Intrauterine devices – past, present and future perspectives

Maternični vložki - preteklost, sedanjost in obeti v prihodnosti

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Abstract: Intrauterine devices (IUDs) are one of the most effective, safe, and economical methods of contraception today. In this paper we present the most frequently used IUDs as well as newly developed IUDs appearing on the market, their mechanism of action, the morphological and biochemical endometrial changes caused by the IUD, systemic absorption of substances through the endometrium in the presence of an IUD, indications and contraindications for IUD use, and complications with the use of the IUD.

Key words: *intrauterine devices (IUD), types, mechanism, systemic absorption, complications*

Povzetek: Maternični vložki so danes ena od najbolj učinkovitih, varnih in ekonomičnih metod kontracepcije. V prispevku so predstavljeni najbolj pogosto uporabljani maternični vložki, kakor tudi novejši maternični vložki, ki se pojavljajo na tržišču, njihovo delovanje, morfološke in biokemične spremembe endometrija zaradi prisotnosti materničnega vložka, sistemska absorpcija učinkovin skozi endometrij ob prisotnosti materničnega vložka, indikacije in kontraindikacije materničnih vložkov ter zapleti pri uporabi le-teh.

Ključne besede: *maternični vložki, tipi, mehanizem delovanja materničnih vložkov, sistemska absorpcija, zapleti*

1 Introduction

Contraceptives are devices or methods for preventing pregnancy, either by preventing the fertilization of the female egg by the male sperm or by preventing implantation of the fertilized egg. Unintended pregnancy is expensive for both women and society in terms of medical costs, the costs of caring for more children, and achieving personal/professional goals (1).

A wide variety of contraceptive methods has been developed, including intrauterine devices (IUDs), intrauterine systems (IUS), hormonal contraceptives (oral contraceptives, implants, injections, contraceptive patch and vaginal rings), barrier devices with or without spermicides (male condom, diaphragm, cervical cap, female condom), natural family planning methods, male sterilization (vasectomy), and female sterilization (tubal ligation) (2, 3).

The intrauterine device (IUD) is one of the most effective, safe, and economical methods of contraception today. It is used by more women worldwide than any other reversible method of birth control.

2 Historical background

The modern era of the IUD started in 1909 when Richard Richter in Germany (4) used a ring from silkworm gut as an intrauterine device. This device was the first genuine IUD. Unfortunately, Dr Richter's invention was of no medical interest at those times and had no impact on the practice of birth control, so clinical data were never supplied.

Ernst Gräfenberg described in 1929 (5) a device consisting of a core of silkworm gut encircled by an alloy of copper, nickel, and zinc that was highly effective in preventing pregnancy. The results of his experiments started a strong controversy on the problem of the induction of PID (pelvic inflammatory disease) and European practitioners rejected the idea. Fortunately, in Japan in 1934, Tenrey Ota (6) presented the results of his studies on the use of elastic metallic rings as IUDs. The idea was accepted and the IUDs rapidly started to be used. After 1950, opinion about the IUD changed in Europe following the studies of Oppenheimer (7) in Israel and Ishihama (8) in Japan. These experiments and studies finally led to the first IUDs on the market in the 1960`s.

3 Types of IUD

3.1 Plastic devices: first-generation IUDs

IUD technology has come a long way since the first plastic IUDs appeared on the scene. The first of the so-called "first generation" IUDs, represented by the "Margulies spiral", was introduced in 1960. After many experiments, Dr Jack Lippes invented the double-S Loop (the Lippes Loop) in 1962 (9). It was made from polyethylene, with barium sulphate added for visibility under X-rays, and was available in four sizes, from A to D. This IUD 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. It

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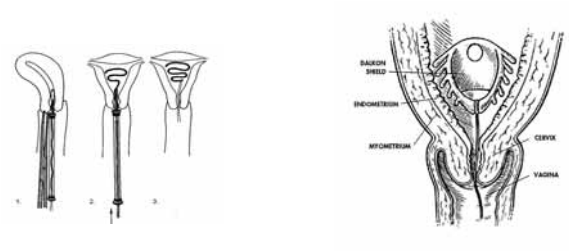
became the standard inert device; all the major studies on the IUD were made using this device. Due to its particular shape (trapezoid) (Figure 1a), the Lippes Loop fits the relaxed uterine cavity snugly. The Lippes Loop was to become extremely popular and, of all the first-generation IUDs, had the greatest worldwide impact.



a)The Lippes Loop *b) The Dalkon Shield*

Figure 1: Plastic devices
Slika 1: Plastični maternični vložki

In subsequent years, resourceful investigators produced scores of original, and sometimes peculiarly shaped, plastic IUDs. One of these was the Dalkon Shield (Figure 1b), developed by Dr Hugh Davis, and released in 1971. The Dalkon Shield was a plastic device which looked like a round bug with one large eye and five legs on each side. It had a unique tail: not a single filament, but many fibres wound together and enclosed in a sheath. Because the Dalkon Shield's unique shape made it difficult to remove, a multifilament string was used (instead of the usual stiff monofilament polyethylene thread) to provide increased tensile strength during removal. The multifilament tail string, unique to the Dalkon Shield, was most probably responsible for the facilitated ascent of bacteria from the vagina upward into the uterine cavity, causing pelvic infections. Shortly after its release, reports of septic abortion and other infections reached a serious level (10).

3.2 Copper-bearing devices: Second generation IUDs

Towards the end of the 1960's, it was discovered that adding copper to the plastic produced an IUD that was more effective in preventing pregnancy and less frequently caused bleeding problems. The development of the first copper-bearing IUD (Cu-IUD) was announced in 1969 by Dr Jaime Zipper and Dr Howard Tatum. Dr Tatum invented the plastic T–IUD and Dr Zipper investigated the device clinically (11). Being aware that the uterine cavity, when contracted, assumes the shape of a capital "T", Dr Tatum postulated that a small T-shaped IUD would be the most appropriate. Moreover, and on account of the "fundal-seeking effect", the T-shaped device would be less prone to expulsion. After some dose-exploration experiments, the team decided that a copper filament with a free (ionizable) surface of 200 mm^2 was optimal in terms of contraceptive efficacy. The first copper-bearing IUD, the TCu200 (Figure 2a), was produced in 1969. Using a T–carrier, with the addition of 200 mm^2 copper wire, reduced the pregnancy rate from 18 per 100 woman-years with the plain T carriers to 1 per 100 woman-years.

