NON-CONTRACEPTIVE EFFECTS OF INTRAUTERINE CONTRACEPTIVE DEVICES

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Summary. There is a need for long-acting birth control methods. Copper-bearing intrauterine contraceptive devices do not have systemic side effects and they are appropriate for parous women who have no excess menstrual flow or cramps at baseline and who have low risk for sexually transmitted infections. Levonorgestrel-releasing intrauterine systems release levonorgestrel directly into uterine cavity. The hormone is mainly concentrated into endometrium but some amount is quickly absorbed into systemic circulation. Most women who use this system will experience a decrease in menstrual blood loss and pain with increase in serum hemoglobin and ferritin levels. During first few months of use some of them will be amenorrhoic or will have unscheduled erratic menstrual bleeding. The levonorgestrel intrauterine system may be a therapeutic option for women with idiopathic menorrhagia or with some inherited bleeding disorders. It provides endometrial protection for women receiving estrogen replacement therapy during menopause or from over stimulation by their own unopposed estrogens.

Key words: Intrauterine contraceptive devices, non-contraceptive effects

Introduction

There is a need for long-acting birth control methods which are easy to use and which avoid the need for specific action at the time of coitus or for daily action (1). The intrauterine contraceptive device (IUD) is the most cost-effective temporary contraceptive method for long term use. Many women choose it for a reason of high efficacy, safety and convenience (2,3). Approximately 160 million women worldwide use this method for birth control (4).

Grafenbeg was the first who introduced intrauterine contraceptive silver ring in 1928 but it vanished from the scene. After 30 years he was rehabilitated as a result of change in mental attitude toward birth control (5).

The second generation devices were plastic, non-medicated ("inert") which were impregnated with barium sulfate to make them radio-opaque. They should no longer be inserted, but women who have it in situ and are content with it, can continue to use it up to menopause (3).

The third generation devices were copper-bearing (Cu-IUD) which release copper ions into uterine cavity, but they do not have systemic side effects.

The fourth generation devices are hormone-releasing. Early efforts produced a progesterone-releasing device which was available for only a short time before being withdrawn because of excessively high ectopic pregnancy rates. Levonorgestrel intrauterine system (LNG-IUS) was introduced in the market in 1995. It was initially only licensed as a contraceptive for 3 years but this was extended to 5 years later (6, 7, 8).

The fifth generation devices are intrauterine contraceptive implants. Miniature frameless copper and hormone-releasing intrauterine implants have no plastic body and they are very flexible. They are suitable for women of virtually all ages including young women who do not have children yet (frameless Cu-IUD, Fyne-Fix IUD and frameless LNG-IUS, FibroPlant) (1, 5).

Menstrual patterns

The copper-bearing intrauterine devices (Cu-IUD) were smaller-sized than non-medicated, plastic ("inert") devices and the menstrual blood loss was lessening. All intrauterine devices create sterile inflammatory response in the uterine cavity which is characterized by a marked increase in the number of neutrophils, mononuclear cells and plasma cells (9). In addition to this, Cu-IUDs provoke much intense inflammatory reaction because of releasing of copper ions into uterine cavity. They alter the metabolism of endometrial cells and even the action of steroid hormone receptors, but there is no measurable increase in the serum copper levels (9, 10, 11). During the first 3 to 6 months after insertion of Cu-IUD, women commonly report that menstrual bleeding has become heavier. Usually this does not cause any harm and it tends to improve with time. In some women, however, the bleeding causes iron-deficiency anemia and they need iron supplements and a diet rich in iron. Excessive bleeding can be treated with non-steroidal anti-inflammatory drugs or the haemostatic agent tranexamic acid. Unacceptable
bleeding disturbance warrants IUD removal (3). Because the use of Cu-IUD can increase flow and cramps, it is appropriate for women who have no excess menstrual flow or cramps at baseline (12, 13).

