashioned from metal and plastic have been used in Japan, Mainland China and the Republic of China (Taiwan) for thirty years. The most popular is the Ota ring, made of polyethylene. The stainless steel ring, described by H. Hall in 1959, is very similar to the silver Gräfenberg ring. More recently, in Chile, Zipper introduced the use of a ring from coils of nylon threads, leaving a length of thread to serve as a transcervical tail. The first plastic device of linear form that could be inserted through a cervical cannula was the Margulies spiral developed in 1959. Shortly thereafter, Lippes designed a linear device of polyethylene which he named "the loop". Almost simultaneously, another plastic IUD was invented by Birnberg which, because of its shape, was called "the bow". By the end of 1967, these devices were the only ones for which adequate testing and statistical evaluation had been completed.

Other forms have been designed, and some are in the process of formal or informal evaluation. The plastic used most commonly is medium-density polyethylene, containing barium to permit X-ray visualization. At least two plastic devices include a magnetic metal insert, which permits detection when a galvanometer is placed near the pelvis. New metal devices have also been designed. Unfortunately, some of the new devices are being distributed before they have been evaluated clinically.

The uncertainties about the relationships between design (shape, size, material, etc.) and clinical performance (pregnancies, expulsions, side effects) of IUDs make it difficult to attempt rational development of new, improved types. Nevertheless, experience gained with the tested IUDs has provided some insight into these relationships.

2. BIOLOGICAL EFFECTS

2.1 Antifertility effects

Antifertility effects of intra-uterine devices have been reported for a large number of vertebrate species, including man, rhesus monkey, domestic cattle, water buffalo, goat, sheep, pig, ferret, rabbit, guinea pig, hamster, rat, mouse and domestic fowl. It has not yet been possible to identify a

common basic mechanism responsible for the antifertility effect in all species. The various reactions observed may be explained in part by species differences in anatomy and physiology, and in part by the variations in size, configuration and composition of the intra-uterine devices that have been used.

In some species, only the tubo-uterine complex seems to be influenced, while studies on other species reveal that the function of the ovary and that of the adenohipophysis and/or neurohypophysis may be influenced indirectly by the presence of an IUD. No observation has yet been reported to suggest any indirect effect of an intra-uterine device on any other organ.

2.2 Systemic effects

The systemic responses noted so far are not known to affect any system outside the hypothalamo-hypophyseal-ovarian axis. First of all, there is no conclusive evidence that the IUD influences anterior pituitary functions in the human female. Secondly, clinical studies involving a large number of endometrial biopsies and vaginal smears, as well as a limited number of ovarian biopsies, have shown that ovulation, an excellent indicator of the normal release pattern of gonadotrophin, occurs normally in women wearing an IUD. Urinary gonadotrophin determinations in two studies have failed to reveal significant deviations from normal excretion patterns, although the number of cycles so far studied has been too small to provide conclusive evidence. The general clinical experience has been that the menstrual cycle is not noticeably lengthened or shortened in IUD-users; this may be taken as additional indirect evidence that the release pattern of gonadotrophic hormone remains normal.

Similarly, in the rat and the mouse there is no evidence, direct or indirect, that an IUD influences the production of gonadotrophins by the anterior pituitary. That production of follicle stimulating hormone (FSH), luteinizing hormone (LH) and luteotropic hormone (LTH) remains normal in these animals may be inferred from the normalcy of cycle length, from the duration of pseudopregnancy following sterile mating, and from the normal establishment and maintenance of pregnancy in a uterine horn contralateral to an IUD-bearing horn. Similarly, it is difficult to envisage a significant effect upon the anterior pituitary in species in which all biological events associated with an IUD are confined unilaterally to the uterine horn containing the device or to its adjacent ovary, as is the case in guinea-pigs, cattle and sheep. The pig may be included in this category, but there are conflicting reports as to whether effects in this species are unilateral or bilateral.

An effect on the release pattern of a pituitary gonadotrophin (LH) occurs in the rabbit. In this reflex-ovulating species, there is a delay in post-coital ovulation in females with IUDs, although the rate of ovulation

is unaffected. Direct LH determinations made on the pituitaries of rabbits after ovulation strongly suggest that the delay in ovulation in this species is truly secondary to an alteration in the LH secretion pattern. Also suggestive of gonadotrophin suppression is the absence of corpus luteum formation in the water buffalo when a device is present, although no gonadotrophin assays have been performed in these animals. Direct measurements of the LH content of the pituitaries of sheep with IUDs have been carried out. These studies have been done on the pituitaries of mated ewes, sacrificed on day 1 and day 4 after mating. In each case there was evidence of LH excess in the pituitary.

No studies in any species have been reported with respect to the influence of an intra-uterine device on the production or release of thyrotrophin, growth hormone or ACTH, or on the histology of the anterior pituitary of animals or women with IUDs. The absence of these observations may reflect the fact that there has been no report of physiological effects that could be attributed to thyroid or adrenal dysfunction or growth-hormone imbalance. Nevertheless, some attention to these parameters of endocrine physiology, particularly in women, is warranted.

The possible neurogenic influence of an intra-uterine device on the neurohypophysis has been explored in both the human female and the rat. Elevation of oxytocin-like substances in the plasma of women using IUDs has been reported in one study, although the number of observations is small. This study requires confirmation and extension. In the female rat, neither oxytocin production and release nor oxytocin sensitivity of the uterus is influenced by the presence of an IUD.

The major conclusions to be drawn from the findings noted above are that in all species, including man, the systemic effects of an IUD are very restricted indeed. What evidence there is suggests that the only systemic effects are of neurogenic origin, due to the influence of the uterus upon the hypothalamo-hypophyseal centres.

2.3 Pelvic organ effects

2.3.1 *The ovary*

As stated in the preceding section, considerable clinical evidence supports the conclusion that the quantitative and temporal aspects of ovulation, corpus luteum formation and corpus luteum function are essentially unaffected by the presence of an IUD. In some experimental animals (rat, mouse, hamster, ferret, rhesus monkey) findings on the ovary are identical to those reported in the human female, while in other species alterations in ovarian function occur as a result of the presence of an IUD. Changes in ovarian function secondary to an apparent disturbance of gonadotrophin release patterns have been mentioned above (section 2.2,

para. 3). In addition, some species reveal changes in ovarian function, apparently evoked by neural or humoral stimuli emanating from the IUD-containing uterine horn. In the ewe, cow and guinea pig, IUDs partially inhibit corpus luteum function, but only in the ipsilateral ovary. This suggests strongly that the luteolytic effect is mediated locally rather than systemically. However, the neural or humoral factors involved have yet to be identified. It is important to note that in no species, with the possible exception of the water buffalo, have the observed changes in ovarian function been held responsible for the antifertility effect; and observations on the water buffalo are limited to a single experiment with a few animals. Thus, comparative studies virtually exclude an effect on ovarian function as the basis for the antifertility effect of an IUD.