Later, an impressive number of "copper-bearing IUDs" were devised, of which only a few have made a clinical career. The Multiload (ML) IUD (Figure 2b), invented in 1974 by the Dutch gynaecologist Dr Willem van Os, was very successful. Its platform is an ingenious hybrid of the T-IUD and the Dalkon Shield, the purpose of the ear-of-corn-shaped skeleton being two-fold: to avert traumatic pressure on the endometrium while enhancing the retention of the device. The Multiload (ML) series of devices were designed to reduce the incidence of expulsion by the addition of plastic fins on the lateral, curved arms. Copper wire is wound onto the central stem of the device. The MLCu-250 was the first version, available in three sizes (standard, mini and short), to allow insertion into different sized uteri, including the nulliparous. The MLCu-375 followed, with more copper to enhance efficacy and length of use. The lower copper-load versions are licensed for 3 years' use and the 375 model for 5 years, although efficacy to 8 years has been demonstrated for the latter device (12).

a) The first copper-bearing IUD - TCu200
b) Multiload device (MLCu-250 and MLCu-375)
c) TCu-220C

d) TCu380A
e) TCu-200-Ag (200mm^2); TCu-380-Ag (380mm^2).
f) TCu380S (Slimline)

Figure 2: Copper-bearing devices
Slika 2: Maternični vložki z bakrom

Over the years, Dr Tatum himself developed a series of copper-bearing T devices. His TCu220C model (Figure 2c) is of particular interest, because, in carrying copper collars instead of a copper filament, metal loss was prevented. In his last (Figure 2d), more flexible model, Dr Tatum combined tubular with filamentous copper and the TCu-380A currently serves as the gold standard for comparative studies.

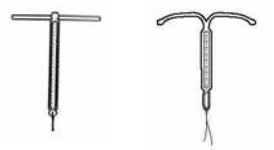
The Copper T 380 series comprises three devices (Figure 2 d, e and f): the TCu-380A, the original device, a device with a silver core wire (in two variants: TCu-200-Ag and TCu-380Ag), and the TCu380S (Slimline) (13). The current license for the TCu380A is for up to eight years. The TCu-200-Ag has been in use since 1978. It consists of a plastic T-shaped frame with silver-cored copper wire wound around its central stem, presenting a total surface area of

200 mm² copper. The addition of the silver core was found to reduce fragmentation, thus prolonging the effective lifespan of the device.

In the early 1990s, a higher load, but otherwise identical, device, the TCu-380-Ag, was developed, bearing a surface area of 380 mm² copper. The TCu-380Ag is made of polyethylene and wound with copper wire with a silver core. The surface area of the copper is 380 mm⊕ The polyethylene body, shaped as a modified T, is impregnated with barium sulphate. Removal threads, pigmented with iron oxide, are attached to the base of the vertical arm of the T. The current license for the TCu-380-Ag is for up to five years. The Slimline (TCu380S) was so called because the copper collars on the side arms were sunk into, and thus flush with, the side arms, making loading into the insertion tube easier. TCu380S (Slimline) was compared to the TCu380A in a four year study (14). The results showed the Slimline to be superior to the TCu380A in pregnancy prevention but to have a higher expulsion rate in the first year of use. This latter finding was thought to be a function of the anomalously low expulsion rate of the TCu380A in this study compared to others, rather than a higher than average expulsion rate with the S version. The lower pregnancy rate with the Slimline may again be anomalous, or may be related to the more lateral placement of the copper collars on the side arms, bringing the copper closer to the tubal ostia. A very large study would be needed to clarify this. The study concluded that both versions provide effective pregnancy prevention. A number of copper-bearing devices are now commercially available in various other forms. The numbers included in the names of the devices refer to the surface area (in mm²) of the copper on the device; a larger surface means a higher activity.

3.3 Steroid-medicated devices: third-generation IUDs

In the late 1960s, Dr Antonio Scommegna (15), having demonstrated the uterine effects of progesterone, postulated that the endometrial atrophy elicited by the natural steroid hormone would be useful in preventing implantation and reducing menstrual bleeding. He developed a hormone releasing device and showed that it is as effective in preventing pregnancy as the copper-bearing IUD. Dr Scommegna devised a T-shaped device (Figure 3a), consisting of a permeable polymer membrane which releases progesterone at a predictable, controlled rate of 65 µg per 24 h over the period of a year (15). Unfortunately, this IUD did not gain wide popularity on account of its short (1-year) effective lifespan.



a) Progesterone T IUD
b) LNG IUS (Levonorgestrel-releasing intrauterine system
Figure 3: Steroid-medicated devices
Slika 3: Steroidni maternični vložki

The levonorgestrel IUS is a T-shaped polyethylene device with a steroid reservoir around the vertical stem (Figure 3b). The cylindrical reservoir contains a mixture of silicone (polydimethylsiloxane) and 52 mg levonorgestrel, a progestin widely used in implants, oral contraceptives, and vaginal rings. This allows a steady, local release of 20 µg levonorgestrel per day through the rate-limiting surface membrane (16). The reservoir is covered by a silicone membrane, and the frame contains barium sulphate, which makes it radiopaque. A monofilament removal thread is attached to a loop at the end of the vertical stem. The introduction of LNG-IUS has brought a significant change in the side effects in IUD users, with a dramatic reduction in blood loss and the number of days of bleeding per cycle. However, during the first months of use, bleeding can be erratic or even heavy at times, with more than 30% of users experiencing prolonged bleeding of more than 8 days duration (16). The LNG IUS is licensed for 5 years' use. Many studies, reporting more than 12,000 women-years of use, have confirmed the excellent efficacy of the LNG IUS, with Pearl indices of 0–0.3. (17). There is no statistically significant difference between the efficacy of the LNG IUS and CuT380 at 7 years (17). A European multicentre trial showed an incidence of ectopic pregnancy of only 0.02 per 100 women-years, representing an 80-90 % reduction in risk compared with women not using contraception. Approximately 20% of conceptions with the LNG IUS are ectopic (17); the possibility of ectopic pregnancy should therefore not be ignored in a woman with an LNG IUS in situ. Expulsion rates have been found to be similar to those with other framed devices (18).

