Italian guidelines on the effective and appropriate use of intrauterine contraception

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ABSTRACT

Several women and doctors are doubtful regarding the use of intrauterine systems (IUS) releasing levonorgestrel and intrauterine devices, due to the limited information about its specific indications and contraindications. The goal of these "guidelines" is to provide informations based on up-to-date scientific evidences regarding intrauterine contraception. Main recommendations are the following: •the intrauterine contraception may be considered as first choice in most women including nulliparous women and adolescents; •the risk of pelvic inflammatory disease associated with the use of intrauterine contraception is low (about 1.6 per 1000 women/year) and the pathogenesis of the infection appears to be linked to the insertion procedure; •a selective testing for infectious diseases based on individual risk factors is preferable to a test involving all women; •women at higher risk should be tested before insertion or at the time of insertion; •routine use of antibiotics before insertion is not recommended: women at high risk of asymptomatic sexually transmitted infections should be tested and, if positive, treated; •a post insertion ultrasound evaluation is not required.

Keywords: Intrauterine contraception, guidelines, levonorgestrel

SOMMARIO

Molte donne e medici sono dubbiosi rispetto all' uso dei sistemi intrauterini che rilasciano levonorgestrel ed i dispositivi intrauterini, a causa delle limitate informazioni sulle sue indicazioni e controindicazioni specifiche. L'obiettivo di queste "linee guida" è quello di fornire informazioni sulla base di evidenze scientifiche up-to-date per quanto riguarda la contraccezione intrauterina. Le raccomandazioni principali sono le seguenti: •la contraccezione intrauterina può essere considerata come prima scelta nella maggior parte delle donne, tra cui le adolescenti e le nullipare; •il rischio di malattia infiammatoria pelvica associato all'uso di contraccezione intrauterina è basso (circa 1,6 per 1000 donne/anno) e la patogenesi dell'infezione sembra essere legata alla procedura di inserzione; •un test nelle donne a rischio per le malattie infettive sulla base di singoli fattori di rischio è preferibile a un test che coinvolga tutte le donne; •le donne ad alto rischio dovrebbero essere testate prima dell'inserimento o al momento dell'inserimento; •non è raccomandato l'uso di routine degli antibiotici prima dell'inserimento; •le donne ad alto rischio di infezioni sessualmente trasmesse asintomatiche devono essere testate e , se positive, trattate; •una valutazione ultrasonografica dopo l'inserimento non è raccomandata.

Parole chiave: Contraccezione intrauterina, Linee guida, levonorgestrel

INTRODUCTION

The intrauterine contraception (IUC) consists of a plastic device that is wrapped in copper (Cu-IUD), but also silver or gold, or contains hormones, generally levonorgestrel (IUS- LNG).

In the recent years, this method of birth control has gained increasing interest by the women and the gynecologists, but it has a long lasting history. IUC was introduced in the early 1900s.

During the last century the intrauterine device changed the form, with the aim of making it more ergonomic, smaller and more effective.

During the last fifty years of the last century, after the introduction of plastic materials, its use increased.

In the '70s, the device, mainly in form of T, was wrapped with copper. This new structure increased greatly the contraceptive efficacy, that now is close to 100%. The T structure, although modified over the years, is still the most commonly used device in the world.

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In the 90s, polymers were added to release daily hormones (generally LNG), in order to increase the contraceptive efficacy and tolerability, but also to obtain therapeutic effects.

Today, the IUC for its high safety and effectiveness, low costs, high compliance and long-term use, is the worldwide most common reversible contraceptive method. Further, its use has been extended to women (such as, adolescents, HIV positive women) for which it was considered contraindicate.

To date, several women, but doctors too, are still doubtful regarding the use of IUC, due to the limited information about its specific indications and contraindications.

The goal of these "guidelines" is to provide informations based on up-to-date scientific evidences regarding medical indications, the mechanism of action, as well as the modalities of insertion, in order to make IUC a conscious and appropriate choice. For the purpose of these guidelines the term IUC includes both IUS releasing LNG and IUDs. Recommendations were classified according to the criteria shown in Table I.

USE OF IUC IN THE WORLD, IN EUROPE AND IN ITALY

The most comprehensive source of information on the use of contraceptive methods in the world is the document of the Department of Economic and Social Affair of the United Nations, published in 2012[1]. This study shows that there are marked differences in the proportion of women reporting the use of a contraceptive methods, even within geographically homogeneous areas.

The differences are even more marked if we consider the IUC, which is the most widely used reversible method of contraception in the world.

In fact, the rate of IUC use is about 40% or more in some areas of Asia (where the 80% of the users live), with peaks in China, Vietnam, Korea and in the republics of the former Soviet Union (Uzbekistan, Tajikistan, Turkmenistan, Kazakhstan). These percentages are lower in Europe and North America, and in some areas of Africa and Oceania. In some North African countries the frequency of use is also elevated (36.1% Egypt, Tunisia 27.8%).

In Europe, the IUC is moderately used, with rates of about 30% in Latvia, Finland, Norway, Moldova, France, Russia, but of about 10% in Belgium, Bulgaria, Denmark, the Netherlands, Montenegro. The rate is lower than 10% in Austria, Portugal, Spain, Switzerland and Italy. Albania is the European nation whit the lower rate of IUC use[1]. The observed geographic differences underline as the socio-cultural aspects and medical habits play a major role in the decision to use a specific method of birth control[2]. Concerns about safety and the mechanism of action are other aspects that limit the use of IUC[3].

The use of long-acting contraceptives, in particular of the IUC, however, is increasing in areas such as the US, traditionally characterized by low rates of use. For example, in an analysis of data for the period 2007-2009 from the National Survey of Family Growth conducted in the US, the frequency of use of IUC increased continuously over the period, driven mainly by the use of IUS[4].

IUC USE IN WOMEN OF DIFFERENT CLASS AGE

No detailed epidemiological data are available in the literature on the use of different contraceptive methods in different class age groups. Up-to-date, age is not considered a

Table I.
Grading of the recommendation.

Grading of the recommendation	
A	Meta-analysis or multiple randomized trials (of high quality)
B	Meta-analysis or multiple randomized trials (of average quality) one RCT, large RCT or case control or cohort studies of high quality
C	One RCT, large RCT or case control or cohort studies of average quality.
D	Non analytic studies or case reports/cases series (of high or average quality)
GPP*	Expert opinion

(GPP: Good Practice Point)*

determinant of IUC use.

The recent literature emphasizes its use in adolescents and young nulliparous[5-8].

EFFICACY AND THE EFFECTIVENESS OF INTRAUTERINE CONTRACEPTION

Table II presents an estimate of the efficacy and effectiveness of the reversible contraceptive methods on the basis of their perfect use, substantially ideal, or the typical one, (i.e. in daily practice). In particular, it shows the percentage of women who experience a pregnancy during the first year of use[9]. LNG-IUS is the most effective method; the efficacy obtained by "perfect" and "typical" use are very similar. The effectiveness of long-acting methods in clinical practice is due to the higher compliance by the woman. The pill, the patch and the ring require daily, weekly or monthly compliance. Conversely, the IUC does not require adherence to treatment by the woman[10].