2.3.2 *The tube*

In women, the possibility that IUDs influence tubal events, as well as uterine events, is suggested by the clinical observation that the number of ectopic pregnancies per total women-months of exposure to pregnancy is smaller than would be expected if the action of the device were confined solely to the phase of the reproductive process which takes place after the blastocyst reaches the uterus.

Not all experiments with IUDs in animals have included investigations of tubal events, but the rate of tubal transport of ova has been studied in the domestic fowl, mouse, rat, hamster, guinea-pig, rabbit, sheep and rhesus monkey. The results of the work with the domestic fowl and the mouse have been interpreted as evidence of altered tubal function in the presence of an intra-uterine foreign body, but the domestic fowl seems an inappropriate species for comparative studies of tubal physiology, since, in reality, there is no anatomical differentiation into oviduct and uterus, and the physiology of the oviduct is highly specialized in this species. In the mouse, a foreign body in one horn of the bicornuate uterus creates an antifertility effect in both horns, but it is reported that the rate of zygote transport is impeded only on the side with the IUD. In all other species studied, in which the only experimental intervention has been the introduction of an IUD, the rate of tubal transport of ova is unaffected.

In the rhesus monkey with an IUD there is an increase in the rate of tubal transport in animals in which ovulation has been induced by exogenous gonadotrophins and followed by artificial insemination. In this situation, ova are transported through the tubes in several hours instead of the three to four days normally required. But gonadotrophins induce multiple ovulation, an abnormal phenomenon in the rhesus monkey, and this overstimulation undoubtedly creates an elevated level of oestrogen secretion, which could be responsible for acceleration in the tubal transport of ova. In two investigations on rhesus monkeys fitted with IUDs in which ovulation

had occurred naturally, fertilized as well as unfertilized ova were found in the tubes at least three days after the estimated time of ovulation, in accordance with normal expectation. It seems, therefore, that the presence of an IUD does not bring about a marked change in the rate of tubal transport in normally ovulating rhesus monkeys. More precise timing of egg transport requires further investigation.

There have been attempts to recover human ova at surgery by flushing the fallopian tubes. In some of these investigations, the post-ovulatory day has been estimated by histological study of the endometrium and/or the corpus luteum. In the limited number of cases studied, tubal ova have been recovered up to the third post-ovulatory day. Until now, this line of investigation has not yielded any evidence to suggest that the rate of tubal transport of ova, fertilized or unfertilized, is altered by the presence of an IUD, although the number of observations is far too small to permit a definite conclusion. Thus, contrary to the view sometimes expressed, the results of animal experiments and clinical investigations on this subject are remarkably similar.

The results of studies on the effect of an IUD on fertilization show a high degree of uniformity too. The process is unaffected in all mammalian species for which adequate information is available, with the exception of the sheep and the artificially inseminated cow. In the sheep, however, the antifertility effect is known to be due to destruction of sperm in the uterus, thereby preventing the ascent of viable sperm to the site of fertilization, rather than an effect on the tubal event of fertilization *per se*. In cows, an IUD exerts an antifertility effect whether they are mated naturally or inseminated artificially. In the former case, fertilized ova can be recovered from the tube but implantation is impaired. In the latter, fertilization does not occur. One possible explanation for this difference could be that the destruction of sperm in the uterus provoked by the IUD, although not sufficient to lower appreciably the number of spermatozoa in normally mated animals, is significant in artificially inseminated animals because of the vastly reduced number of sperm introduced by this method.

Whether or not the presence of an IUD affects fertilization in the human female has not been conclusively demonstrated. It is well known that about 2% per year of women using IUD contraception have become pregnant with the device *in situ*, but it has not yet been established whether fertilization occurs in IUD-users who do not become pregnant. To date, of 11 eggs recovered by flushing the tubes of women with IUDs, one has been found to have been fertilized. The number of patients studied does not provide sufficient data to warrant a final conclusion. However, as shown above, the findings in other species suggest that the prevention of egg-sperm union in the tube is not the explanation of the antifertility action of IUD's in mammals. Indirect prevention of fertilization through destruction of, or damage to, the ascending spermatozoa, cannot be discounted. Observations regard-

ing this possibility in the human female are limited. One study reports that sperm are found in the tube ; another supports the evidence that they are present, but in reduced numbers.

2.3.3 *The uterus*

In all species for which adequate information exists, the presence of an IUD is associated with a direct toxic effect on either the sperm or the blastocysts. As indicated above, sperm are killed in the uterus of ewes. In the rat, hamster, guinea-pig and rabbit, blastocysts arrive from the tubes but are destroyed and do not implant. A toxic effect on sperm is suggested in the cow and the mouse, but additional study is required to analyse the fate of both sperm and blastocyst in the uterine milieu in the presence of an IUD.

Tissue changes in the human uterus in the presence of an IUD are described in section 3. The finding in humans most consistent with those in all animals studies is local cellular infiltration in tissue adjacent to the IUD. In rats, rabbits and mice, there is also an exudation of polymorphonuclear leucocytes into the uterine lumen from those regions of the uterus affected by the presence of the foreign body. Cellular infiltrates of this type occur also in the uteri of cows and sheep fitted with IUDs.

The accumulated evidence from animal studies suggests that a hostile uterine environment having either a spermatotoxic or blastotoxic effect appears to be the common denominator for the antifertility action of IUDs. The precise biochemical or cellular alterations responsible for the toxic effect remain to be established. Probably this basic mechanism by which an IUD exerts an antifertility effect in animals is also responsible for its antifertility effect in the human female.

3. TISSUE REACTIONS

3.1 *The ovary*

There is ample clinical evidence that follicle maturation and ovulation are not prevented by an IUD. Although there have been no investigations of corpus luteum function, in several studies ovarian biopsy has shown normal ovarian structure. Histochemical studies have revealed no alterations in ovarian lactic dehydrogenase, succinic dehydrogenase, or glucose-6-phosphatase activity in the presence of an IUD.