The intrauterine release of levonorgestrel has a local effect on the endometrium, rendering it suppressed and insensitive to oestradiol and resulting in a progressive reduction in the volume and duration of menstruation. Menstrual irregularity – mostly frequent, irregular spotting – is common in the first few months after LNG IUS insertion. From the fourth month onwards a profound reduction in menstrual blood loss (MBL) is typical. The reduction in MBL results in an increase in haemoglobin concentration over the 5-year lifespan of the LNG IUS (18). The tissue concentration of LNG in the endometrium during LNG IUS use far exceeds that found with high systemic doses of levonorgestrel. This explains the marked endometrial suppression seen in all layers of the endometrium, to the myometrium and throughout the uterine cavity, and also in the oligo-amenorrhoea seen with continuous oestrogen replacement in peri- and postmenopausal women (19). The strong, local progesteronic effect of the levonorgestrel-releasing IUS prevents endometrial hyperplasia during hormone replacement therapy, which is an approved indication for its use in some countries.

4 Newly developed IUDs

Several new intrauterine devices (IUDs) are under development or in the early marketing phase (19, 20). These new devices contain various modifications designed to improve patient continuation and physician satisfaction (Figure 4.). Modifications include those designed to facilitate easier insertion and removal, to decrease the rates of accidental expulsion, and reduce complaints of pain or bleeding (responsible for 30 % to 50 % of discontinuations).

Devices are being designed to address these issues by modifying IUD size, shape, and flexibility. Some devices are under development, or have recently been introduced. These devices include (Figure 4):

a) CuSafe 300
b) Fincoid-350®
c) GyneFixâ

d)intracervical fixing device (ICFD)
e) Sof-T
f) Multiload Mark II

Figure 4: Newly developed IUD's.
Slika 4: Novejši maternični vložki

4.1 CuSafe 300

This device was developed specifically to decrease the incidence of unwanted side effects such as bleeding, pain and expulsion. The plastic frame of the device is smaller and more flexible than most other framed devices (Figure 4a). Both ends of the device's transverse arms curve inwards to reduce uterine tissue irritation. The side arms are thinner than the central stem, allowing easier insertion by a simple push-in technique, and are bent back on themselves in order to reduce trauma to the endometrium. In addition, its monofilament tail is welded into the shaft, instead of knotted, to reduce ectocervical abrasion. This design facilitates easier and less painful insertion and removal, but the curved, "fundal-seeking" arms also resist expulsion. The device bears 300 mm^2 copper on its central stem. The CuSafe 300 is a T-shaped copper IUD with flexible, uniquely shaped arms (20). It carries a recommended lifespan of 5 years.

Early studies were encouraging. In a non-comparative study in over 1000 women, 80% of them nulliparous, the 1-year pregnancy and expulsion rates were both 0.6 per 100. Removals for bleeding and pain were also low, at 4.2 and 1.5 per 100, respectively (21). However, a randomised trial, comparing the device to the TCu380A in 600 nulliparous and parous women, apparently produced a higher pregnancy rate which was not significant, and a significantly higher expulsion rate for the Cu-Safe than the TCu380A (22). In the study comparing CuSafe and TCu380A IUDs, removals for pain and bleeding occurred significantly less frequently among CuSafe IUD users (23). On the other hand, the study found that the CuSafe had higher, although statistically nonsignificant, rates of pregnancy and expulsion.

4.2 Fincoid-350

The Fincoid-350 (Figure 4b), is also designed to resist accidental expulsion. The IUD has a plastic skeleton comprised of two parts: curved horizontal arms, and a copper-coated vertical stem. The horizontal arms lock into a groove on the vertical stem. The resulting movable joint easily constricts and expands with uterine contractions, adjusting to variations in uterine size and shape (19). The Fincoid-350 comes in two sizes: standard and short.

Studies indicate continuation rates of 90 % for the Fincoid-350 device (19). A study of 792 women found a pregnancy rate of 0.6 %, an expulsion rate of 3.7%, and a rate of removal for pain or bleeding of 2.6 %. Another study of 90 women found a higher failure rate of 2.8 % (24).

4.3 GyneFix®

To minimize failure and side effects of intrauterine devices (IUDs), especially abnormal bleeding, pain, partial and complete expulsion, and other complications due to disharmony, the "frameless" intrauterine system (IUS) was developed (Figure 4c). Total elimination of the frame would create perfect harmony and reduce the surface area of the foreign body. However, to retain the IUS in the uterine cavity, the device should be fixed to the uterine wall. This approach seemed a logical and practical way to obtain a significant improvement in IUD performance.

This "frameless" IUD consists of six 5 mm copper sleeves with an effective copper surface area of 330 mm^2, fixed on a length of semi-rigid suture thread. The knot at the upper extremity of the device is anchored (implanted) in the myometrium of the uterine fundus. This device was originally called the Cu-Fix 390, then later the FlexiGard 330 (identical to GyneFix in all but insertion instrument). The device has under-gone 10 years of testing and several modifications to its insertion and anchoring mechanisms (24, 25). The upper and lower copper sleeves are crimped onto the suture thread to prevent slippage. The proximal end of the suture contains a knot that is inserteded 1 cm into the fundal myometrium to anchor the device into the uterine muscle. Variations of the device for postpartum use include a larger knot and a cone-shaped biodegradable tip that help anchor it securely (26).

This concept avoids dimensional problems. The effectiveness of this IUS in use is similar to that found with TCu380A. The high initial and ongoing effectiveness of the 'anchored device' is attributed to its constant release of spermicidal copper ions in the upper part of the uterine cavity. As the contraceptive effect of copper-releasing intrauterine devices is closely related to the amount of active agent within the uterine cavity, conception is more likely when the contraceptive substance is reduced as a result of downward displacement of the device or low insertion of the IUD into the uterine cavity. Optimal contraceptive efficacy is obtained when the IUD is located in the fundal part of the uterine cavity (27).

Due to its frameless design, flexibility, and minimal presence in the uterine cavity, this IUD is associated with few expulsions (25). In addition, the device has a high continuation rate at 1 year (90%) due to few removals for complaints of bleeding or pain. Effectiveness depends upon the proper insertion technique because the device must be securely anchored into the uterine myometrium or it will be expelled. The reported failure rate from long-term clinical studies is 0.5 at 3 years, which is as low, or lower than the copper T 380A.