**Levonorgestrel intrauterine systems** (LNG-IUSs) act by releasing about 20 mcg of levonorgestrel directly into uterine cavity mainly concentrated in the endometrium. While levonorgestrel concentrations in the myometrium and tubes are in the same range as with oral administration of 30 mcg, endometrial concentrations are 200-300 times higher with LNG -IUS use (6, 14, 15). Endometrial morphologic changes take place within a month of use and the picture is not affected by the phase of menstrual cycle (antiproliferative effect which leads to endometrial suppression, decidualisation and atrophy) (6, 11). Levonorgestrel released into the uterine cavity is quickly absorbed into the systemic circulation and the maximum plasma levels are reached within few hours. The concentrations are stable in the same user but there are wide interindividual variations. Plasma levonorgestrel is mainly bound to sex hormone binding globulin and it causes the partial inhibition of ovarian follicular development and ovulation. A complete inhibition of ovulation can be achieved via intrauterine release of 50 mcg of levonorgestrel daily. That is more than twice the dose released daily by the Lng-IUS currently available (6, 14, 15).

The most frequent unwanted side effect of LNG-IUS use is unscheduled erratic menstrual bleeding which usually occurs during the first few months following insertion but tends to subside with time and is well tolerated after appropriate counseling (6, 13, 15). Most women with LNG-IUS in situ will experience a decrease in menstrual blood loss (more than 80% at 3 months and 95% at 12 months) and a diminished menstrual pain (16). Mean reduction in blood loss is about 40 ml per month (6).

Within the first year of LNG-IUS use about 20% - 60% of women become amenorrheic (15). After 8 months half of LNG-IUS users experience no menstrual bleeding but most experience occasional scanty spotting (6). Even in the presence of amenorrhea the cyclicity of the pituitarity is preserved, ovulation occurs in most women and the estradiol production is not decreased. The effect of LNG-IUS as a course of amenorrhea is therefore thought to be mainly of local nature (6,14). Oligomenorrhea and amenorrhea are common and usually acceptable in LNG-IUS users. However, irregular, frequent or prolonged light bleeding is a definite problem for which solution is being sought (17). It is not possible to predict the bleeding pattern of the new users, but studies suggested that the majority of women (72%) are satisfied or fairly satisfied with LNG-IUS use (older women were more satisfied than younger ones (6).

Intrauterine contraceptive devices are suitable for breast-feeding women, but, according to the World Health Organization (WHO), they should not be inserted until 4 weeks post-partum. There is a lack of data on the local effects of LNG-IUSs on uterine involution.

There is the same concern that the neonate may be at risk due to exposure to steroid hormones during the first 6 weeks postpartum as for other, progestin only contraceptive methods (18).

**Menorrhagia** occurs in 20-30% of women of reproductive age and it impairs their quality of life (19, 20). The LNG-IUS has a therapeutic effect because it causes strong medical suppression of endometrium and reduction in menstrual blood loss even in women with idiopathic menorrhagia by 79-97% (15) with high patient satisfaction (72-94%) and a continuation rate (65-88%) (14). The major benefit of LNG-IUS was the reduction in menstrual blood loss with an increase in serum hemoglobin and ferritin levels. The reduction in menstrual blood loss at 6, 12, 24 and 36 months of LNG-IUS use was 78.0%, 83.8%, 97.7% and 85.0%, respectively (21).

Menorrhagia may arise from inherited bleeding disorders. A prospective study has shown a reduction in menstrual blood loss, improvement in quality of life in all women with menorrhagia due to a known inherited bleeding disorder when treated with LNG-IUS (22). According to WHO women with thalassaemia, sickle cell disease and iron-deficiency anemia can use LNG-IUS without restriction (Category 1) but Cu-IUD use is possible, but not an optional choice (Category 2) (18).

LNG-IUS has been considered as a therapeutic option for menorrhagia caused by uterine leiomyomas as well as in cases of adenomyosis. A clinical importance of a slight, although statistically significant decrease in uterine leiomyoma volume remains unclear (15, 23, 24). The LNG-IUS use offers a better quality of life and it is an alternative to hysterectomy as a non-surgical, minimally invasive and reversible treatment (15, 17, 24). It is well established that LNG-IUS treatment reduces chronic pelvic pain accompanying endometriosis (25). Although the effect of levonorgestrel is primarily local it is also found in the peritoneal fluid (26, 27).