3.2 *The tube*

No information is available on the effect of an IUD on the morphology, histology, ultrastructure, or histochemistry of tubal tissue. This is true also of the tubal fluid milieu. In one study, an increase in tubal motility

in the presence of an IUD has been reported. In other studies, an IUD has been found to have no effect on tubal motility. Tubal patency has been found to remain normal in women fitted with an IUD.

3.3 The endometrium

Within a few days of IUD insertion, inflammatory cells infiltrate the endometrial stroma in sequential order (i.e., polymorphonuclear neutrophils, lymphocytes, plasma cells). They are mostly focal in distribution. Some investigators have not observed them at all. In general, these changes are not associated with clinical symptoms. In one study, leucocytes appeared in only about 20% of the biopsy specimens from human uteri containing IUDs. The failure to find leucocytes in every uterus by this technique has been interpreted as evidence that inflammation is not a significant part of the response of the human uterus to the IUD. Recent studies, however, which utilized whole human uteri, found that cellular infiltrates were always present in the tissue that was in contact with the IUD. This suggested that inflammation is limited to that region, and that the absence of leucocytes in many biopsy specimens is a consequence of random sampling. Viable bacteria are rarely seen in association with cellular infiltrates because the intrauterine infection immediately following IUD insertion is very transitory (see section 4.4.4, page 21).

In areas where the IUD has contact with the endometrium, there is usually very little morphological change. However, there is occasional thinning and denudation of the surface epithelium with cytoplasmic vesiculation and fragmentation of the cells as seen with electron microscopy. Light microscopy reveals early fibrosis, increased superficial vascularity, and, occasionally, premature deciduoid changes directly beneath the IUD.

Premature maturation and asynchronous development of the endometrium have been shown by light and electron microscopy. Premature appearance of the nucleolar channel system and alterations in the development of mitochondria and endoplasmic reticulum have been observed.

Occurrence of aneurysmal microthrombosis of the endometrial capillaries has been shown in electron microscopic studies, a finding that may be related to the clinical problem of bleeding in IUD users.

No alteration has been found in histochemically demonstrable protein, nucleic acids, some enzymes (phosphatases, enzymes of the glycolytic and oxidative pathways of metabolism), carbohydrates, lipids, and electron-transport co-factors. A reduced depolymerization of mucopolysaccharides in endometrial ground substance is suggested by an increase in alcyan blue reaction. Little is known about the effect of an IUD on the biochemistry and metabolism of the endometrium, except for (a) an increase in fibrinolytic activity, and (b) a retardation of the increase in the non-phospholipid to phospholipid ratio found to occur at the same time as ovulation. The latter

is thought to represent a disturbance in biochemical maturation of the endometrium. A slight increase in beta-glucuronidase activity in menstrual blood has also been reported. Deposits of calcium carbonate on plastic devices have been observed in some studies.

3.4 The myometrium

There are isolated reports of myometrial hypertrophy. A study using the transducer technique has indicated that, although myometrial activity may be increased immediately after IUD insertion, this effect diminishes with time. Another study, using the microballoon method, has shown no such hyperactivity after insertion. A third study, using the catheter technique of measuring myometrial contractility, has shown prelabour-like activity at a time corresponding to transport and nidation of the ovum.

3.5 The uterine fluid

One investigator has found no change in total protein concentration of the uterine fluid but a slight increase in total carbohydrate concentration. Studies of the pH of uterine fluid *in vitro* have revealed no change from normal; one study of intrauterine pH in the presence of an IUD has suggested a slight decrease. In another investigation a marked increase in total protein concentration of the uterine fluid was recorded.

3.6 The cervix

An IUD has no effect on the histology of the cervix. Cervical secretions are increased without any alterations in consistency or in physical properties.

3.7 The vagina

A high cornification index in vaginal smears has been observed in some studies.

3.8 Carcinogenesis

Since there is no evidence that an IUD in the human uterus gives rise to a generalized systemic effect, consideration of carcinogenesis should be confined to local action on the endometrium and/or cervix.

Until now, there have been no reports of endometrial cancer among women using IUDs, nor have any case histories been published of women with endometrial cancer reporting a history of previous IUD use. It is, of course, inevitable that such cases will occur, for there is no reason to suggest that IUD-users will be exempt from the normal incidence of this disease as they approach the menopause. The possibility of a cancer-

initiating effect by a foreign body cannot be ruled out, of course, until long-term prospective data are available.

Animal experimentation has clearly established the oncogenic property of plastics implanted subcutaneously. One study has revealed that subcutaneous tumours may be induced in rats by the presence of plastic loops and spirals after long periods of time. A stainless steel contraceptive device implanted in the same manner did not cause tumours. The investigators point out, however, that the production of subcutaneous sarcomata by plastic devices in rats cannot necessarily be considered as indicative of any oncogenic potential in man, particularly as in clinical use these devices are placed within the uterine cavity rather than embedded in connective tissue. A similar study has revealed the development of subcutaneous sarcomata and intra-uterine epidermoid carcinomata in rats after long-term exposure to segments of plastic or stainless steel IUDs. The fact that the rat does not have a reproductive cycle which includes periodic sloughing of the endometrium may explain the extensive upper genital tract infection associated with the intra-uterine tumour development in these experiments. In any event, these dissimilarities prompted the workers to advise caution in the interpretation of their findings in terms of human carcinogenesis.

Because several devices have a trans-cervical tail or attachment, possible effects on the uterine cervix have had to be examined. Furthermore, altered secretions from the endometrial cavity due to the presence of an IUD could be a cause of cervical irritation, although the presence of such secretions in the cervix has not yet been demonstrated. Prospective study by cervical smear cytology is an indispensable tool for evaluating the possibility of pre-malignant changes in the cervix associated with the use of IUDs. In many countries, studies of this kind are in progress, and several reports involving many thousands of women are already available. So far, all reliable studies suggest that the incidence of cervical cancer is not increased in women fitted with IUDs. With respect to dysplasia, all IUD studies report that the frequency of newly found abnormal smears does not appear to be greater than in control populations, but such studies have been neither systematic nor adequately controlled. Furthermore, consideration must be given to the relative shortness of the period of observation, as most of these prospective studies have not progressed beyond four years of follow-up. On the other hand, there is no acceptable evidence that the rate of change from normal or early abnormal cervical smears to smears indicating carcinoma in situ is greater than usual in women with IUDs. On the contrary, recent studies, adequately controlled and statistically evaluated, have failed to reveal any significant influence of the presence of the device on the rate of progression from dysplasia to carcinoma in situ. In one of these studies, the progression rate in 114 women fitted with IUDs was compared with that in 221 women using

other contraceptives or no contraceptives. The progression rates in these two groups, calculated by the life-table method, were not significantly different, suggesting that the IUD exerts no significant carcinogenic effect on the human uterine cervix.