4.4 intracervical fixing device (ICFD)

The intracervical fixing device (ICFD) differs substantially in both construction and placement from other IUDs (Figure 4d). The device consists of a rod-shaped, copper-coated polyethylene frame that is about 4 cm long, with a 5 mm projection at the distal end (20). Through this projection, the ICFD is anchored (fixed) to the inner cervical wall using a modified tenaculum. Removal is facilitated by grasping the stem with sponge forceps (20). Investigators believe the ICFD's anchoring mechanism could be improved, however, and new fixing techniques are being studied. Better anchoring mechanisms could help to prevent expulsions. One potential advantage of the device is that the insertion procedure is not blind. In addition, because of the intracervical location, the device is less likely to be associated with spotting, bleeding and pain.

4.5 Sof-T

The Sof-T is a copper IUD with a unique shape to enhance effectiveness. The device has soft, flexible knobs, or occlusion bodies, on each end of its flexible transverse arms (Figure 4e). These knobs theoretically block the entrances into the fallopian tubes. The insertion procedure for the Sof-T is similar to that for currently available copper IUDs (20). Ultrasound must be used, however, to ensure exact placement of the device. The device's potential ability to occlude the fallopian tubes could, in theory, reduce the incidence of tubal infection and ectopic pregnancy; however, comparative trials have yet to be performed (20).

4.6 Multiload Mark II

The Multiload Mark II (Figure 4f) is an updated version of the original Multiload 375 (ML 375) (20). The original device has a record of dependability, with low patient cessation rates due to pregnancy, expulsion or bleeding and pain. The ML 375 has been associated with problematic insertions, however, because its arms do not fit into the inserter; the arms are open during insertion, making placement more difficult.

Developers hope the Multiload Mark II will overcome these insertion limitations (20). Like its prototype, the Multiload Mark II has a 375 mm^2 copper-coated shaft; however, it has shorter, more flexible arms that allow the device to be folded completely into its inserter. As a result, the new inserter's diameter is smaller than the original model. In addition, the inserter has three other improvements: its design prevents the IUD from getting pushed beyond the inserter; it can function as a uterine sound; and it has a single-handed expulsion action. These innovations may help limit the risk of uterine perforation (20).

5 Mechanisms of action

The mechanisms by which the IUD effects contraception have not yet been fully elucidated. The IUD induces an intense local inflammatory response, especially by the copper containing devices, which in turn leads to lysosomal activation and other inflammatory changes that are spermicidal. Whenever fertilization occurs, the same inflammatory actions are directed against the developing embryo. Inert devices, such as the Lippes-loop, are more effective with increased size and extent of contact with the endometrium. Certain metals, especially copper, greatly enhance the contraceptive action of inert devices, probably by inducing a more intense local intrauterine inflammatory response. The progesterone carrying devices induce atrophic endometrial changes which make the endometrium a hostile site for implantation if fertilization and successful tubal transport have occurred.

It is not possible to demonstrate a single mode of action of the levonorgestrel-releasing IUS. The main factors behind the contraceptive action of the device are scanty cervical mucus and strong suppression of the endometrium. The local effect of progestogen causes the cervical mucus to thicken. The constantly elevated circulating levels of levonorgestrel prevent the normal thinning of cervical mucus at mid-cycle so that it remains scanty and viscid, as in women treated with levonorgestrel-releasing implants. The changes in the cervical mucus clearly have a strong effect on contraceptive efficacy but there is insufficient research on this effect of the levonorgestrel-releasing IUS. Other suggested mechanisms to prevent conception are inhibition of sperm motility and function inside the uterus and in the fallopian tubes, preventing fertilization and endometrial growth. Early studies on the progestogen 2 μg/day device suggest that the contraceptive effect occurs before fertilization, since elevation in beta human chorionic gonadotropin (βHCG) levels has not been demonstrated and fertilized eggs from the reproductive tract have not been detected (28). Even though ovulation is inhibited in some women, it is not believed that it has a major effect on contraceptive efficacy. A foreign body effect, similar to that of other intrauterine contraceptive devices, is also present.

6 Morphological and biochemical endometrial changes caused by the 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. Increased vascular permeability, oedema, and stromal infiltration of leukocytes, including neutrophils, mononuclear cells and macrophages, have been shown (29). It should be emphasized that the foreign body reaction seen with both medicated and non-medicated IUDs occurs in the absence of bacterial infection and particularly 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, which does not exist in the endometrial reaction to IUD.

It has been suggested that the anti-fertility action of plastic IUDs is directly related to the presence of increased numbers of intrauterine endometrial leukocytes (30) and, in particular, macrophages (31). The high levels of intrauterine protein reported in IUD users (32) might reflect the cellular degradation of these neutrophils and macrophages, thereby contributing further to the anti-fertility effect. The foreign-body reaction caused by plastic devices is enhanced by the addition of copper to the IUD (33, 34). In addition, copper-bearing IUDs affect endometrial enzymes, the amount of DNA in endometrial cells, glycogen metabolism and estrogen uptake by the uterine mucosa (34).

Steroid-releasing IUDs exert specific morphological effects on the endometrium, such as suppressed proliferation of the endometrial stroma. A biochemical reaction following these morphological changes is the generally lower enzymatic activity, as compared with that in normal cyclical endometrium and in endometrium exposed to copper-bearing IUDs. In some animal species, the IUD has been shown to increase prostaglandin (PG F_2) production in the uterus and induce luteolysis (35). Many of the cellular and vascular changes observed in the IUD-influenced endometrium and in the uterine fluid can, in principle, be induced by prostaglandins. Moreover, cells attached to the surface of IUDs, both inert and copper-bearing, have the capacity to produce both PGF_2 and PGE_2 (36). Arachidonic acid metabolites produced by the lipoxygenase pathway, such as leukotrienes and lipoxins, are known to be products of human polymorphonuclear leukocytes. These compounds produce a variety of biological effects, such as cytotoxicity, chemotaxis and increased vascular permeability. The presence of levonorgestrel in endometrial cells causes high expression of insulin-like growth factor binding protein-I in the endometrium, which inhibits the activity of insulin-like growth factor-I (IGF1). IGF-I, on the other hand, is considered to mediate the mitogenic action of estrogens: inhibition of its activity causes suppression of endometrial proliferation (37). It has also been suggested that the continuous induction of plasminogen activator inhibitor-I by levonorgestrel could contribute to the therapeutic effect of the IUS on heavy menstrual blood loss (38). Glycodelin A messenger RNA and protein expression before and mid-cycle in women using the levonorgestrel-releasing IUS have been described. Possibly this untimely production of glycodelin A adds to the contraceptive action of the levonorgestrel-releasing IUS (38). This inappropriate production of glycodelin A coincides with the observed downregulation of the progesterone receptor (39).