**Dismenorrhea** may develop or become worse in women after insertion of a Cu-IUD, whereas it is often improved by LNG-IUS. Non steroidal anti-inflammatory drugs reduce the discomfort. When pelvic pain, other than dysmenorrhea develops at any time after IUD insertion, the women should be investigated for possible incorrect placement of the device or infection (13).

**Ovarian cysts** may develop in 17.5% of women at 6 month of LNG-IUS use and in 21.5% at 12 month, but most of them were asymptomatic, functional and spontaneously disappeared by 6 month. **Other less common side effects** of LNG-IUS use are: lower abdominal pain 10.5%, acne 3.5%, back pain 3.5%, mastalgia 3.1%, headache 2.8%, vaginal discharge 2.7%, mood changes 2.5%, nausea 2.4% (6, 15).

**Infection**

The concern over pelvic inflammatory disease (PID) and IUD use arose because of a number of early observational studies which suggested causal associations. The evidence is now clear that PID is associated with
the insertion of an IUD, just as it is with any instrumenta-
tion of the uterus, but after around 3-4 weeks from
insertion. The presence of the IUD does not predispose
a woman to PID. Moreover, where the prevalence of
sexually transmitted infections (STIs) is low and the
IUD is inserted with correct technique the actual inser-
tion related risk has been shown to be very small (1 in
1000) and it is largely confined to the first 4 weeks after
insertion presumably due to introduction of microor-
ganisms during procedure (3, 7). It is a good practice to
screen for Chlamydia trachomatis and other STIs before
fitting an IUD, especially in populations where the
prevalence of STIs is high. Where this is not possible,
such as a postcoital fitting of Cu-IUD, it is reasonable to
proceed and give antibiotic cover (doxycyclin or azitro-
mycin). However, studies have failed to demonstrate
any benefit from routine antibiotic cover for low-risk
populations (7, 8, 28). Theoretically, cervical mucus
changes may explain a possible lower risk of PID in
LNG-IUS users compared with Cu-IUD users, but it is
clinically inappropriate to use the LNG-IUS any differ-
ently from other IUDs solely on this basis (8, 17).

It has become quite clear that the IUD does not fa-
cilitate STIs (29). An intrauterine contraception do not
protect against STI/HIV. If there is a risk of STI/HIV
(including the postpartum period) the correct and con-
sistent use of condoms is recommended, either alone or
with another contraceptive method (18).

According to WHO current PID is absolutely con-
traindication for initiation (Category 4) and is not op-
tional for continuation of intrauterine contraception
(Category 2). Past PID (assuming no known current risk
factors for STIs) with subsequent pregnancy is without
restriction (Category 1). Women without subsequent
pregnancy can generally use the method, but it is not an
optional choice (Category 2). It is necessary to treat the
PID using appropriate antibiotics (18,30).

The WHO recommended that women with current
purulent cervicitis or cervical chlamydial infection or
gonorrhoea or within 3 months should not have a Cu-
IUD or LNG-IUS insertion (it is absolutely contraindi-
cated- Category 4). Women who already have an in-
trauterine contraceptive device in situ and are found to
have a cervical infection can generally continue using it,
if they wish, but it is not optional (Category 2). Women
with other STIs (excluding women with HIV and hepa-
titis) and women with vaginitis (including trichomonas
vaginalis and bacterial vaginosis) can generally initiate
and continue the use of Cu-IUD or LNG-IUS but it is
not an optional contraceptive method for them (Cate-
gory 2). A very high individual likelihood of exposure
to gonorrhoea or chlamydial infection is a relative con-
traindication for initiation (Category 3) and is not op-
tional for continuation of intrauterine contraception
(Category 2) (4, 18, 30).

Among women at risk of HIV, intrauterine contra-
ception does not increase risk of HIV acquisition. There
is limited evidence showing no increased risk of overall
complications or infection-related complications when
comparing HIV-infected women with non-infected
women. Furthermore, IUD among HIV-infected women
was not associated with increased risk of transmission to
sexual partners. Women with high risk of HIV, HIV
infected women or women who are clinically well on
antiretroviral therapy can generally continue the use the
intrauterine contraception but it is not an optional
method for them (Category 2) (18). Dual contraception
(LNG-IUS and condoms) might be an ideal contracep-
tive strategy for HIV-infected women (31).