MECHANISM OF ACTION OF Cu-IUD AND LNG-IUS

Cu-IUD

Cu-IUD causes a marked local reaction associated with a cytotoxic effect of copper ions on sperm[11]. These findings are supported by in vivo and in vitro studies on human endometrial cells[12,13]. An interesting finding rises from endometrial

Table II.
Efficacy of the contraceptive methods.

Method	%		% of women [c]
	Typical use [a]	Perfect use [b]	
No method	85	58	-
Spermicides	28	18	42
Fertility awareness-based methods	24	-	47
Condom Female Male	 21 18	 5 2	 41 43
Diagphragm	12	6	57
Combined oral contraceptive or progestin only pills	9	0.3	67
Patch	9	0.3	67
Ring	9	0.2	56
DMPA injection	6	0.2	56
IUC IUD-Cu IUS-LNG	 0.8 0.2	 0.6 0.2	 78 80
Implant	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

- Data not available

a Percentage of unwanted pregnancy during the first year of use (if not suspended for any other reason), among couples who initiate use of a method. The estimates of the probability of pregnancy during the first year of typical use for spermicides, periodic abstinence, the diaphragm, the male condom, the pill is taken from the National Survey of Family Growth 1995 to 2000 adjusted for underreporting of abortion; See the text for the deviation of the estimates for the other methods.

b Percentage of unwanted pregnancy during the first year of use (if not suspended for any other reason), among couples who initiate use of a method perfectly (using both constant and correct).

c Percentage who continue to use a method of contraception for a year, among those couples who want to avoid pregnancy. (Source: Trussel J. Contraceptive failure in the United States. Contraception. 2011; 83 (5): 397-404.)

biopsies of Cu-IUD users. There is a significant reduction in the concentration of estrogen receptors (but not progesterone ones), resulting in lowered mitotic activity. The Cu-IUD also causes changes in the subendometrial microvascularization, over-production of prostaglandins[14,15] and reduced local production of nitric oxide[15]. These findings may explain the bleeding and the increased frequency of dysmenorrhea observed particularly during the first months of use.

***Conclusions**: Cu-IUD causes marked local reaction and cytotoxic action of copper ions on the male gametes.*

LNG-IUS

The mechanism of action of the LNG-IUS is more complex and multifactorial than that of Cu-IUD. The following data are related to the use of the system releasing 20 µg/day of LNG. LNG-IUS causes modifications of the cervical mucus score with unfavorable effect on sperm penetration and negative Ferning test[16,17]. Further, the down regulation of receptors for estrogen and progesterone has a clear anti-proliferative effect. Consequently, the thickness of the endometrium is reduced (hypotrophy-atrophy) due to the reduction of the number and size of endometrial glands. Further decidualization of the stroma, and increased apoptosis is observed[18]. Changes in the levels of cytokines and integrins are also observed at the endometrial level. In "in vitro" studies, capacitated spermatozoas exposed to LNG (20 µg) showed a reduction in the number that interact with the zona pellucida[19]. Furthermore, in women using LNG- IUD, Glycodelin A (GdA) - a uterine glycoprotein that has local contraceptive activity by inhibiting sperm–egg binding and that is normally absent from endometrium during the fertile midcycle and it is not expressed until the fifth postovulatory day - is expressed between days 7 and 16 of the menstrual cycle[20]. IGF-I mRNA[19] is also suppressed. The reduction of mast cells in eutopic and ectopic endometrium[20] and nerve-growth factor (NGF, NGFR p75, TrkA) in the endometrium and myometrium[21] explain the effects on pain in women with endometriosis and adenomyosis.

LNG-IUS use is commonly associated with irregular endometrial bleeding. Metalloproteinases contribute to remodel the extracellular matrix (ECM). Matrix metalloproteinase (MMP)-1, active MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12 are more prevalent in the short-term LNG-IUS users, suggesting their important contribution to ECM breakdown and transient bleeding. The decrease in the percentage of women expressing MMP-2 and -3 might contribute to the decreased occurrence of unwanted spotting and bleeding in long-term LNG-IUS users[21]. Further, changes of the endometrial vascular structure are observed[22].

The system releasing LNG 6µg/day causes changes in the cervical mucus comparable to those observed with LNG 20 µg/day. In LNG6 6µg/day –IUS users the endometrium appears in the secretory phase[23] and the blood levels of estradiol are constantly slightly over 100 ng/L.

Conclusions

The LNG-IUS releasing 20µg /day causes local reaction and major changes of the cervical mucus score with unfavorable effect on sperm penetration The endometrial receptivity is lowered by the antiproliferative effect exerted by LNG.

The LNG-IUS release of 6 µg/day causes local reaction in association with major changes of the cervical mucus, similar in the available preliminary data to those reported for the 20µg/day IUS. The endometrium is in the secretory phase.

WOMEN ELIGIBLE FOR INTRAUTERINE CONTRACEPTION

The document published by the WHO, "Medical Eligibility Criteria for Contraceptive Use"[24], provides evidence-based recommendations for the choice of the most appropriate method of contraception without unnecessary restrictions of use (Table III). The WHO document is not intended to provide rigid guidelines, but to give to the gynecologist up-to-dated recommendations on the eligibility criteria of the different contraceptives methods. The woman must receive

Table III.
Risk categories for the use of contraceptive methods.

1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risk
3	A condition where the theoretical or proven risk usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used

(From Medical Eligibility Criteria, WHO, 2009)

adequate information in order to give a voluntary and informed consensus, taking into account medical and not medical criteria.

According to the WHO, "Medical Eligibility Criteria for Contraceptive Use" are eligible:

- women, regardless age and parity (<20 years: Category 2; ≥ 20 years: Category 1) requiring a reversible long lasting and safe contraception;
- women wishing a contraceptive methods not requiring daily, weekly or monthly intake, with the risks associated with poor compliance;
- women who do not wish to use oral drugs;
- women with contraindications to the use of estrogen;
- women seeking safe contraception immediately after induced abortion[25, 26];
- women seeking contraception during lactation[25, 27];
- women in their postpartum period ≥ 4 weeks;
- smoking, obese, hypertensive women or with multiple risk factors (cat. 1 for Cu-IUD and cat. 2 for LNG-IUS)[24];
- women with a first degree history of deep vein thrombosis or pulmonary embolism;
- women with superficial vein thrombosis;
- women with headache;
- women with migraine with aura (cat. 1 for Cu-IUD, cat. 2 for initiation LNG-IUS, Cat. 3 for continuation LNG-IUS)[24].

CONTRAINDICATIONS TO IUC USE

Contraindications to the use of the IUC are few, and mainly involve current infections or undiagnosed conditions.

Absolute contraindications are[24, 28, 29-32]:

- pregnancy;- current or <3months PID;
- current sexually transmitted disease;
- puerperal or post abortions sepsis or purulent cervicitis;
- undiagnosed abnormal uterine bleeding;
- uterine malignant diseases;
- pelvic tuberculosis;
- myomas distorting the womb cavity;
- uterine anomalies.

SPECIFIC CONTRAINDICATION TO Cu-IUD USE

The Cu-IUD may increase menstrual flow, menstrual pain and cause spotting. These effects should be considered and discussed during counseling, especially in women treated with anti-coagulant therapy or with severe thrombocytopenia.

