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I. Horbachevsky Ternopil National Medical University

## LEVONORGESTREL INTRAUTERINE SYSTEM AND CERVICAL CANCER. CLINICAL DIFFICULTIES

**Introduction.** In recent years, intrauterine systems releasing levonorgestrel became popular. They are a reliable and safe means of contraception. However, the hormonal effects of such systems sometimes mask the clinical manifestations of intercurrent diseases, including those manifested by irregular uterine bleeding.

**Case Description:** The emergence of diagnostic difficulties in the occurrence of cervical cancer in two women who used intrauterine systems releasing levonorgestrel.

**Conclusion.** Proper evaluation of irregular vaginal bleeding, including cervical cytology, is a prerequisite for all women who are carriers of intrauterine systems releasing levonorgestrel.

**Key words:** intrauterine systems releasing levonorgestrel; contraception; irregular bleeding, cervical cancer.

### ЛЕВОНОРГЕСТРЕЛ-ВНУТРІШНЬОМАТКОВА СИСТЕМА І РАК ШИЙКИ МАТКИ. КЛІНІЧНІ ТРУДНОЩІ

**Вступ.** В останні роки набули популярності внутрішньоматкові системи, що вивільняють левоноргестрел. Вони є надійним та безпечним засобом контрацепції. Однак гормональні ефекти подібних систем іноді маскують клінічні прояви інтеркурентних захворювань, в тому числі тих, що проявляються нерегулярною матковою кровотечею.

**Опис випадку:** труднощі діагностики при виникненні раку шийки матки у двох жінок, які використовували внутрішньоматкові системи, що вивільняють левоноргестрел.

**Висновок.** Належна оцінка нерегулярної вагінальної кровотечі, включаючи цитологію шийки матки – обов'язкова умова для усіх жінок, які є носіями внутрішньоматкових систем, що вивільняють левоноргестрел.

**Ключові слова:** внутрішньоматкові системи, що вивільняють левоноргестрел; контрацепція; нерегулярні кровотечі; рак шийки матки.

### ЛЕВОНОРГЕСТРЕЛ-ВНУТРИМАТОЧНАЯ СИСТЕМА И РАК ШЕЙКИ МАТКИ. КЛИНИЧЕСКИЕ ТРУДНОСТИ

**Введение.** В последние годы стали популярными внутриматочные системы, высвобождающие левоноргестрел. Они являются надежным и безопасным средством контрацепции. Однако гормональные эффекты подобных систем иногда маскируют клинические проявления интеркуррентных заболеваний, в том числе проявляющихся нерегулярным маточным кровотечением.

**Описание случая:** сложности диагностики при возникновении рака шейки матки у двух женщин, использовавших внутриматочные системы, высвобождающие левоноргестрел.

**Вывод.** Надлежащая оценка нерегулярного вагинального кровотечения, включая цитологию шейки матки – обязательное условие для всех женщин, которые являются носителями внутриматочных систем, высвобождающих левоноргестрел.

**Ключевые слова:** внутриматочные системы, высвобождающие левоноргестрел; контрацепция; нерегулярные кровотечения; рак шейки матки.

**INTRODUCTION.** The frequency of unplanned pregnancies remains quite high worldwide. About 35–50 % of all pregnancies are unintended, with a higher proportion among adolescents and young women belonging to certain racial and ethnic minorities or with a low level of education and income. Intrauterine hormone-releasing systems (IHRs) are more effective than other IUDs of the first and second generation. Levonorgestrel (LNG) releasing intrauterine systems remain the most effective and promising IHRs, used worldwide [1–7].

LNG as a component of HCV was chosen because it is one of the most potent progestins, has a pronounced affinity for progesterone receptors, and exhibits 100 % biological activity. It is a synthetic gestagene from the group of 19-norsteroids, the most active of the known gestagens. LNG has strong antiestrogenic and antigonadotropic effects and weak androgenic properties. LNG is not metabolized in the endometrium as fast as progesterone [1, 4]. Its contraceptive mechanism is based on:

– changes in the viscosity and chemical properties of cervical mucus (prevention of sperm penetration, as well as pathogens);

– impaired sperm function, including their motility (significant suppression of endometrial function can also contribute to impaired sperm migration into the fallopian tubes);

– changes in the structure of the endometrium (inhibition of proliferative processes; suppression of the mitotic activity of endometrial and myometrial cells; decidual-like stroma reaction; thickening and fibrosis of the vessel walls; thrombosis in capillaries; decreased vascularization; development of atrophic processes and amenorrhea);

– suppression of antiperistaltic activity of the fallopian tubes;

– suppression of the hypothalamic-pituitary function (mild inhibition of LH secretion, changes in the ovulation process and corpus luteum function).