4. CLINICAL EXPERIENCE

Over the past few years, a vast number of observations relevant to clinical and field experience with IUDs have been assembled and analysed. Investigations have been focused on three principal questions :

- (a) effectiveness of the method in preventing pregnancy ;
- (b) incidence and nature of side effects and complications ; and
- (c) continuation of use over prolonged periods following the insertion of the device.

4.1 Sources of data

The sources of information on the IUD can be conveniently grouped into three major categories : (a) clinical observations, (b) special investigations, and (c) national family planning programmes. Data from the last two categories are amenable to statistical analysis. Clinical observations provide important contributions to knowledge about IUDs. In evaluating these contributions, one must always be aware of the pitfalls inherent in drawing conclusions from a limited number of cases, insufficient follow-up data, and subjective impressions.

Most clinicians conducting special investigations with IUDs have not had access to users in sufficient numbers to permit valid statistical analysis of the results of their work. In the USA, a Cooperative Statistical Program (CSP) was established to overcome this difficulty. Its most recent report is based on data from 30 participating investigators who had submitted individual case records for almost 27 600 women, covering an aggregate of more than 477 000 woman-months of use. More than 90% of these women were non-private patients. The period of follow-up is now five years for the loop and two years for most of the other devices.

Another pioneering special investigation is the Taichung Medical Follow-up Study, based on a large-scale family planning programme initiated in Taiwan in 1963. The study comprises about 6 600 women and the follow-up now extends over two years.

Further special investigations have been based on experience in hospitals, especially teaching hospitals, and other medical service facilities. Important contributions of this type have come from Chile, India, Korea, the United Kingdom and other countries.

Family planning programmes have been established in a number of countries over the past few years and some of them are making use of the IUD on a vast scale. None of these programmes has yet undertaken to

evaluate its entire field experience, but several have produced data on carefully designed sample surveys of women who had been fitted with an IUD at some prior time. Two such sample surveys have been conducted in Korea and two in Taiwan.

Generally speaking, the women included in the special studies may be assumed to have enjoyed a higher level of medical care and personal attention than those served by busy, and in some instances overburdened, public health personnel. Such differences make it difficult to compare the results of any one study with those of another.

4.2 Statistical methods and clinical trials

A basic requirement for the correct interpretation of the quantitative findings in special investigations and in sample surveys is the use of appropriate statistical methods.

Clinical trials should be designed in keeping with basic statistical principles and the specific objects of the particular investigation, whether it be the study of contraceptive effectiveness, side effects and complications, or the continuation of use. Special consideration should be given to appropriate techniques of statistical analysis, to the size of the sample required in order to obtain statistically significant results, and to the full utilization of all practicable procedures to minimize possible bias on the part of the investigator.

In the assessment of experience with the IUD in large-scale family planning programmes, a sound organizational principle is to separate the evaluation unit from personnel directly responsible for the day-to-day administration of the programme.

Even under favourable circumstances, routine "service" statistics from clinics should not be expected to provide adequate information on contraceptive effectiveness and continuation of use, and certainly not on the incidence of side effects and complications. Provision should therefore be made for periodic sample surveys.

Any statistical method for measuring the incidence of the major events in IUD use—pregnancies, expulsions, and removals—should yield results that can be compared with those of other investigators. Since the monthly incidence of these phenomena varies with the length of time that has elapsed since the insertion of an IUD, it is essential that the statistical method should take into account the duration of use. This requirement is met by the "life-table method", which permits valid comparisons between types of devices, types of users, and other factors—comparisons that could not be made by simpler procedures because of differences between groups in the average length of observation. The life-table method permits analysis of the rates of pregnancies, expulsions, and removals during successive

months, and yields cumulative rates per 100 users at the end of a finite period of time after insertion.

Cumulative rates may be based on experience subsequent to the first insertion only or on total experience, including reinsertions, and they may be computed either as event rates or as "closure rates". Until now, events have been customarily defined as pregnancies, expulsions and removals, whether or not followed by reinsertion, but cumulative rates could be computed also for side effects not leading to removal. "Closures" are defined as events not followed by a reinsertion.

Cumulative event rates and closure rates may be computed either as gross rates or as net rates. Gross rates are designed to measure the incidence of each type of event separately, without regard to other types of event. For this reason, gross cumulative rates for the several types of event and closure cannot be added together to obtain total event and closure rates.

Net rates are computed by means of a multiple-decrement table and are designed to measure the incidence of each type of event or closure in the presence of all other types of event or closure. Net cumulative closure rates can be added to obtain a total closure rate. Subtraction of the total closure rate per 100 users from 100 yields the percentage of continuing users at a given time after insertion.

4.3 Contraceptive effectiveness

The effectiveness of any method of contraception is measured in terms of the pregnancy rates associated with its use. For the most effective types of IUD, in carefully supervised studies involving large numbers of users, rates of the order of two or three pregnancies per 100 women have been reported for the first year of use, and somewhat lower rates for subsequent years. Higher or lower pregnancy rates with the same devices, reported from different localities, may reflect sampling variations as well as such other factors as completeness of follow-up. In general, the pregnancy rates encountered in special investigations tend to be a little lower than those obtained in national programmes.

For any given type of IUD, pregnancy rates tend to be higher for the smaller sizes than for the larger sizes. Among devices of comparable size, pregnancy rates seem to be highest for the bows, followed in descending order by rings, loops and spirals. Pregnancy rates tend to be higher for younger women than for older women fitted with the same type of device. Within each age group, the pregnancy rates tend to increase in proportion to the number of children born prior to the first insertion.

The majority of pregnancies occur with the IUD *in situ*. A minority occur after unnoticed expulsion through the cervix, and a few have been found to occur after extra-uterine translocation of the device resulting from perforation of the uterus.

A comparison of the effectiveness of the IUDs with that of other contraceptive methods requires consideration of the difference between theoretical effectiveness and use-effectiveness. The concept of theoretical effectiveness is based on the assumption that the method is used consistently and according to instruction, while use-effectiveness is based upon actual performance, which is reduced by inconsistent and incorrect use of the method.

For the IUDs, use-effectiveness approximates theoretical effectiveness, since this method does not require adherence to a regimen of medication or manipulation before, during or after coitus. However, the level of effectiveness can be improved by minimizing the possibility of unnoticed expulsion. This can be accomplished by inspection of menstrual pads or tampons by the user herself or, if the IUD has a transcervical extension or attachment, by ascertaining its presence, particularly after each menstrual period.