In patients with Wilson's syndrome the use of Cu-IUD is not recommended.

SPECIFIC CONTRAINDICATION TO LNG-IUS USE

- Systemic Lupus Eythematosus with antiphospholipid antibodies;
- current deep vein thrombosis or pulmonary embolism;
- breast and liver cancer.

CONDITIONS IN WHICH CU-IUD SHOULD BE CONSIDERED AS FIRST CHOICE

Cu-IUD should be considered as first choice with respect to a LNG-IUS in the following conditions:

- absolute contraindication to the use of hormones;
- current venous thrombosis or pulmonary embolism[33];
- breast cancer [33,34],
- hepatitis[33];
- liver cancer[33];
- SLE with antiphospholipid antibody positive (1; 2 for initiation in women treated with immunosuppressive drugs, 3 in case of severe thrombocytopenia),
- breast-feeding in the immediate post partum period (<48h)[1]
- emergency contraception (up to 5 days)[33, 35];
- previous stroke[33].

CONDITIONS IN WHICH LNG-IUS SHOULD BE CONSIDERED AS FIRST CHOICE

The presence of LNG, even in low doses, has some therapeutic effects, and therefore gives some advantage in specific clinical conditions (especially with LNG-IUS 20 g/day):

- heavy menstrual flows[24, 33, 36, 37];
- premenstrual syndrome[38];
- endometriosis (including recto-vaginal endometriosis)[39];
- adenomyosis[40, 41];
- endometrial hyperplasia (high rate of regression in not atypical hyperplasia; possible use in atypical hyperplasia with close follow up)[40-44];
- myomas (not submucosal myomas)[45].

IUD USE IN HIV POSITIVE WOMEN.

It is possible to use Cu-IUD and IUS-LNG in HIV positive women. There is a contraindication to the insertion, but not the continuation of use, for women with AIDS[30, 46, 47].

Recommendations

- *In women at risk, Cu IUD use does not increase the risk of HIV infection (B).*
- *There is limited evidence of no increased risk of general or infective complications in HIV-IUD users in comparison to HIV negative IUD users (B).*
- *IUDs use in HIV-infected women was not associated with an increased risk of transmission to sexual partners (B).*
- *IUD users with AIDS should be carefully followed up for the risk of pelvic infection (B).*

USE OF IUC IN NULLIPAROUS WOMEN AND ADOLESCENTS

The use of the IUC in nulliparous women, particularly in teenagers, has always been hampered by a number of issues and myths, but it should be reconsidered according to recent data[8,48].

Two ACOG documents (2007 and 2012) highlight the usefulness of the IUC also in the adolescents, and emphasize how the teenagers should be encouraged use of Long Acting Reversible Contraception to prevent unwanted pregnancies and induced abortions[6,49].

A study of WHO published in year 1992[50] showed that nulliparity is not associated with any pelvic infection. The risk of pelvic infection was associated with to exposure to sexually transmitted diseases and sexual relations with multiple partners. These data were confirmed in more recent studies[8,16,48].

The expulsion and removal rate may be higher in nulliparous than in multiparous women. The size and shape of the IUC play an important role in determining the risk of expulsion[51,52]. The more recent CU or LNG releasing IUC are small in size.

IUC insertion in a nulliparous women can have slight additional difficulties. Some psychological and practical "tricks" can be useful in order to reduce discomfort during insertion.

The high and long lasting efficacy, the substantial low cost, make the IUC suitable as first choice for nulliparous women[8,53,54].

Recommendation

- *The intrauterine contraception may be considered as first choice for nulliparous women and adolescents (A).*

RISK OF PELVIC INFLAMMATORY DISEASE AFTER INSERTION OF IUC

The use of intrauterine contraception has been associated with a higher risk of PID and septic abortion[55, 56]. These conditions were associated with the Dalkon Shield intrauterine device. The multifilaments threads of the Dalkon Shield was structurally and functionally different from the monofilament ones of the recent IUCs. The unique characteristics of the Dalkon threads was cause of the ascendant mechanism of pathogenic bacteria from the vagina enter the uterine cavity.[48, 57].

In fact, the scientific literature of the last 20 years has shown that now the risk of PID after application of a IUC is very low.

A recent retrospective study conducted in California and including 57 728 IUC users, showed a risk of PID of 0,54% within the first 90 days[58]. This finding is in agreement with previous studies showing a low risk of PID after IUC insertion.

A review of 12 randomized and one non-randomized studies published between 1970 and 1980 and including 22 908 women, showed an infection rate of 1.6 for 1000 women/year[50]: the infection rate was 9.7 per 1000 women/year in the first 20 days and dropped to 1.4 for 1000 women/year thereafter. These findings suggest that the infection may be due to the insertion procedure rather than the IUC itself. Several studies[59-61] have also shown that the risk of PID varies with race and age, being higher in younger patients and in African women. A randomized controlled trial comparing the risk of infection among IUD and IUS users has shown an increased risk among younger women in the Cu-IUD arm[62].

Several studies indicate that the number of pelvic infection in LNG-IUS users is lower than in Cu-IUD users[16,62-64].

The LNG effect at the level of the cervical mucus and endometrium, and the reduction of menstrual flow may lower the risk of PID observed in young and sexually active women[16,64].

The analysis of risk factors associated to the risk of PID after application of Cu-IUD showed how women at low risk of sexually transmitted diseases (STDs) (i.e. married or with a single partner women) have a very low risk of PID after Cu-IUD insertion. The risk is similar to that observed in women reporting no contraception[58,65,66].

In case of PID it is recommended to treat the disease without removing the IUC.

Recommendation

- *The risk of pelvic inflammatory disease (PID) associated with the use of IUC is low (about 1.6 per 1000 women / year) and the pathogenesis of the infection appears to be linked to the application procedure rather than the IUC itself.*
- *The risk is higher during the first 20 days from insertion (A).*
- *The use of a LNG-IUS seems to be associated with a lower risk of PID compared to the Cu-IUD (B)*

ROLE OF AND INDICATIONS FOR TESTING FOR SEXUALLY TRANSMITTED INFECTIONS (STI) BEFORE INSERTION OF IUC

In 2006, a systematic review of the literature has evaluated the risk of developing PID after IUC insertion in women with asymptomatic STIs.

The rate of PID ranged from 0% to 5% in women with STI at insertion, and from 0% to 2% in women without STI at insertion[67, 68].

The ACOG and the RCOG do not recommend any testing for cervical infection in asymptomatic women: they recommend to identify, through a careful medical history (including sexual habits) and physical examination women at high risk of STIs. In these cases, testing for infectious diseases before inserting intrauterine contraceptive[69, 70] is recommended.

Women at high risk are [10, 69]:

- sexually active women aged <25 years;
- women aged> 25 years with multiple sexual partners in the year before insertion;
- women having a history of a STI;
- "vulnerable populations" (injection drug users and women who are incarcerated)[71].

In accordance with the guidelines of the National Institute for Health and Clinical Excellence (NICE[72] women at increased risk of STIs candidates for intrauterine contraception should be tested for :

- Chlamydia trachomatis;
- Neisseria gonorrhoeae;
- all other sexually transmitted diseases (as specifically requested/clinical judgment).