The most common adverse effects of LNG include changes in blood loss, spotting, oligomenorrhea, amenorrhea, vulvovaginitis, genital tract infections, pelvic infections, ovarian cysts, dysmenorrhea, breast pain, expulsion IUD (full or partial), headache, abdominal pain, pelvic pain, migraine, back pain, blue mood, depression, nausea, acne, hirsutism [4].

LMG-IUS could be an alternative to hysterectomy and endometrial ablation for menorrhagia especially among perimenopausal women [3, 5]. However, since irregular bleeding is quite common amongst the users of LNG IUS in the first months after its introducing, this symptom could mask underlying cervical pathology, e.g. cervical cancer. We faced two such cases in our practice:

Case 1. Ukrainian female, S., 41 year-old, had irregular uterine bleeding irresponsible for combined oral contraceptives during last 18 months. PAP test was negative. No abnormalities were found during inspection of the cervix. Patient had intramural fibroid in the fundus with the size 4.3 × 4,9 cm. LNG IUS was introduced for menorrhagia control. However in two weeks patient came back to a clinic with the complains to abdominal pain. Pelvic inflammatory disease was diagnosed, antibiotics non-steroid anti-inflammatory drugs were recommended. In two months later patient suffered from irregular uterine bleeding again. Because such manifestation could occur during 2–3 months after LNG-IUS introduction she got instructions to make a new appointment if continuous bleeding. Advanced medical examination was performed. PAP-test demonstrated suspicious lesions for neoplasia with abnormal vessels. The diagnosis of cervical cancer in stage IIA was approved histologically. The first PAP smear was false-negative due to blood staining but perhaps this lady had cervical cancer even before LNG-IUS inserting. A radical extended hysterectomy was performed in this case.

Case 2. A 32-year-old woman requested insertion of LNG-IUS due to family issues. She did not report any medical problems, PAP smear was performed and was negative at the moment of admission. In a half of year LNG-IUS was removed due to continuous uterine bleeding. Patient was recommended to use oral contraceptives. The irregular bleeding was attributed to LNG-IUS, no PAP-test was performed. Only in three months after second appointment

the patient was examined again. We found tenderness during bimanual palpation and cervical ulceration suspected for neoplasia. Cervical cytology showed moderate dysplasia and micro-invasive adenosquamous carcinoma of the cervix (stage IIB) was detected after biopsy. Combined treatment (radical hysterectomy with pelvic node dissection plus radiotherapy) was performed.

**DISCUSSION.** Regularly the use of an intrauterine system can halve the risk of cervical cancer. There is good reason to believe that the use of an intrauterine system containing levonorgestrel can reduce the growth of human papillomavirus into cervical cancer. However, in some cases vaginal bleeding in carriers of LNG-IUS could be by mistake accepted as an adverse effect of LNG. Relatively low sensitivity of PAP smear (50–80 %) could produce false-negative results, However, repeating PAP test could significantly improve its diagnostic value.

The advantage of Papanicolaou staining is that the method allows to evaluate the degree of maturity of the cytoplasm, while revealing well the nuclei of atypical cells. The technique allows to diagnose pathology in the early stages, when almost 100 % cure is possible. In traditional cytology, a smear is prepared manually. Such a smear contains not only mucous cells, but also blood elements, mucus, pathogens (if any), which can complicate the study and lead to an incorrect assessment of the results. Atypical cells can be masked by layered cell elements. All these shortcomings cause not very high information content of the traditional test. To eliminate errors in the preparation of smears and their test study, modern medical equipment for conducting liquid cytology could be used.

The main advantage of liquid cytology is an advanced automated smear preparation technique. The material is taken by a special design cyto-brush, which allows to get material from all areas of the cervix. All material is placed in a special vial with a stabilizer, in which it is stored for a sufficiently long time, and can be re-examined if necessary.

#### CONCLUSIONS.

1. Irregular bleeding requires advanced examination including repeated PAP-test.
2. Liquid citology method could be a good alternative to a regular PAP smear.

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