In terms of theoretical effectiveness the IUDs are unquestionably less effective than hormonal contraceptives, and they are probably no more effective than some of the conventional methods of contraception, such as the condom, the vaginal diaphragm, or calendar and temperature "rhythm" methods, when these are used correctly by the couple.

In terms of use-effectiveness, the IUDs have proved themselves far more effective than the traditional methods, if continuous motivation is lacking. The relative use-effectiveness of IUDs and hormonal contraceptives under similar circumstances cannot yet be evaluated, owing to the lack of adequate statistical information on the hormonal contraceptives.

4.4 Side effects and complications

4.4.1 *Bleeding*

Abnormal vaginal bleeding is the commonest complaint of women fitted with IUDs. In addition to the bleeding that often occurs for a few days immediately following insertion, menorrhagia and/or metrorrhagia are frequently encountered. These menstrual irregularities are very common during the first few months, after which they tend to disappear; in some cases, however, they become chronic. Occasionally, bleeding abnormalities arise only after one or two years. It is unknown whether the incidence of delayed abnormal bleeding among women with IUDs is higher than that of menstrual irregularities in a comparable group of women in the general population, without IUDs, followed up over a similar period of time. With the types of IUD most widely used, bleeding during the first few months is moderate to marked in about 10% of users. In later months, bleeding, where it is a problem, tends to take the form of prolonged and/or profuse menstruation; inter-menstrual bleeding is less often observed. Although this menorrhagia rarely reaches haemorrhagic proportions,

even a moderate increase in blood loss may, of course, require medical attention, especially in the presence of intercurrent anaemia. Removal of the device may be indicated if the bleeding is profuse or persistent.

Most of the menstrual difficulties occurring soon after IUD insertion are thought to be related to the initial traumatic, physical and biochemical reactions of the uterus to the presence of the IUD. There appears to be a relationship between the incidence of abnormal bleeding and the bulk, configuration and other physical properties of the device.

Many varieties of treatment have been used to control the abnormal bleeding sometimes caused by an IUD. For the short-term management of prolonged menstrual periods occurring several months or more after IUD insertion, ergot and, at times estrogens or progestogens have been tried with some success. In isolated studies, other compounds, such as vitamin C, vitamin K₁, calcium, and even placebos have been found to have a restrictive effect on bleeding. In one study, the intra-uterine instillation of absolute alcohol was found effective as a local haemostatic agent. The cyclic use of combined oestrogen-progestogen preparations has been shown to control bleeding temporarily. However, when these preparations are withdrawn after several cycles of use, bleeding problems of even greater magnitude tend to develop. In short, no known mode of therapy has been found to be consistently successful for counteracting abnormal bleeding in women fitted with IUDs.

4.4.2 *Pain and pelvic discomfort*

Uterine colic immediately following insertion occurs mainly in nulligravidae and in women who have not had a child for a number of years. However, the likelihood of its occurrence is unpredictable for any individual woman. The pain may be quite severe but can often be relieved by rest and the application of heat to the lower abdomen. More specific measures include the use of analgesics and autonomic sedatives. It is rarely necessary to remove the IUD for this complaint alone.

A milder form of uterine cramps can occur during the first few days after insertion. The estimated frequency of this is 10-20%. It tends to recur at the time of the menses for the first few months. The measures mentioned above may be applied for these complaints.

Some patients complain of pelvic discomfort, varying from a non-specific sensation to an ache in the lower abdomen and/or back. In such cases, physical signs are often absent, and the symptoms may be related to pelvic congestion; the customary treatment for pelvic congestion may afford relief.

It must be kept in mind of course that pelvic pain may be due to infection, and the usual measures should be taken to investigate this possibility.

4.4.3 *Vaginal discharge*

Leucorrhoea is not uncommon among women fitted with IUDs, but may be due to many conditions unrelated to the IUD, and these should be diagnosed and treated. It is probable that the irritative effect of the IUD upon the endometrial and/or cervical mucosa contributes to this problem. In any case, leucorrhoea never becomes a serious clinical problem.

4.4.4 *Pelvic infection*

In general, pelvic infection is not a significant problem. Apprehension that if the IUD has a transcervical attachment this would facilitate the ascent of bacteria into the uterine cavity has proved to be unfounded.

Cultures obtained transfundally from hysterectomy specimens in one study have demonstrated the relationship between IUD insertion and bacterial invasion of the uterus (see Table 2). Within 24 hours after insertion, the endometrial cavity was found to be contaminated with the same bacteria that had been cultured from the cervical canal. Forty-eight hours after insertion, the endometrial cavity was free of bacteria in the majority of cases and after 30 days the cavity was bacteria-free in all cases. Cultures of the IUD itself and the intrauterine portion of its threads were sterile whenever the endometrial cultures were sterile.

TABLE 2. RELATIONSHIP BETWEEN BACTERIAL CONTAMINATION OF THE ENDOMETRIAL CAVITY AND TIME OF IUD INSERTION

Days after insertion	Number of positive cultures	Number of negative cultures	Percentage of positive cultures
0-1	5	0	100
1-2	1	4	20
2-7	1	4	20
7-14	1	11	8
14-30	2	22	8
30-201	0	8	0

When inserted into a postpartum uterus, even 6-8 weeks after delivery, an IUD may cause exacerbation of puerperal endometritis. Severe septicaemia has on rare occasions been precipitated by the introduction of an IUD into an infected uterus or in the presence of salpingitis, even at a time remote from pregnancy. Insertion should therefore be postponed if pelvic infection is suspected.

When salpingitis occurs in women who have used an IUD for more than a month, the device is not necessarily responsible for it. There is no con-

clusive evidence that the incidence or severity of pelvic inflammatory disease is greater in these women than in the general population. When such an infection occurs, it usually responds to antibiotic therapy without removal of the IUD.

Low-grade parametritis may develop occasionally in women using IUDs. Lower abdominal discomfort and pelvic tenderness are encountered without fever or significant leucocytosis. Cure is sometimes effected with antibiotics ; in unresponsive cases removal of the device may be indicated.

4.4.5 *Uterine perforation*

One of the risks associated with intra-uterine contraception is perforation of the uterus. The incidence of perforation reported from various sources ranges from 1 : 9000 to 1 : 150 insertions, both values based on very large numbers of insertions of loops. The reported incidence varies with the type of device, the skill of the operator, the time of insertion, and the intensity of effort devoted to diagnosis. The risk appears to be smallest if the IUD is inserted immediately after delivery or three or more months post partum ; the precise time of maximum risk has not been established conclusively.