If the assessment infectious disease should be offered at the time of IUC insertion or before insertion is still open to debate.

In the latter case, consideration must be given to the likelihood of the patient being able to return, and the potential benefit of decreasing the risk of PID from 0-5% to 0-2% must be weighed against the risk of unintended pregnancy during this time[67].

Conversely, if the decision is to test at the time of insertion, it is important to consider the likelihood of contacting the woman again in case of a positive result. If the follow-up in these women was difficult or woman was considered at high risk for STDs, antibiotic prophylaxis immediately prior to insertion may be indicated.

Recommendation

- *A selective testing for infectious diseases based on individual risk factors is preferable to a test involving all women.*
- *Women at higher risk should be tested before insertion or at the time of insertion (B).*

ANTIBIOTIC PROPHYLAXIS PRE/ POST IUC INSERTION

Several randomized trials have assessed the role prophylactic antibiotics, in the prevention of pelvic infection after IUC insertion, but no significant reduction in the rate of PID in women treated with prophylactic antibiotics have been showed[60, 61, 73, 74].

A Cochrane review of 2010 has showed that the risk of PID is low after IUC insertion, and giving women either 500 mg of azithromycin or 200 mg of doxycycline does not reduce the risk of PID[75].

The ACOG and RCOG differ slightly in their recommendations[76,77].

The ACOG does not recommend routine antibiotic prophylaxis, and suggest testing women at increased risk of STIs at the time of insertion and treating those with positive results as soon as possible.

The RCOG does not recommend routine prophylactic antibiotics and suggests to consider prophylactic antibiotics in women at high risk of STIs and whose results are not available at the time of insertion.

The antibiotic should be specifically active against C. trachomatis. Furthermore, in cases where there is a high local prevalence of N. gonorrhoeae treatment should be given[60, 61 ,73-75].

Recommendation

- *Routine use of antibiotics before IUC insertion is not recommended. (A)*
- *Women at high risk of asymptomatic STIs*

should be tested and, if positive, treated.(B)

- *In high risk women prophylactic antibiotics can be useful if test results not available at the time of insertion and patient are not able to return for treatment in case of positive test).(B)*

IUC AND RISK OF ECTOPIC PREGNANCY

Some doctors and patients do not wish to use intrauterine contraception for the incorrect belief that IUC is associated with a higher risk of ectopic pregnancy. The high contraceptive efficacy of IUC lower the absolute risk of ectopic pregnancy[76,78,79].

Data from large series show an ectopic pregnancy rate of 0.2 per 1000 women/year in users of IUS, 0.3 per 1000 women/year in users of IUDs-Cu and 3,25-5,25 per 1000 women/year in women not using any contraceptive method [80-86].

Recommendation

- *Women should be informed that the absolute risk of ectopic pregnancy is lowered with the use of intrauterine contraception in comparison with women who do not use any contraceptive method (B).*

INFORMATION TO BE GIVEN TO WOMEN DURING COUNSELING ON IUC

Careful counseling is crucial.

The information should be provided in a simple way and focused to answers any questions about IUC.

A pre-printed form can be used[77,87,88].

• *What IUC is.*

To describe in an easy way the method.

• *How it works.*

To describe in broad terms the mechanisms of action of IUC , and to differentiate IUD and IUS.

• *How well it works.*

The woman must understand the high contraceptive efficacy of IUC.

• *Duration of use.*

To give information about how long IUC has to stay in**.**

• *Risks.*

To inform about risks due to the insertion and the use of IUC.

• *How soon after having IUC removed a woman can get pregnant.*

To inform that after the removal of IUC, a woman can get pregnant quickly.

• *Eligible women to IUC.*

The use of the IUC should be guided by the criteria of the WHO medical eligibility.

• *Tests to be required before insertion.*

To inform that before IUC insertion a careful medical history and general gynecological examination is required. In women at high risk of STIs, tests for infectious diseases are recommended.

• *Insertion and follow up.*

To underline that the procedure takes only a few minutes and can be done usually in a doctor's office. The follow-up usually includes a gynecological examination after the first menstruation after insertion. Other controls are not required unless doubts or clinical problems.

• *How the menstrual pattern changes.*

To inform that during the first few months post-insertion the menstrual characteristics may change.

To show IUC to the woman before insertion may be useful.

Pay attention to use words appropriate to the socio-cultural level of the woman.

Recommendation

- *An appropriate counseling is crucial(GPP).*
- *Apply general rules of the doctor-patient relationship (GPP).*
- *Take care to maintain a non-judgmental attitude and the use verbal and not verbal languages (GPP).*
- *The information should to be given in a simple way.*
- *During counseling give the following information: -What IUC is; -How it works; -How well it works; -How long IUC has to stay in;- Risks;- How soon after having IUC removed a woman can get pregnant; -Women eligible for IUC; -Tests required before insertion -Insertion and follow up; -How the menstrual pattern changes (GPP).*

CLINICAL SETTING FOR THE INSERTION

The insertion of IUC requires a comfortable office, with all the requirements of safety and sterility.

The office must be provided with appropriate equipment (cervical tenaculum, cotton balls moistened with antiseptic solution or povidone-iodine (Betadine) swabs, long suture scissor, ring forcep, sterile and nonsterile examination gloves, sterile tray for the procedure, sterile vaginal

speculum , hysterometer) and qualified personnel.

In Italy the activities remboursed by the National Health Service are defined by the Decreto Ministeriale 22/07/1996. According to this, the IUC insertion (ICD coding 9CM: 69.70) does not need an office for surgery[89].

Some Italian regions have implemented this Decreto[90].

Recommendation

- *The insertion of an IUC can be performed in any clinic or doctor's office, according to the requirements defined by local health authorities (GPP).*

INSERTION OF IUC

To insert IUC, we need of an inserter. The LNG-IUS have a more ergonomic inserter.

The insertion is a surgical procedure. The gynecologist must be trained before inserting IUC.

The specialist should perform an adequate and continuous number of insertions in order to improve its performance.

When

IUC should be inserted after documentation of a negative pregnancy test .

- during menstruation or immediately after;
- immediately after a miscarriage or an induced abortion;
- >4 weeks after delivery

Equipment

The equipment for IUD Insertion includes: cervical tenaculum, cotton balls moistened with antiseptic solution or povidone-iodine (Betadine) swabs, long suture scissor, ring forcep, sterile and nonsterile examination gloves, sterile tray for the procedure, sterile vaginal speculum, hysterometer

Insertion

1. Bimanual examination with nonsterile gloves should be performed to determine the position, the size of the uterus and to diagnose any genital infections or other contraindications.

2. Insert the speculum. The cervix and adjacent vaginal fornices should be cleansed with an antiseptic solution to remove the mucus and vaginal secretions.

3. The cervix should be stabilized during the insertion of the IUD with a tenaculum (Collins or other) on the anterior lip of the cervix. The posterior lip can be appropriate in the case of reverted uterus.

4. A gentle traction with tenaculum should be made. Such traction must be maintained throughout the time necessary for the insertion. This traction favors the correct insertion and reduces the risk of perforation.

5. A sterile uterine sound should be insert to determine the depth of the uterine cavity. In selected cases a local anesthetics, anti-inflammatory, anti-anxiety drugs, etc. may be useful.