7 Systemic absorption of substances through the endometrium in the presence of an IUD

It is well known that a wide variety of substances, ranging from antibiotics to steroids, can be absorbed through the genital tract. It was shown (40) that demonstrable quantities of d-norgestrel are absorbed from progesterone-bearing IUDs. Copper containing IUDs release certain amounts of copper daily, so that its systemic absorption through the endometrium was assumed to occur in their presence. It has also been suggested that the copper released from an IUD interacts with the contents of the endometrial fluid and this may render it nonabsorbable. Another theory attempts to account for the fact that, despite the high copper levels in uterine fluid and cervical mucus, very little copper is found in the endometrium or uterus (41). It is suggested that a dynamic equilibrium exists between a copper IUD and endometrial fluid. Copper from the device may be released until it reaches equilibrium with endometrial fluid. Fresh secretions wash the copper-rich fluid down the cervical canal and further release of copper then takes place.

Levonorgestrel released from the IUS is quickly absorbed into the capillary network in the basal membrane of the endometrium and thereby into the systemic circulation (42). It is detectable in plasma just 15 minutes after insertion. The maximum plasma levels (175-1589 nmol/dm^3) are reached within hours following insertion. The individual plasma concentrations remain fairly stable during the first weeks but decline with time (42). At three months after insertion the mean plasma concentrations are 142 ±46 ng/dm^3 and, after 48 months, are 81 ±22 ng/dm^3. The mean plasma concentrations are between 100 and 200 ng/dm^3. However, there is considerable inter-individual variation in levonorgestrel plasma concentrations. The concentrations reached with the levonorgestrel-releasing IUS are lower than those reached with levonorgestrel releasing implants and progestogen-only pill (42). In the circulation, levonorgestrel strongly binds to sex hormone-binding globulin (SHBG) (43). Higher levels of both SHBG and levonorgestrel have been detected in women with anovulatory cycles. The levonorgestrel concentrations in the endometrium are very high. The concentrations in the myometrium and in the fallopian tubes are significantly lower than in the endometrium (44).

8 Indications and contraindications for IUD use

IUDs are especially indicated for:

- women who seek a reversible, effective, coitally independent method of contraception;
- women seeking a private form of contraception (this may require that the IUD strings are removed or cut short);
- women who are concerned that they may not remember to use a daily method;
- women who are considering sterilization;
- following delivery or abortion;
- women who are breastfeeding;
- women who cannot use a hormonal method of contraception.

Like other contraceptive methods the IUDs are not indicated for all women at all times. The contraindications are absolute or relative.

a) Absolute contraindications are: pregnancy or possible pregnancy; current pelvic inflammatory disease (PID), cervicitis, bacterial vaginosis, or chlamydial or gonococcal genital infection; lifestyle with increased risk of STD (sexually transmitted diseases); allergy to any constituent of the device; Wilson's disease (copper devices); conditions leading to increased susceptibility to infection, especially AIDS, leukaemia, IV drug abuse; undiagnosed irregular genital tract bleeding; immunosuppressed individuals.

b) Relative contraindications are: valvular heart disease; past history of PID; presence of a prosthesis potentially at risk with blood-borne infection (e.g. hip); abnormalities of the uterus resulting in a distorted cavity or a cavity that sounds to less than 6.0 cm; history of ectopic pregnancy; severe primary dysmenorrhoea; menorrhagia; cervical stenosis; uterine fibroids or congenital uterine anomaly.

9 Complications with the use of the IUD

Several complications have been described with the use of the IUD. These complications must be addressed when IUD insertion is considered.

9.1 Uterine perforation

Although rare, the most serious complication of an intrauterine contraceptive device is uterine perforation. An intra-abdominal IUD can lead to serious consequences such as bowel obstruction or bowel perforation. Therefore, the device should be removed as soon as possible after the diagnosis has been made (45, 46). Laparoscopy (an operative procedure using a small optic device inserted through the abdominal wall without large incisions) can often be used to remove abdominally located IUDs. Copper devices 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 (using large abdominal wall incision).

9.2 Pregnancy with the IUD

This complication may lead to spontaneous abortion, especially septic abortion in the second trimester. It is important to recognize that 3-9 % of pregnancies with IUD in place are ectopic. Septic abortion carries the risk of maternal as well as fetal death. Thus, because of the risk to the woman's health the IUD should be removed as soon as pregnancy is diagnosed. If the IUD cannot be removed because the tail is not visible, the woman has to have special obstetric care because of an increased risk of premature birth and a decreased likelihood of live birth (43).

9.3 Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is a broad term for any infection ascending from the cervix into the uterus, fallopian tubes, and ovaries. The increased risk of PID is largely concentrated in the first few weeks after insertion and is due to poor infection prevention during insertion. Thereafter, the risk is among women exposed to STDs. In addition to STDs, postpartum and postabortion infections are major causes of PID (49).

The complications of PID are sometimes severe. Even a single infection can permanently damage the lining of the fallopian tubes. This may partially or totally block one or both tubes, substantially increasing the chances of ectopic pregnancy and infertility.

Diagnosis of pelvic inflammatory disease (PID) is based on a series of signs and symptoms that include: low abdominal pain, motion tenderness of the uterus, purulent cervical discharge, temperatures of 38°C or more, palpable, painful adnexal swelling and intermenstrual bleeding. Any combination of the above signs and symptoms is possible in patients with PID. In addition, the probability of the disease increases if the erythrocyte sedimentation rate is more than 15 mm/h, there are more than 10,000 white blood cells per mm^3 of blood, C-reactive protein is positive, and if the cervical culture is positive for *Neisseria gonorrhoea* or *Chlamydia trachomatis*. In view of the serious consequences of PID, including pelvic adhesions and infertility, antibiotic treatment is often given if PID is suspected, especially in the young nulliparous woman. The IUD is usually removed in women suspected to have PID. The microorganisms causing infection of the endometrium and fallopian tubes in the presence of an IUD are divided into two main groups, exogenous and endogenous. The exogenous microorganisms are usually transmitted sexually and include *Neisseria gonorrhea*, *Chlamydia trachomatis* and *Mycoplasma hominis.* Endogenous microorganisms include the microbial flora of the lower female genital tract, many of them with potential pathogenic capacity. However, species belonging to the endogenous vaginal flora have often been isolated in patients with pelvic inflammatory disease associated with sexually transmitted disease. This infection is called "poly-microbial" PID (49). These mixed infections are marked by anaerobic bacteria which are favoured by the local conditions. This often leads to abscess formation in the form of tubo-ovarian abscess. Several studies indicate that the risk of PID is highest in the first few months after insertion but decreases dramatically thereafter to become probably not greater than in women not using an IUD (49).