It is thought that the majority of perforations occur, or are initiated, at the time of insertion, but with untailed devices, they may also occur occasionally at the time of attempted removal.

Most perforations do not produce clinical symptoms. In general, therefore, perforations are suspected only when the IUD is not found at the time of routine examination or delivery. Hystero-graphy is usually required to differentiate between perforation and unnoticed expulsion.

In rare cases, a perforation involving a closed IUD (bow or ring) has led to intestinal obstruction ; no such complication has been reported with the open IUDs (loop). Surgical removal of an IUD from the abdominal cavity following uterine perforation is therefore mandatory for closed devices and optional for open devices.

4.4.6 *Effect on pregnancy*

It is not known whether or not the presence of an IUD increases the likelihood of spontaneous abortion. No other obstetrical complication, such as premature delivery or foetal deformity, has been attributed to an IUD. Disturbance of placental function has not been found. If an IUD still lies in the uterus after the diagnosis of pregnancy is made, it is probably preferable to leave the device *in situ*. It is then usually expelled at the time of delivery, in association with either the placenta or the membranes, and has always been found outside the chorionic sac. In 20% of cases it is retained *in utero*, in which case it should be removed after delivery.

4.4.7 *Effect on subsequent fertility*

Women who have an IUD removed in order to conceive, do so normally: three-fifths become pregnant within three months and nine-tenths within a year (see Table 3).

TABLE 3. PLANNED PREGNANCIES AFTER REMOVAL OF IUD

Follow-up (months)	Number of cases by outcome			Pregnancy rate	
	Conceived	Did not conceive	Total	Monthly	Cumulative
0-1	167	—	167	32.9	32.9
1-2	94	3	97	27.8	51.6
2-3	48	5	53	20.0	61.2
4-6	83	21	104	19.0	79.4
6-9	31	10	41	15.0	87.3
9-12	13	9	22	12.5	91.5
Longer	2	21	23		
Total	438	69	507		

4.4.8 *Effect on the male partner*

Discomfort to the male partner and, occasionally, injury to the penis have been caused by the stiff, beaded tail of the Margulies spiral. These problems are almost never encountered with devices that have trans-cervical attachments made of nylon threads.

4.4.9 *Expulsions*

The incidence of expulsions varies widely among the different types of IUDs. For each device for which there are comparative data, higher expulsion rates have been found with smaller sizes. Size, however, is associated with other factors, such as thickness, overall elasticity, stiffness, etc., which may account for the observed differences in expulsion rates. Among the widely used devices, the highest rates occur with the spiral, followed by the nylon and stainless steel rings. The expulsion rate with the loop is substantially lower and the bow has the lowest rate. There is no consistent pattern of difference in rates between different geographic regions nor between special investigations and country-wide programmes.

Expulsion rates for all types of IUDs tend to decline quite steeply with increasing age of the woman, and less steeply with parity. Cross-tabulation by age and parity confirms that age is the more important of the two factors. Expulsion rates are very high following insertion on the delivery table or

during the first few days after childbirth ; they are lower following insertion at the time of the post partum examination, customarily performed 6-8 weeks after delivery, and lowest following insertion three or more months after childbirth. In one study, involving several thousand insertions of the largest loop, the incidence of primary expulsions during two years of use was of the order of 45%, 15% and 10%, respectively, for the three periods mentioned.

The great majority of expulsions occur during the first year of use ; about one-half of the total within four months after insertion. More devices seem to be expelled with the menstrual flow than at other times. If an IUD is reinserted after an expulsion, the rate of re-expulsion is higher than the rate of expulsion after the first insertion of the same type of IUD.

4.4.10 *Removals*

In all regions for which data are available, removal of an IUD is the event most often responsible for discontinuation of use of all types of IUD.

Removal rates are not as closely related to differences among the types of IUD so far evaluated as are pregnancy rates and expulsion rates. Removal rates for the nylon ring, as used in one country, were lower than those for other IUDs in other countries. Also, it appears that larger sizes of a given device are more likely than smaller sizes to produce side effects that lead to removal. In general, removal rates have tended to be appreciably higher in country-wide programmes than in special investigations conducted in the same countries.

According to all reports, removals are more often performed for "medical" than for "personal" reasons, but the two categories are not clearly definable and they often overlap in individual cases. By far the commonest reasons for removal are menstrual disturbances and other forms of abnormal uterine bleeding, as well as pelvic pain ; abnormal bleeding and pelvic pain often occur together. In the US Cooperative Statistical Program, bleeding and pain accounted for about 60% of all removals while other "medical" reasons accounted for 25% and "personal" reasons for only 15%. Comparable figures from the Korean country-wide family planning programme were 75%, 10% and 15%, respectively.

Like the expulsion rate, the removal rate is highest in the first months after insertion. However, the subsequent decline of the rate is not as steep as that for the expulsion rate. A significant incidence of removals has been reported throughout the period of use for which data are available.

4.5 **Continuation of use**

Along with the effectiveness of the method used, continuation of use is a most important criterion of successful contraceptive practice. Continued use can be measured conveniently in terms of continuation rates, indicating

the proportion of couples still using the method after a specified period of time. The reasons for discontinuation are pregnancy, expulsion and removal.

Because the life-table method has been developed so recently, not all investigators have utilized it to its full extent. At present, an extensive international comparison of findings is possible only in terms of event rates based on the experience following first insertions. Table 4, which has been prepared on this basis, shows net cumulative rates of pregnancies, expulsions and removals to the end of the second year after insertion, as well as total termination rates (pregnancies, expulsions and removals combined) and continuation rates.

In most of the studies included in Table 4, the polyethylene loop (all sizes) was used; the data from Chile refer to the nylon ring. Several types of IUDs, but mostly small loops, were used in the Taichung study. The Cooperative Statistical Program in the USA has published rates for several types and sizes of IUDs.