6. The cursor should be aligned with the IUD arms and set at the distance the uterus was sounded. When required, the IUC should then be placed into the insertion tube.

7. While pulling tenaculum you advance the inserter through the cervical canal to the bottom of the uterine cavity and release the IUC.

8. Release gently the device by pulling back the slider; cut the threads to a length of 3-4 cm approximately.

9. Inform the woman about the correct insertion and the follow up control.

A post insertion ultrasound evaluation is not required[5, 77].

GYNECOLOGYCAL EXAMINATION AFTER INSERTION OF IUC

A visit should be scheduled after the first menstruation or 3-6 weeks after insertion to rule out an infection, perforation or expulsion of IUC[5].

After this visit the woman should be invited to come back only in case of clinical problems or concerns.

If the LNG-IUS 20 µg/day use is also aimed to the treatment of heavy menstrual flows, periodic follow up visits may be useful[77].

Women should be allowed to come back at any time in case of doubts or problems or discomfort[91,92].

Recommendation

- *The woman must undergo at least one follow-up visit after the menstrual cycle (after 3-6 weeks) following the IUC insertion (C).*

REMOVAL OF IUC

In women of childbearing age it is preferable to remove the intrauterine contraceptive during menstruation[77, 53]. If the contraceptive is removed in mid-cycle, and the woman has had sex during the week before removal, a pregnancy may occur. If the woman is seeking pregnancy, IUC may be removed at any time. At the same time pre-conceptional advices, including the use of folic acid should be given[93].

To remove the IUC you must gently pull the

threads.

If required by the woman, a new intrauterine contraceptive can be inserted immediately after removal[53,77,93].

In case of PID, removal of IUC is not recommended[8].

Recommendation

- *IUC can be removed either during the menstruation or at any time.*
- *Woman should be informed about the risk of pregnancy for sexual intercourses 7 days before removal (GPP).*
- *A new intrauterine contraceptive can be inserted immediately after removal (GPP).*

PROBLEMS ASSOCIATED WITH INSERTION AND REMOVAL OF IUC

Insertion

Difficulties in passing the sound through the cervix may be due to abnormalities of the cervical canal, such as:

- stenosis of the external uterine orifice;
- cervical canal stenosis;
- isthmocele.

In most cases, the stenosis of the cervical canal is related to a marked anteverted or retroverted uterus. In these cases the correct traction of the cervix with a tenaculum facilitates the insertion.

In case of stenosis of the external uterine orifice mechanical instruments such as a small Bengolea is useful to dilatate the cervix.

The rate of perforation is about of 0.1%[94]. In case of perforation, the hospitalization of the woman is required[95-98].

A vasovagal syncope can occur during insertion. Symptoms are sweating, bradycardia, fainting, nausea and vomiting. It should be treated with physical maneuvers and/or with sub-lingual atropine 0.5 mg. In women at risk of vasovagal syncope (medical history), premedication with atropine can be useful.

Removal

The most common problems during removal are:

- To broke the threads during removal;
- Lost threads.

If threads are not visible you must exclude pregnancy and perform an ultrasound examination in order to verify the presence of the IUC in utero or in abdomen[95,96]. If the IUC is in the uterus, you can try to retrieve the threads with instruments such as Klemmer or other devices[95,96,99,100]. This method is howerver painful and may cause endocervical and endometrial traumas: hysteroscopy is recommended. This method allows to replace correctly the IUC, if useful, or an atraumatic removal[97].

If IUC is not detectable, spontaneous expulsion (3-5%) or perforation should be considered. In the latter case an X-ray of the abdomen allows diagnosis (all IUC are radiopaque)[97,98,101].

MENSTRUAL CHANGES THAT MIGHT OCCUR AFTER IUC INSERTION

In some women IUC causes menstrual changes mostly reversible and of limited clinical relevance. This occurrence should be considered during counseling for at least two reasons.

These changes can cause discomfort to the woman and represent one of the most common reasons for early termination of the use of IUC[102], infections, pregnancy, endometrial or cervical diseases.

Although in most cases these are functional changes, they must be carefully investigated because they can sometimes be associated with IUC dislocation[103-105].

The most common observed changes in the menstrual pattern are: spotting, intermenstrual bleeding, hypermenorrhea, menstrual irregularities or amenorrhea.

Cu-IUD

Menstrual irregularities such as intermenstrual spotting or bleeding are common in users of Cu-IUDs, and are one of the main reasons for discontinuation[106]. In women with Cu-IUDs, an increase of menstrual flow by 20-50% has been reported[107]. In such cases, to reduce bleeding and prevent secondary anemia, NSAIDs and antifibrinolytic drugs should be considered[106].

LNG-IUS

Among the users of LNG-IUS abnormal bleeding occurs in a low percentage of cases, which varies slightly according to the dosage of progestin released[108]. The menstrual flow tends to be reduced and, in some cases, within one year by the insertion, you may experience a temporary amenorrhea[109,110]. Amenorrhea is more frequent in women using IUS that releases the higher dosage of progestin (52 mg with a release of 20 µgr/day)[107].

It may be a discomforting experience for the woman.

Using the LNG-IUS20 µg/day the reduction of menstrual flow may be beneficial in women with menorrhagia and secondary anemia, being able to influence, in these cases, the improvement of haematological parameters[110].

Recommendation

- *The occurrence of abnormal menstrual patterns in users of IUC, generally mild and clinically irrelevant, must always be the subject of an exhaustive counseling (GPP).*
- *In case of menorrhagia NSAIDs and antifibrinolytic drugs should be considered (A).*
- *In women with menorrhagia Cu-IUD is not recommended. In these cases, LNG-IUS is recommended (A).*
- *In women with heavy menstrual bleeding and secondary anemia LNG IUS-20 µg/day represents the contraceptive method of choice (A).*

HOW SOON AFTER HAVING IUC REMOVED A WOMAN CAN GET PREGNANT

After removal of an intrauterine device a woman can get pregnant immediately. In general, studies show that 71-96% of women are pregnant within one year from the removal of IUC (mean time to pregnancy about three months in users of IUS and 4 months in users of IUDs)[111]. These data are comparable to those of women who have used other contraceptive methods[51, 111-113].

Recommendation

- *To inform the patient that after removal of an intrauterine device she can get pregnant immediately and in general after few months(B).*

MAGNETIC RESONANCE IMAGING (MRI) IN WOMEN WITH IUC

Concerns about women who have IUC in situ and undergoing magnetic resonance (MR) imaging is often raised by the women and radiologists. Some radiologists suggests a gynecological examination after MRI to check correct IUC position. Several studies have shown that the magnetic fields (up to 3 Tesla) do not move the IUC inside the uterine cavity. Further the LNG-IUS 20 µg/day does not contain metals, the LNG-IUS 6 g/day contains a small silver ring and the Cu-IUD copper which are not affected by magnetic fields[114-118].

Recommendation

- *There is no risk of dislocation, perforation, expulsion, pregnancy connected with the MRI examination(C).*

DRUGS AND EFFICACY OF LNG-IUS

The release of levonorgestrel into the uterine cavity is not influenced by liver metabolism. LNG-IUS can be used in association with other drugs, including liver enzymes inducers[119].