Antibiotic treatment is the first priority if PID devel-
ops when an IUD is in place. There is no need to re-
move the device if the woman wishes to continue with
it, but if she does not wish to keep the device or in rare
cases where response to antibiotic therapy is poor, the
device should be removed after start of antibiotic treat-
ment. The clinicians must consider the possibility of
pregnancy if there has been an intercourse in the pre-
ceeding 7 days (Masters 2002, Milena monografija). She
also needs comprehensive management for STIs and
counseling about condom use.

Age and parity

According to the WHO young women and nullipa-
rour generally can use intrauterine contraception but
they are not ideal candidates. Nulliparity is related to an
increased risk of expulsion. Young age (<20 years)
combined with multiple sexual partners is a known risk
for STIs and PID. In IUDs users young age, rather than
parity, has been more often associated with infections and
problems with pain and bleeding (32). The risk of PID is
closely connected with a risk of STIs, than with the
parity. More than usual follow-up may be needed if a
young woman chooses the method (Category 2) (18, 30).

Intrauterine contraception can be a good choice for
an older woman as it provides a reliable but low-input
method of contraception. In women over the age of 40
at the time of fitting of a Cu-IUD it does not need to be
replaced. It should be left in situ until 2 years from her
final menstrual period if it occurs before the age of 50,
and 1 year from the final menstrual period if it occurs
after the age of 50 (7).

The LNG-IUS use in perimenopausal women offers
a very effective contraception control, a complete elimi-
nation of excessive or painful bleeding, endometrium
protection if she takes estrogen replacement therapy or
from over-stimulation by her own unopposed estrogens
(17). It is currently licensed for this purpose in some
countries. The reluctance to use LNG-IUS may be based
on concerns that low stabile levels of LNG may be suf-
cient through its progestogenic effect to promote tu-
morigenesis in the breast (particularly if given with ex-
genous estrogen) or blunt the anti-tumor effect of ta-
moksifen on the breast (15).

Some health conditions

Women with simple goitre, hyperthyreosis, hypo-
thyreosis, history of gestational diabetes and epilepsy
can use intrauterine contraception without restriction (Category 1). Women with other forms of diabetes can use Cu-IUD without restriction (Category 1), but LNG-IUS use is possible but not a good option (Category 2). Levonorgestrel may slightly influence carbohydrate and lipid metabolism, but it is unclear whether the amount of levonorgestrel released by the LNG-IUS causes such change (18, 30).

Obesity (30kg/m² body mass index and more), severe arterial hypertension, multiple risk factors for cardiovascular disease, known hyperlipidaemias, history of deep venous thromboembolism, known thrombogenic mutations (e.g., factor V Leiden, prothrombin mutation, protein C, protein S and antithrombin deficiencies), surgery with prolonged immobilization, complicated valvular heart disease, ischemic heart disease, stroke and migraine: the use of Cu-IUD is without restriction but the LNG-IUS is not an optional contraceptive method (18, 30).

Women with asymptomatic or symptomatic current gall-bladder disease or medically treated or by cholecystectomy, and women with history of cholestasis related to combined oral contraception use or with pregnancy can use Cu-IUD (Category 1), and can generally use LNG-IUS but the method is not optional (Category 2). Women with liver tumors or active viral hepatitis are relatively contraindicated for LNG-IUS use (Category 3) but viral hepatitis carriers can use it (Category 1) (18, 30).

Cancer risk

Although IUD use is one of the oldest and most widely used forms of contraception through the world, its potential long-term effects on the uterus have been poorly evaluated (33). Analyses have found that IUD use is associated with a decreased risk for endometrial cancer. A similar negative association was demonstrated for combined oral contraceptive use (10).

Theoretically, IUD use may decrease endometrial cancer risk through at least two mechanisms. It directly provokes the intense sterile inflammatory response that alters the composition of fluids in the uterine cavity and the morphology of the endometrium. This response is more pronounced with Cu-IUDs than with “inert” devices. The other theoretical mode of action may be a more complete shading of the endometrium. Here endometrial response to hormones includes inhibition of estrogen and progesterone receptors with leaving the balance between them unchanged, and a decreased risk of endometrial hyperplasia, which is a known factor for endometrial cancer. It is possible that LNG-IUS provides some protection against endometrial cancer by suppressing endometrial growth. It leads to atrophy of the endometrial glands, thin mucosa and inactive epithelium. The results should be interpreted carefully (10, 33).