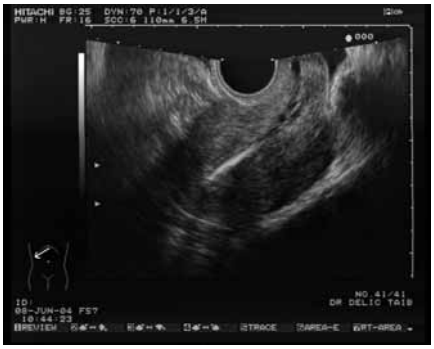
9.4. Expulsion of the IUD

Expulsion or uterine perforation is suspected whenever the threads attached to the IUD are not visible on vaginal inspection. If the retrieval threads cannot be visualized, the IUD may have been expelled. Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain (50).

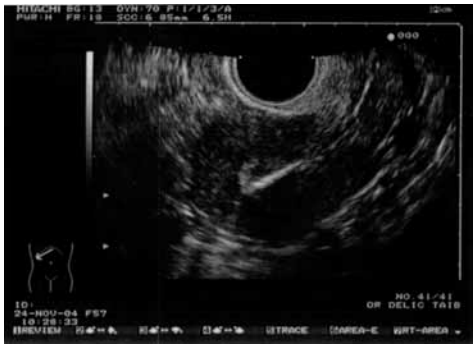
The expulsion rate for IUDs varies considerably between trials and different devices, ranging from 11 to 1.3 per 100 women. Non-medicated devices have higher expulsion rates. Nulliparous women have a higher expulsion rate than multiparous women, particularly for the larger devices such as the Lippes loop. An estimated 2% to 8% of IUDs are expelled from the uterus within the first year. Expulsion is most likely to occur during the first three months after insertion. More than two-thirds of the expulsions occur within the first year of use (50). In some studies the expulsion rate has been higher with the levonorgestrel-releasing IUS during the first year of use (50), while in others expulsions have occurred at a fairly constant rate (51, 52).

Ultrasound may be used to ascertain the position, and to visualize the typical ultrasonographic appearance of the IUD. It is based on their ultrasonic reflectivity, so it is possible to differentiate IUD types. IUDs appear as clearly marked, linear hyperechogenic structures, echogenicity of bone tissue.

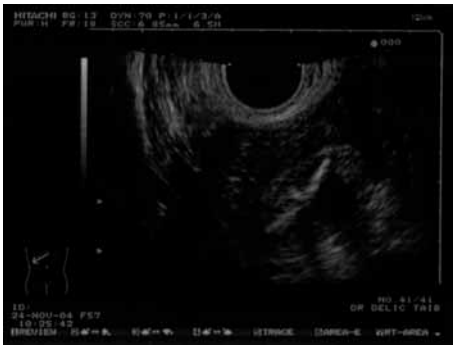
Typical sonographic images of the IUD device (normal and expulsions) are shown on Figure 5.



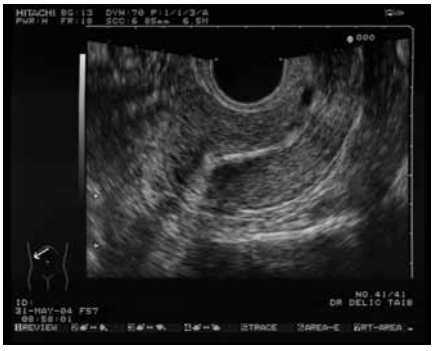
a) Normal uterus- IUD in situ-vertical section



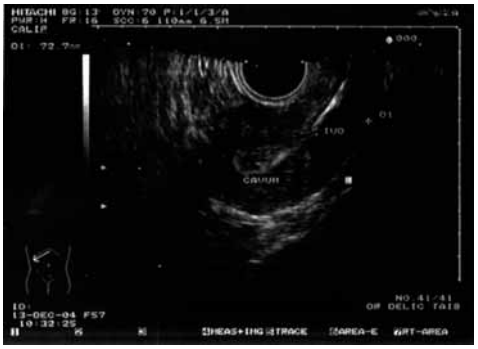
b) Uterus bicornis- IUD in situ-vertical section



c) Uterus bicornis- IUD in situ-transversal section



d) Normal uterus- IUD partial expulsion-13 mm-vertical section



e) Normal uterus-IUD complete expulsion- IUD in cervical canal-vertical section

Figure 5: Sonographic images of the IUD device
Slika 5: Ultrazvočni posnetki vstavljenih maternični vložkov

However, a device can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may also decrease the effectiveness of IUD. Pregnancy, both uterine and ectopic, should be considered before attempting to locate the IUD. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, the device may have been expelled.

9.5 Fertility problems

There is no evidence of impairment in fertility in women who discontinue the use of an IUD in order to become pregnant (53). Most women who discontinue IUD use to become pregnant conceive as quickly as non-users. The opinion of authors in general is that IUD does however increase the risk of developing PID and sometimes this leads to tuba infertility.

US case control studies (54) reported that nulliparous women with tuba infertility are two to three times more likely to have used IUDs than women having the first child. The risk of tuba infertility varied with the type of IUD and with the number of the woman's sexual partners. The copper IUD users had only slightly greater risk of tuba infertility than women who had never used it, in contrast to the former Dalkon Shield users, who had the higher relative risk. Most cohort studies that have followed women who stopped using IUDs have found no indication of impaired fertility. In 10 studies involving about 3800 women, from 72 to 96 % of them conceived within a year after stopping the IUD use. This rate is in the same range as rates among women who have never used contraception.

One cohort study (55) involved women who at some time had discontinued IUD use because of complications (pain, bleeding or discharge). These women gave birth at only a slight lower rate than groups of other women who had discontinued IUD or other methods to become pregnant.