REFERENCES

1. United Nations Department of Economic and Social Affairs, Population Division,. **World Contraceptive Use 2012** (POP/DB/CP/Rev2012). 2012.
2. Skouby SO. **Contraceptive use and behavior in the 21st century: a comprehensive study across five European countries**. Eur J Contracept Reprod Health Care. 2004;9:57-68.
3. Buhling KJ, Zite NB, Lotke P, Black K. **Worldwide use of intrauterine contraception: a review. Contraception**. 2014;89:162-73.
4. Black K, Lotke P, Buhling KJ, Zite NB. **A review of barriers and myths preventing the more widespread use of intrauterine contraception in nulliparous women.** Eur J Contracept Reprod Health Care. 2012;17:340-50.
5. Finer LB, Jerman J, Kavanaugh ML. **Changes in use of long-acting contraceptive methods in the United States**, 2007-2009. Fertil Steril. 2012;98:893-7.
6. National Institute for Health and Care Excellence (NICE). **Long acting reversible contraception (update), issued September 2014.** NICE Clinical Guideline 30, guidance.nice.org.uk/cg30; http://www.nice.org.uk/guidance/cg30. 2014.
7. ACOG. **Adolescent and Long-acting reversible contraception: implants and intrauterine devices.** ACOG, Committee Opinion, n. 539 (reaffirmed 2014). . 2012.
8. Merki-Feld GS, Gruber IM. **Broad counseling for adolescents about combined hormonal contraceptive methods: the choice study**. J Adolesc Health. 2014;54:404-9.
9. Ott MA, Sucato GS. **Contraception for adolescents. Pediatrics.** 2014;134:e1257-81.
10. Trussell J. Contraceptive failure in the United States. Contraception. 2011;83:397-404.
11. National Collaborating Centre for Women's and Children's Health (UK). **Long-acting Reversible Contraception: The Effective and Appropriate Use of Long-Acting Reversible Contraception.** London: RCOG Press. 2005.
12. Larsson B, Ljung B, Hamberger L. **The influence of copper on the in vitro motility of the human Fallopian tube.** Am J Obstet Gynecol. 1976;125:682-90.
13. Ortiz ME, Croxatto HB. **Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action.** Contraception. 2007;75:S16-30.
14. Wu J, Wang L, He J, Zhu C. **In vitro cytotoxicity of Cu(2)(+), Zn(2)(+), Ag(+) and their mixtures on primary human endometrial epithelial cells. Contraception.** 2012;85:509-18.
15. Xin ZM, Cao LM, Xie QZ, Sun Y, Su YC, Guo YH. **Effects**

of the copper intrauterine device on the expression of cyclooxygenase-1 and -2 in the endometrium. Int J Gynaecol Obstet. 2009;105:166-8.
16. Coskun E, Cakiroglu Y, Aygun BK, Muezzinoglu B, Caliskan E. **Effect of copper intrauterine device on the cyclooxygenase and inducible nitric oxide synthase expression in the luteal phase endometrium.** Contraception. 2011;84:637-41.
17. Lewis RA, Taylor D, Natavio MF, Melamed A, Felix J, Mishell D, Jr. **Effects of the levonorgestrel-releasing intrauterine system on cervical mucus quality and sperm penetrability.** Contraception. 2010;82:491-6.
18. Natavio MF, Taylor D, Lewis RA, et al. **Temporal changes in cervical mucus after insertion of the levonorgestrel-releasing intrauterine system.** Contraception. 2013;87:426-31.
19. Gomes MK, Rosa-e-Silva JC, Garcia SB, et al. **Effects of the levonorgestrel-releasing intrauterine system on cell proliferation, Fas expression and steroid receptors in endometriosis lesions and normal endometrium.** Hum Reprod. 2009;24:2736-45.
20. Munuce MJ, Nascimento JA, Rosano G, Faundes A, Bahamondes L. **Doses of levonorgestrel comparable to that delivered by the levonorgestrel-releasing intrauterine system can modify the in vitro expression of zona binding sites of human spermatozoa.** Contraception. 2006;73:97-101.
21. Mandelin E, Koistinen H, Koistinen R, Affandi B, Seppala M. **Levonorgestrel-releasing intrauterine device-wearing women express contraceptive glycodelin A in endometrium during midcycle: another contraceptive mechanism?** Hum Reprod. 1997;12:2671-5.
22. Labied S, Galant C, Nisolle M, et al. **Differential elevation of matrix metalloproteinase expression in women exposed to levonorgestrel-releasing intrauterine system for a short or prolonged period of time.** Hum Reprod. 2009;24:113-21.
23. Stephanie R, Labied S, Blacher S, et al. **Endometrial vessel maturation in women exposed to levonorgestrel-releasing intrauterine system for a short or prolonged period of time.** Hum Reprod. 2007;22:3084-91.
24. Apter D, Gemzell-Danielsson K, Hauck B, Rosen K, Zurth C. **Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies.** Fertil Steril. 2014;101:1656-62 e1-4.
25. WHO. **Medical eligibility criteria for contraceptive use.** 4th ed. Geneva: WHO. 2009.
26. Kapp N, Curtis KM. **Intrauterine device insertion during the postpartum period: a systematic review.** Contraception. 2009;80:327-36.
27. Tsikouras P, Vrachnis N, Grapsa A, et al. **IUD in first-trimester abortion: immediate intrauterine contraceptive devices insertion vs delayed insertion following the next menstruation bleeding.** Arch Gynecol Obstet. 2014;290:99-105.
28. Helmerhorst FM, Belfield T, Kulier R, Maitra N, O'Brien P, Grimes DA. **The Cochrane Fertility Regulation Group: synthesizing the best evidence about family planning.** Contraception. 2006;74:280-6.
29. **Canadian Consensus Conference on Contraception. Contraindications to Intrauterine Device Use. Data from The intra-uterine device.** J SOGC. 1998;20:769-73.
30. IMAP. **IMAP on emergency contraception. Statement developed by the International Medical Advisory Panel to IPPF (IMAP),** 1994. Entre Nous Cph Den. 1995:19.
31. Caddy S, Yudin MH, Hakim J, Money DM. **Best practices to minimize risk of infection with intrauterine device insertion.** J Obstet Gynaecol Can. 2014;36:266-76.
32. Nelson AL. **Contraindications to IUD and IUS use.** Contraception. 2007;75:S76-81.
33. ACOG Practice Bulletin. No. 59, January. 2005.
34. ESHRE Capri Workshop Group. **Intrauterine devices and intrauterine systems.** Hum Reprod Update. 2008;14:197-208.
35. Dinger J, Bardenheuer K, Minh TD. **Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer.** Contraception. 2011;83:211-7.
36. Cheng L, Che Y, Gulmezoglu AM. **Interventions for emergency contraception.** Cochrane Database Syst Rev. 2012;8:CD001324.
37. Lethaby AE, Cooke I, Rees M. **Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding.** Cochrane Database Syst Rev. 2005:CD002126.
38. Fraser IS. **Non-contraceptive health benefits of intrauterine hormonal systems.** Contraception. 2010;82:396-403.
39. Barrington JW, Bowen-Simpkins P. T**he levonorgestrel intrauterine system in the management of menorrhagia.** Br J Obstet Gynaecol. 1997;104:614-6.
40. Varma R, Sinha D, Gupta JK. **Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview.** Eur J Obstet Gynecol Reprod Biol. 2006;125:9-28.
41. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. **Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up.** Hum Reprod. 2013;28:1231-6.
42. Kelekci S, Kelekci KH, Yilmaz B. **Effects of levonorgestrel-releasing intrauterine system and T380A intrauterine copper device on dysmenorrhea and days of bleeding in women with and without adenomyosis.** Contraception. 2012;86:458-63.
43. Bahamondes L, Ribeiro-Huguet P, de Andrade KC, Leon-Martins O, Petta CA. **Levonorgestrel-releasing intrauterine system (Mirena) as a therapy for endometrial hyperplasia and carcinoma.** Acta Obstet Gynecol Scand. 2003;82:580-2.
44. Varma R, Soneja H, Bhatia K, et al. **The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia--a long-term follow-up study.** Eur J Obstet Gynecol Reprod Biol. 2008;139:169-75.
45. Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. **LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomized controlled trial.** J Gynecol Oncol. 2013;24:128-34.
46. Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. **A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia**. Int J Gynaecol Obstet. 2011;112:126-30.
47. Stringer EM, Kaseba C, Levy J, et al. **A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus.** Am J Obstet Gynecol. 2007;197:144 e1-8.
48. European Study Group on Heterosexual Transmission of HIV. **Comparison of female to male and male to female transmission of HIV in 563 stable couples.** . BMJ. 1992;304:809-13.
49. Russo JA, Miller E, Gold MA. **Myths and misconceptions about long-acting reversible contraception (LARC).** J Adolesc Health. 2013;52:S14-21.
50. ACOG Committee Opinion. **Intrauterine device and adolescents.** n. 392. 2007.
51. Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. **Intrauterine devices and pelvic inflammatory disease: an international perspective.** Lancet. 1992;339:785-8.
52. Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. **Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women.** N Engl J Med. 2001;345:561-7.
53. Deans EI, Grimes DA. **Intrauterine devices for adolescents: a systematic review.** Contraception. 2009;79:418-23.
54. National Institute for Health and Care Excellence (NICE). **Long acting reversible contraception (update), issued September 2014.** NICE Clinical Guideline 30, guidance.nice.