TABLE 4. NET CUMULATIVE RATES FOR PREGNANCIES, EXPULSIONS, REMOVALS, TOTAL TERMINATIONS, AND CONTINUATION OF USE AT THE END OF THE SECOND YEAR AFTER INSERTION OF AN IUD

Source of data	Net cumulative rates per 100 first insertions				
	Preg-nancies	Expul-sions	Removals	Total termina-tions	Continu-ations
Chile Barros Luco Hospital, San-tiago	5.4	18.2	11.9	35.5	64.5
India Saidar Jang Hospital, New Delhi	1.2	11.0	17.8	30.0	70.0
Country-wide data	1.9	14.0	24.9	40.8	59.2
Korea National University Hospital, Seoul	3.3	8.2	23.4	34.9	65.1
Country-wide data	3.5	14.8	38.0	56.3	43.7
Taiwan Taichung Medical Follow-up Study	8.2	14.9	28.2	51.3	48.7
Country-wide data	10.3	10.1	39.2	59.6	40.4
United Kingdom Devon Family Planning Clinics	4.7	8.1	17.3	30.1	69.9
USA Cooperative Statistical Pro-gram					
Loop A (smallest)	7.9	20.8	26.4	55.1	44.9
Loop B	4.6	19.5	25.3	49.4	50.6
Loop C	3.5	16.1	24.9	44.5	55.5
Loop D (largest)	3.7	10.8	27.2	41.7	58.3
Small spiral	3.3	30.2	25.9	59.4	40.6
Large spiral	1.7	21.4	33.5	56.6	43.4
Small bow	14.1	4.7	29.5	48.3	51.7
Large bow	7.4	2.0	26.8	36.2	63.8
Steel ring	6.6	16.5	19.3	42.4	57.6

The rates shown in the last column of Table 4 refer to continuation following the first insertion of an IUD, i.e., excluding reinsertions. These data show a rather marked difference between the continuation rates reported for the special investigations and those reported for the country-wide programmes of the same countries. In Korea, for example, 65.1% of the patients in the hospital of the National University were still wearing the IUD two years after the first insertion, compared with only 43.7% of the women served by the country-wide family planning programme.

Data on continued use, including reinsertions, are available from a few studies only. According to the experience of the CSP, continuation rates for the various types of IUDs are quite similar, averaging about 75% at the end of the first year and about 65% at the end of the second year. Limited data for one type of device suggest a further drop to about 50% at the end of the fifth year.

The continuation rates with the nylon ring, as reported from Chile (77% after two years), are significantly higher than the rates found with any of the devices evaluated elsewhere.

Continuation rates with the loop, computed on the basis of data obtained in the sample surveys of country-wide family planning programmes, have been consistently lower than the rates observed in the above-mentioned special investigations: 51% after two years in Korea and 49% after two years in Taiwan. The factor mainly responsible for this difference has been the higher removal rate.

4.6 Further factors affecting utilization

The utilization of any contraceptive method may be affected by a variety of circumstances; some of these have a favourable effect on utilization, others interfere with acceptance and continued use of the method. The IUD is no exception.

The main factor operating in favour of the IUD is the preference of many couples for a reversible contraceptive method that does not require any further action on their part beyond the decision to have the device inserted. This unique property of the IUD is reflected in the widespread opinion that the method is particularly suited to the needs of those who may not yet be accustomed to the practice of contraception. This advantage is reinforced by the low cost of the IUD, compared with other effective methods, and by the fact that continued use is less apt to be jeopardized by deficiencies in the distribution of contraceptive supplies.

The main factor on the negative side is the apprehension felt by many women that having a foreign body in the uterus could be detrimental to their health. Bleeding and spotting, which are common side-effects of all IUDs, are widely resented, especially in societies where any degree of

vaginal bleeding is thought to make the women ritually unclean, thus prohibiting marital relations or the performance of religious duties.

Little is known about the differences between societies and between sociocultural strata within societies with regard to sensitivity to pain and discomfort. In some societies, pelvic examination by a male medical practitioner is unacceptable and female doctors may not be available in sufficient numbers. Some husbands may resent the fact that intra-uterine contraception, like other methods dependent on the woman alone, reduces their immediate control of the reproductive process, thus affecting their status with respect to their wives.

Unfounded and/or malicious reports about alleged deleterious side effects have circulated in a few countries and led to great apprehension and numerous removals of IUDs. Some of these rumours were caused by the incorrect interpretation in the lay press of articles originally published in medical and technical journals.

As with all other methods of contraception, the availability of alternative methods of fertility control influences acceptance and continued use of the IUD.

5. PATIENT MANAGEMENT

5.1 Indications

There are two situations in which the IUD is the contraceptive method of choice:

- (a) when the maintenance of continuous motivation is a problem, and
- (b) when there are contraindications to the use of other effective methods.

The latter category includes women in whom continued adequate lactation is essential to the survival or wellbeing of the infant.

5.2 Contraindications

Active pelvic inflammatory disease constitutes an absolute contraindication to the insertion of an IUD, but insertion may be safely performed in these cases after the disease has become quiescent.

An IUD will not provide reliable protection in the presence of congenital malformations of the uterus, or of fibroids of sufficient size to deform the uterine cavity.

IUDs are less suitable for women who have never been pregnant, because insertion in these cases is more often associated with pain and expulsion and, occasionally, with syncope. If an IUD is, nevertheless, to be inserted in a nulligravida, a smaller-size device should be used.

An IUD should never be inserted in a woman known to be pregnant. Suspicious Papanicolaou smears do not in themselves constitute a contraindication to insertion of an IUD.

5.3 Immediate medical care

Before an IUD is inserted, an adequate history must be taken, with particular reference to gynaecological problems, and a pelvic examination must be performed that is sufficiently thorough to detect uterine position, genital abnormalities, and pregnancy. It is desirable to do a Papanicolaou smear at this time. If menstrual abnormalities, cervicitis, cervical erosion or carcinoma are present, they should, of course, be treated.

Women should be apprised of the probability of spotting and discomfort and the possibility of bleeding and pain immediately following insertion and during the next few months. They should be encouraged to seek medical advice if these symptoms persist. They should be instructed to be attentive to the possibility of expulsion, especially during the first few months and at the time of menstruation. It is, of course, advisable that a woman examine herself for the presence of the transcervical attachment of an IUD, where applicable, but this practice should not be insisted upon when individual or general social resistance is encountered.

5.4 Paramedical personnel

Ideally, all IUDs should be inserted by qualified medical practitioners. It should be recognized, however, that strict adherence to this principle is not always possible. Over the past few years, paramedical personnel have been successfully trained, in various parts of the world, to recognize contraindications to the use of the IUD and to perform insertions and removals.

Paramedical personnel assigned to these duties should work under the supervision of a qualified medical practitioner. At the very least, a doctor should be readily available to cope with unforeseen difficulties. The importance of thorough training, with ample opportunities for practice, cannot be overstressed.

5.5 Time of insertion

IUDs may be inserted at almost any time during a woman's reproductive years, except during pregnancy. A convenient time for insertion is 6-8 weeks after delivery, this being the time when women in many countries return for a medical check-up, when their desire for contraception is greatest, and when IUD insertion is technically easy.