In conclusion, use of the IUD does not affect the fertility of the women to such a degree as to be considered important, and the return of fertility after stopping its use is less than 12 months.

9.6 Carcinogenicity

Implantation of a foreign body subcutaneously in rats results in a high frequency of sarcoma. Moreover, it has been shown that the introduction of either plastic or stainless steel implants in the uterus of Wistar rats results in a higher frequency of carcinoma and sarcoma than that found in the control group (56). However, in primates (rhesus monkey), no evidence of uterine malignancy after 7 years of copper T use has been shown. Despite the increasing use of IUDs around the world, the potential long term risk of developing endometrial carcinoma has been insufficiently studied in large scale studies (57).

10 Conclusions

Intrauterine contraceptive devices (IUDs) have been extensively used as a cheap, effective, reversible and dependable method for controlling fertility in women. The IUD offers a reasonable degree of acceptability for family planning, although in recent years its popularity has declined considerably. One of the major causes for this decline is attributed to bleeding episodes associated with its use. The widespread use of the IUD has prompted numerous investigations on the mechanism of action of the device. However, the precise mode of action of the IUD is not yet understood.

New IUDs are being designed with modifications to help enhance patient and physician acceptance. The modifications are aimed to decrease removals for pain and bleeding, make insertion and removal easier, and limit the risk of expulsion.

Assessing the evidence is difficult, since different studies report different event rates for the same devices, either by statistical chance or due to differences in women recruited, and much of the early data about devices derive from noncomparative studies.

The CuT380A remains the “gold standard” copper device, offering the best protection against pregnancy, although perhaps rivalled by the “frameless” intrauterine system. However, larger and longer-term studies are needed to confirm the latter.

Other framed high-dose copper devices offer slightly lowers protection against pregnancy, with similar adverse event rates. The “frameless” intrauterine system may offer advantages over framed devices but only when problems with expulsion in routine use can be overcome. The LNG IUS is the appropriate choice for women with heavy periods, either spontaneously or when using a copper IUD.

Any risk of PID and infertility must be weighed in relation to these factors when a patient expresses interest in an IUD. For most women, the benefit of excellent pregnancy protection and ease of use will outweigh the very low risk of serious adverse effects. If therefore the IUD is used only by women who are not at risk of sexually transmitted infection, its reputation can flourish and the method can provide most couples with years of effective contraception.

These positive effects may well overcome barriers to IUD provision, rid the device of its tainted image and lead to expanded reproductive health choices. Investigators are working on improving existing models and developing entirely new ones which may also reach the market in the near future.

11 References

1. Klima CS. Unintended pregnancy. Consequences and solutions for a worldwide problem. J Nurse Midwifery 1998; 43: 483-491
2. Chiou C-F, Trussell J, Reyes E. et al. Economic analysis of contraceptives for women. Contraception 2003; 68: 3-10
3. Davis AJ. Advances in contraception. Obstet Gynecol Clin North Am 2000; 27:597-610
4. Richter R. Ein Mittel zur Verhütung der Konzeption (A means of preventing pregnancy). Deut Med Wochensshr 1909; 35: 1525-1527
5. Gräfenberg AE. An intrauterine contraceptive method. In: Sanger M, Stone MH ed. The practice of contraception: an international symposium and survey. Proceedings of the 7th International Birth Control Conferences, Zurich, September 1930: Baltimore; Williams and Wilkins: 33-47
6. Ota T. A study on the birth control with an intrauterine instrument. Jpn J Obstet Gynecol 1934; 17: 210-214
7. Oppenheimer W. Prevention of pregnancy by the Grafenberg ring method. Am J Obstet Gynecol 1959; 78: 446-450
8. Ishihama A. Clinical studies on intrauterine rings, especially the present state of contraception in Japan and the experience in the use of intrauterine rings. Yokohama Med Bull 1959; 10: 89-93
9. Lippes J. A study of intrauterine contraception: development of a plastic loop. In: Teitze C. and Lewit S. (Eds.) Intrauterine contraceptive devices, Excerpta Amsterdam, 1962: 69-75
10. Tatum JH, Schmidt FH, Phillips D, et al. The Dalkon Shield controversy. Structural and bacteriologic studies of IUD tails. JAMA 1973; 231:711-717
11. Zipper J, Medal M and Prager R. Suppression of fertility by intrauterine copper and zinc in rabbits. A new approach to intrauterine contraception. Am. J. Obstet. Gynecol. 1969; 105: 529-534
12. Castro A, Abarca L, and Rios M. The clinical performance of the Multiload IUD. II. The influence of age. Adv Contracept 1993; 9: 291-298
13. WHO Special Programme of Research, Development and Research Training in Human Reproduction. The TCu380A, TCu220C, Multiload 250 and Nova T IUDs at 3, 5 and 7 years of use – results from three randomized multicentre trials. Contraception 1990; 42: 141–158.
14. Sivin I, Diaz J, Alvarez F. Four-year experience in a randomized study of the Gyne T380 Slimline and the standard Gyne T380 intrauterine copper devices. Contraception 1993; 47: 37–42.
15. Scommegna A, Pandya GN, Christ M. et al. Intrauterine administration of progesterone by a slow release device. Fertil Steril 1970; 21: 201-210
16. Zalel Y, Gamzu R, Shulman A et al. The progestative effect of the levonorgestrel-releasing intrauterine system-when does it manifest. Contraception 2003; 67: 473-476
17. Sivin I, Stern J. Health during prolonged use of levonorgestrel 20 mcg/d and the Copper TCu 380Ag intrauterine contraceptive devices: a multicenter study. Fertil Steril 1994; 61: 70–77.
18. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. Contraception 1994; 49: 56–72.
19. Suhonen S, Holmstrom T, Lahteenmaki P. Three-year follow-up of the use of a levonorgestrelreleasing intrauterine system in hormone replacement therapy. Acta Obstet Gynecol Scand 1997; 76: 145-150.