org.uk/cg30; http://www.nice.org.uk/guidance/cg30. . 2014.
55. Lyus R, Lohr P, Prager S. **Use of the Mirena LNG-IUS and Paragard CuT380A intrauterine devices in nulliparous women.** Contraception. 2010;81:367-71.
56. Lee NC, Rubin GL, Ory HW, Burkman RT. **Type of intrauterine device and the risk of pelvic inflammatory disease.** Obstet Gynecol. 1983;62:1-6.
57. Meirik O. **Intrauterine devices - upper and lower genital tract infections.** Contraception. 2007;75:S41-7.
58. Tatum HJ, Schmidt FH, Phillips D, McCarty M, O'Leary WM. The Dalkon Shield controversy. **Structural and bacteriological studies of IUD tails**. JAMA. 1975;231:711-7.
59. Sufrin CB, Postlethwaite D, Armstrong MA, Merchant M, Wendt JM, Steinauer JE. **Neisseria gonorrhea and Chlamydia trachomatis screening at intrauterine device insertion and pelvic inflammatory disease.** Obstet Gynecol. 2012;120:1314-21.
60. **International Collaborative Post-Marketing Surveillance of Norplant. Post-marketing surveillance of Norplant contraceptive implants: I. Contraceptive efficacy and reproductive health.** Contraception. 2001;63:167-86.
61. Ladipo OA, Farr G, Otolorin E, et al. **Prevention of IUD-related pelvic infection: the efficacy of prophylactic doxycycline at IUD insertion.** Adv Contracept. 1991;7:43-54.
62. Sinei SK, Schulz KF, Lamptey PR, et al. **Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion.** Br J Obstet Gynaecol. 1990;97:412-9.
63. 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.
64. Jonsson B, Landgren BM, Eneroth P. **Effects of various IUDs on the composition of cervical mucus.** Contraception. 1991;43:447-58.
65. Luukkainen T, Pakarinen P, Toivonen J. **Progestin-releasing intrauterine systems.** Semin Reprod Med. 2001;19:355-63.
66. Lee NC, Rubin GL, Borucki R. T**he intrauterine device and pelvic inflammatory disease revisited: new results from the Women's Health Study.** Obstet Gynecol. 1988;72:1-6.
67. Morrison CS, Murphy L, Kwok C, Weiner DH. **Identifying appropriate IUD candidates in areas with high prevalence of sexually transmitted infections.** Contraception. 2007;75:185-92.
68. Mohllajee AP, Curtis KM, Peterson HB. **Does insertion and use of an intrauterine device increase the risk of pelvic inflammatory disease among women with sexually transmitted infection? A systematic review.** Contraception. 2006;73:145-53.
69. Society of Obstetricians and Gynecologists of Canada. Committee opinion No 305, March 2014: **Best practices to minimize risk of infection with intrauterine device insertion.** 2014.
70. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 121: **Long-acting reversible contraception: Implants and intrauterine devices.** Obstet Gynecol. 2011;118:184-96.
71. **RCOG. Faculty of Sexual & Reproductive Healthcare Clinical Guidance. Clinical Effectiveness Unit** November. 2007.
72. Public Health Agency of Canada. **Primary care and sexually transmitted infections. In: Canadian guidelines on sexually transmitted infections.** Ottawa: PHAC. pp. 2–20. 2010.
73. National Institute of Health and Care Excellence. **Long-acting reversible contraception Issued: October 2005 last modified: April 2013 NICE clinical guideline 30 guidance.** nice.org.uk/cg30. . 2005.
74. Walsh T, Grimes D, Frezieres R, et al. **Randomised controlled trial of prophylactic antibiotics before insertion of intrauterine devices. IUD Study Group.** Lancet. 1998;351:1005-8.
75. Walsh TL, Bernstein GS, Grimes DA, Frezieres R, Bernstein L, Coulson AH. **Effect of prophylactic antibiotics on morbidity associated with IUD insertion: results of a pilot randomized controlled trial. IUD Study Group.** Contraception. 1994;50:319-27.
76. American College of Obstetrics and Gynecologist Practice Bulletin. **Long-acting reversible contraception.** N.121. July. 2011.
77. **Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Intrauterine Contraception,** November. 2007.
78. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. **UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2005–2006).** http://www.fsrh.org/admin/uploads/298_UKMEC_200506.pdf [Accessed 12 October 2007]. 2006.
79. Xiong X, Buekens P, Wollast E. **IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies.** Contraception. 1995;52:23-34.
80. Mishell DR, Jr. **Intrauterine devices: mechanisms of action, safety, and efficacy.** Contraception. 1998;58:45S-53S; quiz 70S.
81. World Health Organization. **A multinational case-control study of ectopic pregnancy. The World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction: Task Force on Intrauterine Devices for Fertility Regulation.** Clin Reprod Fertil. 1985;3:131-43.
82. Sivin I. **Dose- and age-dependent ectopic pregnancy risks with intrauterine contraception.** Obstet Gynecol. 1991;78:291-8.
83. French RS, Cowan FM, Mansour DJ, et al. I**mplantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.** Health Technol Assess. 2000;4:i-vi, 1-107.
84. Sivin I, Stern J, Coutinho E, et al. **Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDS.** Contraception. 1991;44:473-80.
85. Sivin I, Stern J. **Health during prolonged use of levonorgestrel 20 micrograms/d and the copper TCu 380Ag intrauterine contraceptive devices: a multicenter study. International Committee for Contraception Research (ICCR).** Fertil Steril. 1994;61:70-7.
86. Dannemiller Memorial Educational Foundation. **The Contraception Report, Modern IUDs Part 2,** Grimes DA (ed.), Vol. 9, No. 5. Totowa, NJ: Emron, pp. 2–16. 1998.
87. Faculty of Family Planning and Reproductive Health Care of the Royal College of Obstetricians and Gynaecologists. S**ervice Standards for Record Keeping.** http://www.fsrh.org/admin/uploads/ServiceStandardsRecord Keeping.pdf [Accessed 12 October 2007]. 2005.
88. FPA (Family Planning Association). **Your Guide to the IUS.** http://www.fpa.org.uk/attachments/published/154/PDF [Accessed 12 October 2007]. 2006.
89. **Prestazioni di assistenza specialistica ambulatoriale erogabili nell'ambito del Servizio sanitario nazionale e relative tariffe. G.U.** Serie Generale, n. 216 del 14/09/1996 Suppl. Ordinario n.150 1996.
90. **Consiglio Sanitario Regionale Toscana. Parere 10**/2005. http://servizi.salute.toscana.it/csr/img/getfile_img1.php?id=3224 (last access 27 november 2014). 2005.
91. World Health Organization. **Selected Practice Recommendations for Contraceptive Use (2nd edn)**. http://www.who.int/reproductive-health/publications/spr_2/index.html [Accessed 12 October 2007]. 2005.
92. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. UK Selected Practice **Recommendations for Contraceptive Use.** http://www.fsrh.org/admin/uploads/Final%20UK%20recommendations1.pdf [Accessed 12 October 2007]. 2002.
93. Stephen Searle E. T**he intrauterine device and the**