It is sometimes advantageous to perform the insertion soon after delivery before the patient leaves the hospital. The risk of expulsion is very high

if this is done immediately postpartum, but substantially reduced if the insertion is delayed until after the third day. Other risks, such as perforation and infection, do not appear to be increased. Patients should be urged to return for a check-up after about six weeks in order to detect early expulsions.

Following therapeutic interruption of pregnancy in a hospital, an IUD may be inserted as soon as the uterus is empty. With other abortions, the possibility of infection must be carefully ruled out prior to insertion. The prophylactic use of antibiotics may serve as a safeguard in these cases.

The IUD may be inserted at any time during the menstrual cycle. The slight advantages of insertion during menstruation (assurance against early pregnancy and masking of post-insertional bleeding) are usually outweighed by the advantages of inserting the IUD at whatever point in the cycle the woman attends the clinic.

5.6 Technique of insertion

The IUDs should be sterilized chemically (i.e., by soaking for 20 minutes in a 1 : 1000 benzalkonium chloride or 1 : 2000 aqueous iodine solution). Ideally, appropriate surgical standards of asepsis should be observed during the insertion procedure and the cervix should be prepared by swabbing with an antiseptic solution. The maintenance of asepsis may be facilitated by the use of sterile prepackaged devices and disposable inserters. Dilatation of the cervix is usually not required except in the nulligravida or for the insertion of devices of larger diameter. Care should be taken to insert the device so that it will lie in the frontal plane of the uterine cavity.

5.7 Follow-up care

Ideally, IUD-wearers should be re-examined after the first menstrual period following insertion in order to detect possible early expulsions ; again after the third menstrual period in order to evaluate problems of early pain and bleeding ; and at annual intervals thereafter as part of routine gynaecological care, in order to repeat the cytological smear, to allay unwarranted apprehension and to treat any adverse reactions. Whether such a strict schedule of check-ups is practicable or not, all patients should be urged to report troublesome symptoms ; medical facilities must be made available for this purpose.

If the cervical attachment of the IUD cannot be visualized at these follow-up examinations, expulsion of the device cannot be presumed unless actually observed by the patient. Sometimes, in these cases, the IUD, together with its attachment, lies *in utero* or, rarely, in the abdominal cavity. It is therefore necessary that appropriate investigation be carried out if the threads are not seen.

The evaluation and treatment of other side effects and complications have been discussed in section 4.4.

5.8 Long-term safety

Experience with the Ota ring, in a large number of cases, goes back thirty years ; with the stainless steel ring, in a small number of cases, almost twenty years ; and with the plastic devices, also in a large number of cases, six years. Within the limits of the knowledge gained through this experience, there is no definite period of time after insertion when an IUD must be removed or changed. A decision as to whether the devices may be safely left *in utero* indefinitely must, of course, await further experience.

6. RESEARCH NEEDS

6.1 Basic research

Further studies are required on all the aspects of reproduction and intrauterine contraception enumerated below, both in women and in experimental animals.

1. Sperm capacitation and ovum and sperm transport, particularly in primates and ruminants.
2. Sperm and ovum recovery and transfer.
3. Recovery, at elective hysterectomy, of ova at specific stages of the menstrual cycle, and determination of their state of fertilization (or fertilizability) and normal development.
4. Chemistry and enzymology of the tubal, uterine, and cervical secretions.
5. Uterine and tubal motility.
6. Spermatotoxic, blastotoxic and bacteriocidal effects of uterine fluid *in vitro*.
7. Histological, histochemical and biochemical studies of the endometrium during the postpartum period.
8. Foetal morphology in cases of abortions in hospitals.
9. Precise timing of egg transport in infra-human primates, with and without IUDs.
10. Effects of IUDs on corpus luteum function.
11. Qualitative and quantitative changes in intraluminal secretions of the female genital tract, in the presence of IUDs.

12. Effects of uterine fluid from animals with IUDs, especially primates, on spermatozoa and blastocysts *in vitro*.
13. Relationship of leucocytic infiltration of the endometrium and of the fluid milieu to the mechanism of action of IUDs.
14. Effect of IUDs on the rate of uterine blood flow, especially in relation to bleeding problems (e.g., in the rhesus monkey).
15. Response of the genital tract to an IUD in women and in experimental animals suffering from protein deficiency.
16. Steroid and protein hormone metabolism in women wearing IUDs.
17. Incidence and mechanism of development of ovarian pregnancies in women wearing IUDs.
18. Long-term effects of IUDs on endometrial histology, histochemistry, biochemistry and metabolism.
19. Possible effects on endocrine glands other than the ovary (adrenal, thyroid, pituitary).
20. Effects of IUDs on the course of pelvic infections.
21. Biochemistry of calcium deposition on the IUD.
22. Evaluation of drugs in the prophylaxis and treatment of bleeding and pain associated with the use of IUDs.

6.2 Clinical and epidemiological studies

To ensure adequacy and correctness of bio-statistical methodology in conducting clinical trials, reference should be made to section 4.2 of this report.

The Scientific Group considered that further investigations were desirable into each of the aspects of IUD contraception listed below.

1. Systematic and controlled evaluation of pregnancies with the device *in situ*, including the incidence of congenital malformations.
2. Study of menopausal women following long-term continued use of an IUD, or of women who had a device inserted at a time approaching the menopause.
3. Long-term evaluation (15-20 years or longer) of endometrial and cervical histology and exfoliative cytology, using adequate controls.
4. Comparative studies, in different parts of the world, of haematological status, state of nutrition, etc., before and after insertion of an IUD.
5. Double-blind studies of the relation of clinical variables (effectiveness, side effects, continuation of use) to physical characteristics of the device, such as shape, size, rigidity, material, surface, etc.

6. Relation of clinical variables to anatomy, physiology, and pathology of pelvic organs.
 7. Relation of clinical variables to ethnic and socio-cultural factors.
 8. Relative frequency of comparable physical complaints and pathology among women with and without IUDs.
 9. Application of the life-table method to the study of side effects and complications not leading to removal of the IUD.
 10. Study of physicochemical and morphological changes in IUDs after prolonged use.
 11. Development of techniques other than radiography to detect IUDs *in utero* and when translocated *ex utero*.
 12. Development of IUDs suitable for nulligravidae.
 13. Evaluation of new intra-uterine contraceptive devices with regard to each of the parameters : shape, size, consistency and material, considered independently.
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