20. Boateng J, Chi I-C, Jones DB. An evaluation of six new intrauterine devices. Adv Contracept 1994; 10:57-70.
21. Kurz KH, Meier-Oehlke PA. The Cu safe 300 IUD, a new concept in intrauterine contraception: first-year results of a large study with follow-up of 1017 acceptors. Adv Contracept 1991; 7: 291-300.
22. Van Kets HE, Van der Pas H, Delbarge W, et al. A randomized comparative study of the TCu380A and Cu-Safe 300 IUDs. Adv Contracept 1995; 11: 123-129.
23. Chi I. What we have learned from recent IUD studies: a researcher's perspective. Contraception 1993; 48: 81-108.
24. Rosenberg MJ, Foldesy R, Mishell DR Jr., et al. Performance of the TCu380A and Cu-Fix IUDs in an international randomized trial. Contraception 1996; 53:197-203.
25. International Study Group on Intrauterine Drug Delivery. The GyneFix® implant systems for interval, postabortal and postpartum contraception: a significant advance in long-term reversible contraception. Eur J Contracept Reprod Health Care 1997; 2:1-13.
26. Wildemeersch D, Batar I, Biran A et al. The 'frameless' intrauterine system for long-term, reversible contraception: A review of 15 years of clinical experience. J Obstet Gynaecol Res 2003; 29: 160-169
27. Anteby E, Revel A, Ben-Chetrit A et. al. Intrauterine device failure: relation to its location within the uterine cavity. Obstet Gynecol 1993; 81:112-114.
28. Fraser IS, Tiitinen A, Affandi B, et al. Norplant : consensus statement and background review. Contraception 1998; 57: 1-9
29. Shaw ST and Macaulay LK. Morphologic studies on IUD-induced metrorrhagia. II. Surface changes of the endometrium and microscopic localization of bleeding sites. Contraception 1979; 19: 63-80.
30. Sedlis A and Ryiniak JV. Endometrial leukocytes in patients using intrauterine contraceptive devices. Am J Obstet Gynecol 1970; 108: 1209-1212
31. Sagiroglu N and Sagiroglu E. Bilologic mode of action of Lippes-loop in intrauterine contraception. Am J Obstet Gynecol 1970; 106: 505-515
32. Kar AB, Engineer AD, Goel R, et al. Effect of an intrauterine contraceptive devices on biochemical composition of uterine fluid. Am J Obstet Gynecol 1968; 101: 966-970
33. Sheppard BL and Bonnar J. The response of endometrial blood vessels to intrauterine contraceptive devices: an electron microscopic study. Br J Obstet Gynaecol 1980; 87: 143-154
34. Cuadros A, and Hirsch JG. Copper on intrauterine devices stimulates leukocyte exudation. Science 1972; 175: 175-176.
35. Spillman CH and Dury RT. Prostaglandin mediated luteolytic effect of an intrauterine device in sheep. Prostaglandins 1972; 2: 159-165.
36. Myatt L, Bray MA, Gordon D et al. Macrophages on intrauterine contraceptive devices produce prostaglandins. Nature 1975; 257: 227-228
37. Rutanen EM, Salmi A, Nyman T. mRNA expression of insulin-like growth factor-I (IGF-I) is suppressed and those of IGF-II and IGF-binding protein-I are constantly expressed in the endometrium during use of an intrauterine levonorgestrel system. Mol Hum Reprod 1997; 3: 749-754
38. Mandelin E, Koistinen H, Koistinen R, et al. Levonorgestrel-releasing intrauterine device-esaring women express contraceptive glycodelin A in endometrium during midcycle: another contraceptive mechanism? Hum Reprod 1998; 12: 2671-2675
39. Critchley HOD, Wang H, Kelly RW, et al. Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intrauterine system. Hum Reprod 1998; 13: 1210-1217
40. Nillson CG and Luukkainen T. Improvement of a d-norgestrel-releasing IUD. Contraception 1977; 15: 295.
41. Hagenfeldt K. Intrauterine contraception with the copper device. I. Effect on trace elements in the endomtrium, cervical mucus and plasma. Contraception 1972; 6: 37.
42. Ratsula K, Toivonen J, Lahteenmaki P, et al. Plasma levonorgestrel levels and ovarian function during the use of a levonorgestrel-releasing intracervical contraceptive device. Contraception 1989; 39: 195-204
43. Jia M, Zhou L, Ren S, et al. Serum SHBG levels during normal menstrual cycle and after insertion of levonorgestrel-releasing IUD. Adv Contracept 1992; 8: 33-40
44. Barbosa I, Bakos O, Olsson S-E, et al. Ovarian function during use of a levonorgestrel-releasing IUD. Contraception 1990; 42: 51-66
45. Silva PD, Larsson KM. Laparoscopic removal of a perforated intrauterine device from the pererectal fat. J Soc Laparosc Surg 2000; 4: 159-162
46. Haimov-Kochman R, Doviner V, Amsalem H, et al. Intraperitoneal levonorgestrel-releasing intrauterine device following uterine perforation: the role of progestins in adhesion formation. Hum Reprod 2003; 18: 990-993
47. Tatum HJ. Management and outcome of pregnancies associated with the Copper T intrauterine contraceptive device. Am J Obstet Gynecol 1976; 126: 869-874.
48. Grimes DA. Intrauterine device and upper-genital-tract infection. Lancet 2000; 356: 1013-1020
49. Fiorino AS. Intrauterine contraceptive device-associated actino-mycotic abscess and actinomyces detection on cervical smear. Obstet Gynecol 1996; 87: 142-9
50. Luukkainen T, Allonen H, Haukkamaa M, et al. Five years' experience with levonorgestrel-releasing IUDs. Contraception 1986; 33: 139-48
51. Cox M, Tripp J, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report. J Fam Plann Reprod Health Care 2002; 28 (2): 73-77
52. Xiao BL, Gu SJ, Wang SL, et al. NORPLANT and the levonorgestrel IUD in Chinese family planning programmes. Ann Med 1993; 25: 161-165
53. Tietze C. Fertility after discontinuation of intrauterine and oral contraception. Int J Fertil 1968; 13: 385-389
54. Cramer DV. Tuba infertility and the intrauterine device. New Engl J Med 1995; 312: 941-947
55. Vessey MP. Fertility after stopping use of intrauterine contraceptive device. BMJ 1983; 286: 39-45
56. Corfman PA and Richart RM. Uterine epidermoid carcinoma induced in rats by plastic and stainless steel intrauterine devices. In: Sobrero A and Lewit S (Eds.), Excerpta Medica. Amsterdam,1986; pp. 89-91.
57. Castellsague X, Thompson WD and Dubrow R. Intra-uterine contraception and the risk of endometrial cancer. Int J Cancer 1993; 30: 911-916