intrauterine system. Best Pract Res Clin Obstet Gynaecol. 2014;28:807-24.
94. Heinemann K, Westhoff CL, Grimes DA, Moehner S. **Intrauterine Devices and the Risk of Uterine Perforations: Final Results From the EURAS-IUD Study**. Obstet Gynecol. 2014;123 Suppl 1:3S.
95. Marchi NM, Castro S, Hidalgo MM, et al. **Management of missing strings in users of intrauterine contraceptives.** Contraception. 2012;86:354-8.
96. Mizia K, Ramsay P. **The effectiveness and safety of ultrasound-guided removal of a Mirena((R)) intrauterine system when the strings are not visible and conventional office procedures have failed.** Aust N Z J Obstet Gynaecol. 2013;53:386-8.
97. Nappi C, Di Spiezio Sardo A. **Approccio isteroscopico moderno alle patologie del tratto genitale.** Endo Press.176. 2014.
98. Braaten K.P., Goldberg A.B. Malpositioned IUDs: **When you should intervene and when you should not.** OBG Management. 2012;24.
99. Guney M, Oral B, Mungan T. **Efficacy of intrauterine lidocaine for removal of a "lost" intrauterine device: a randomized, controlled trial.** Obstet Gynecol. 2006;108:119-23.
100. Prabhakaran S, Chuang A. **In-office retrieval of intrauterine contraceptive devices with missing strings.** Contraception. 2011;83:102-6.
101. Andersson K, Ryde-Blomqvist E, Lindell K, Odlind V, Milsom I. **Perforations with intrauterine devices. Report from a Swedish survey.** Contraception. 1998;57:251-5.
102. Backman T, Huhtala S, Blom T, Luoto R, Rauramo I, Koskenvuo M. **Length of use and symptoms associated with premature removal of the levonorgestrel intrauterine system: a nation-wide study of 17,360 users.** BJOG. 2000;107:335-9.
103. Ronnerdag M, Odlind V. **Late bleeding problems with the levonorgestrel-releasing intrauterine system: evaluation of the endometrial cavity.** Contraception. 2007;75:268-70.
104. Ozalp S, Kabukcuoglu S, Tanir HM. **Should endometrial hyperplasia be regarded as a reason for abnormal uterine bleeding in users of the intrauterine contraceptive device?** Eur J Contracept Reprod Health Care. 2003;8:17-20.
105. Tsanadis G, Kalantaridou SN, Kaponis A, et al. **Bacteriological cultures of removed intrauterine devices and pelvic inflammatory disease.** Contraception. 2002;65:339-42.
106. Godfrey EM, Folger SG, Jeng G, Jamieson DJ, Curtis KM. T**reatment of bleeding irregularities in women with copper-containing IUDs: a systematic review.** Contraception. 2013;87:549-66.
107. Ronnerdag M, Odlind V. **Health effects of long-term use of the intrauterine levonorgestrel-releasing system. A follow-up study over 12 years of continuous use.** Acta Obstet Gynecol Scand. 1999;78:716-21.
108. Gemzell-Danielsson K, Schellschmidt I, Apter D. **A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena.** Fertil Steril. 2012;97:616-22 e1-3.
109. Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. **Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years.** Contraception. 2002;65:129-32.
110. Arisi E. **Flussi mestruali abbondanti: le raccomandazioni della SIGO.** Gyneco AOGOI, 1, 18. 2007.
111. Mansour D, Gemzell-Danielsson K, Inki P, Jensen JT. **Fertility after discontinuation of contraception: a comprehensive review of the literature.** Contraception. 2011;84:465-77.
112. Grimes DA. **Intrauterine devices and infertility: sifting through the evidence.** Lancet. 2001;358:6-7.
113. Sivin I, Stern J, Diaz S, et al. **Rates and outcomes of planned pregnancy after use of Norplant capsules, Norplant II rods, or levonorgestrel-releasing or copper TCu 380Ag intrauterine contraceptive devices.** Am J Obstet Gynecol. 1992;166:1208-13.
114. Hess T, Stepanow B, Knopp MV. **Safety of intrauterine contraceptive devices during MR imaging.** Eur Radiol. 1996;6:66-8.
115. Mark AS, Hricak H. **Intrauterine contraceptive devices: MR imaging.** Radiology. 1987;162:311-4.
116. Pasquale SA, Russer TJ, Foldesy R, Mezrich RS. **Lack of interaction between magnetic resonance imaging and the copper-T380A IUD.** Contraception. 1997;55:169-73.
117. Shellock FG. **New metallic implant used for permanent contraception in women: evaluation of MR safety.** AJR Am J Roentgenol. 2002;178:1513-6.
118. Zieman M, Kanal E. **Copper T 380A IUD and magnetic resonance imaging.** Contraception. 2007;75:93-5.
119. Faculty of Sexual &. Reproductive Healthcare. **Clinical Guidance. Drug Interactions with hormonal Contraception.** Clinical Effectiveness Unit. January. 2011.