IUD users may have more contact with health care providers and for screening for cervical cancer. There is no restriction for women with ectopia. There is some theoretical concern that LNG-IUD may enhance progression cervical intraepithelial neoplasia, so it is not an optimal method of contraception for these women, but they can use Cu-IUDs without restriction (18).

Factors that influence the breast cancer risk include factors related to genetic background, reproductive and hormonal factors, factors related to life-style and environmental factors (such as smoking and alcohol use and geographic location) as well as various factors related to socioeconomic status and education (34). According to WHO there is no restriction for LNG-IUS use if a woman has benign breast disease or positive family history of breast cancer. LNG-IUS is not an optimal method if a woman have an undiagnosed mass in the breast (Category 2) and it is relatively contraindicated if she had breast cancer in the past and no evidence of current disease for 5 years because theoretical or proven risks usually outweigh the advantages of the method (Category 3). The LNG-IUS use is absolutely contraindicated if there is a current breast cancer (Category 4) (18).

Although numerous epidemiological studies have tried to find whether there is an association between the oral contraceptive use and breast cancer, relatively little has been published relating to non-oral hormonal contraception (34). A large post marketing study examined the incidence of breast cancer between women who were current or former LNG-IUS users and compared it with the incidence in general population. There were no significant difference in incidence between LNG-IUS users and general female population across five age groups. In the two younger age groups (30-34 and 35-39 years) the incidence was slightly higher among LNG-IUS users than among general female population. In the three older groups (40-44, 45-49 and 50-54 years) the rates were slightly higher among general female population than among LNG-IUS users. There was no apparent association between the device insertion time and the occurrence of breast cancer (10). Furthermore, according to product information women are encouraged to undergo an annual gynecologic examination (including an examination of the breast) after the insertion of LNG-IUS so that close surveillance for the incidence of breast cancer could be further accentuated. Moreover, the LNG-IUS is considered as the first line contraceptive only for parous women. Additional studies with different methodological approach are needed either to confirm or refuse these findings (15, 34).

There is no restriction for Cu-IUD use in relation to breast cancer (18).

Conclusion

The contemporary Cu-IUD is one of the safest, most effective, convenient and least expensive reversible contraceptives available for appropriately selected women: those who are in low risk for STIs. It has no systemic effects and can be safely used by breast-feeding women. Some studies suggest that Cu-IUD protect against endometrial cancer. The LNG-IUS offers the additional health benefits of substantially reducing men-
strual blood loss and pain and providing endometrial protection for women receiving estrogen replacement therapy during menopause or from over-stimulation by their own unopposed estrogens.

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NEKONTRACEPTIVNI EFEKTI INTRAUTERINIH KONTRACEPTIVNIH ULOŽAKA

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Kratki sadržaj: Postoji potreba za dugodoboj učinkom kontraceptivnim metodama. Bakarni intrauterini uložci nemaju sistemsko sporedne efekte i pogodni su za žene multipare koje nemaju obilne ili bolne menstruacije i koje su sa niskim rizikom za pojavu polnoprenosive infekcije. Levonorgestrel intrauterini sistemi oslobađaju hormon levonorgestrel direktno u kavum uterusa ali se

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Mala količina brzo resorbuje u sistemsku cirkulaciju. Većina korisnica ovog sistema ima oskudniju i manje bolnu menstruaciju uz sklonost ka povećanju nivoa hemoglobinina i feritina u krvi. Neke žene tokom prvih meseci primene su amenorične ili imaju oskudno produženo krvavljenje. Levonorgestrel intrauterini sistem može biti terapijska opcija za žene sa idiopatskim metroragijama ili sa nekim naslednim poremećajima u koagulaciji krvi. Štiti endometrijum u toku primene estrogene supstitucione terapije tokom menopauze i od hiperstimulacije njenih vlastitih estrogena u uslovima nedostatka progesterona.

Ključne reči: Intrauterini kontraceptivni uložak, nekontraceptivni efekti.