

Levonorgestrel-releasing Intrauterine Systems: Device Design, Biomaterials, Mechanism of Action and Surgical Technique

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The mechanism of action and adverse reactions of 52 mg levonorgestrel-releasing intrauterine system and also level of pain during the insertion and techniques of anesthesia or analgesia for this procedure have been well documented. On the opposite pole the 13.5 levonorgestrel-releasing intrauterine system has been recently launched in Europe. To our knowledge there are no studies correlating the device design and biomaterials, mechanism of action, surgical technique and level of pain during the insertion of levonorgestrel-releasing intrauterine systems. This study was undertaken in order to determine whether there is a different level of pain during the insertion of 52 mg levonorgestrel-releasing intrauterine system compared to 13.5 mg levonorgestrel-releasing intrauterine system, considering the mechanism of action and the structural and dimensional discrepancies between the two intrauterine devices.

Keywords: Levonorgestrel-releasing intrauterine systems, device design, mechanism of action, level of pain during the insertion

Intrauterine systems are small devices, which are inserted inside the uterine cavity in order to prevent pregnancy; these apparatuses are among the most used long-acting reversible methods of contraception due to high efficacy, reversibility and high patient-satisfaction-cost ratio [1-3].

The effectiveness of the 52 mg levonorgestrel-releasing intrauterine system (52-LNG-IUS) has been demonstrated in large clinical trials and it is considered to be the most efficient intrauterine device available, with a pregnancy rate at 1 year of use that varies between 0.2% and 0.3%, according to the different studies [4-7].

Due to the fact that a smaller, lower dose version - the 13.5 mg levonorgestrel-releasing intrauterine system (13.5-LNG-IUS) has been recently launched in Europe, to our knowledge, its effectiveness has not been demonstrated in large clinical trials. However, data from phase II and III studies report similar efficacy, bleeding profile and safety to those of 52-LNG-IUS [8,9].

The levonorgestrel intrauterine systems are small, flexible, T-shaped devices composed of a low density polyethylene frame. At the level of the vertical arm each system presents a cylindrical hormone reservoir that contains a mixture of polydimethylsiloxane and levonorgestrel (fig.1). The concentration of progesterone is different: the 52-LNG-IUS contains 52 mg of levonorgestrel, while the 13.5-LNG-IUS, only 13.5 mg of the same active substance [8-13]. This core is covered by a semi-opaque membrane, made of polydimethylsiloxane and silica, but it also contains barium sulfate to render it radio-opaque. Additionally the 13.5-LNG-IUS, is equipped with a silver ring, located superiorly to the hormone

reservoir, close to the horizontal arms, which facilitates detection using sonography and also aids the physician to differentiate this system from other intrauterine devices [13].

Although both levonorgestrel-releasing intrauterine systems present a vertical arm and two horizontal stems, the dimensions differ - 52-LNG-IUS: 32 x 32 x 2.5 mm, while the 13.5-LNG-IUS: 28 x 30 x 1.55 mm [10, 13]. At the end of the vertical stem of the T-body, both intrauterine devices present a loop to which, brown-colored removal threads, composed of high density polyethylene, with a length of approximately 50 cm and a diameter of 0.1 – 0.2 mm, are attached (fig. 1). The polyethylene of the removal threads also contains iron oxide as a colorant [10, 13]. Therefore, structurally the two levonorgestrel-releasing intrauterine systems are similar; they are composed of the same excipients: dimethylsiloxane cross linked elastomer, colloidal anhydrous silica, polyethylene, barium sulfate, iron oxide black C177499. In addition the 13.5-LNG-IUS also contains silver [10, 13].

The levonorgestrel-releasing intrauterine systems are packaged sterile within a special insertion tube and a handle designed to insert the device into the uterine cavity (fig. 2). The inserter, consist of a symmetric two-sided body and a slider that are integrated with flange, lock, insertion tube and plunger. The inferior part of the vertical arm is loaded in the tip of the inserter. The outer diameter of the insertion tube of 52-LNG-IUS is 4.4 mm and 3.8 mm in case of 13.5-LNG-IUS [10, 13].

The insertion technique of both levonorgestrel-releasing intrauterine systems is similar and it follows the subsequent steps. First a bimanual examination is mandatory to

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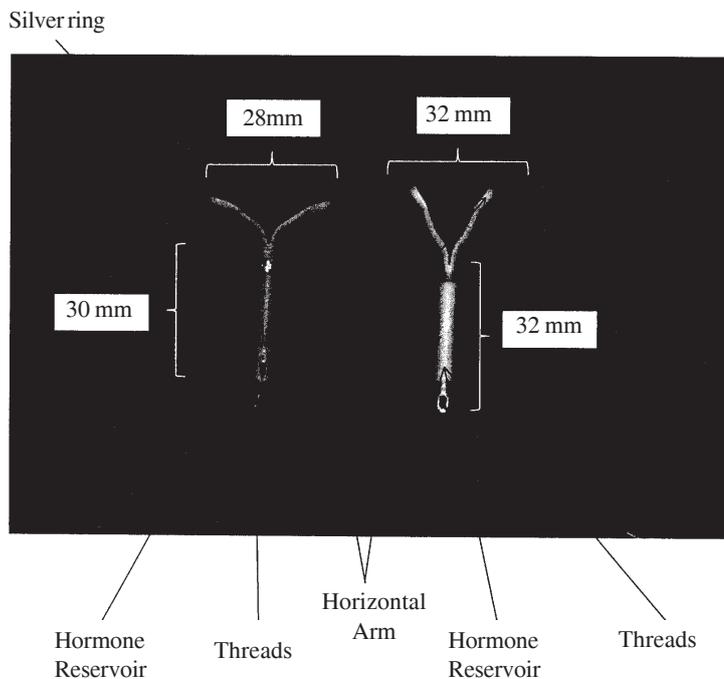


Fig. 1. 13.5 mg levonorgestrel-releasing intrauterine system (left) and 52 mg levonorgestrel-releasing intrauterine system (right)

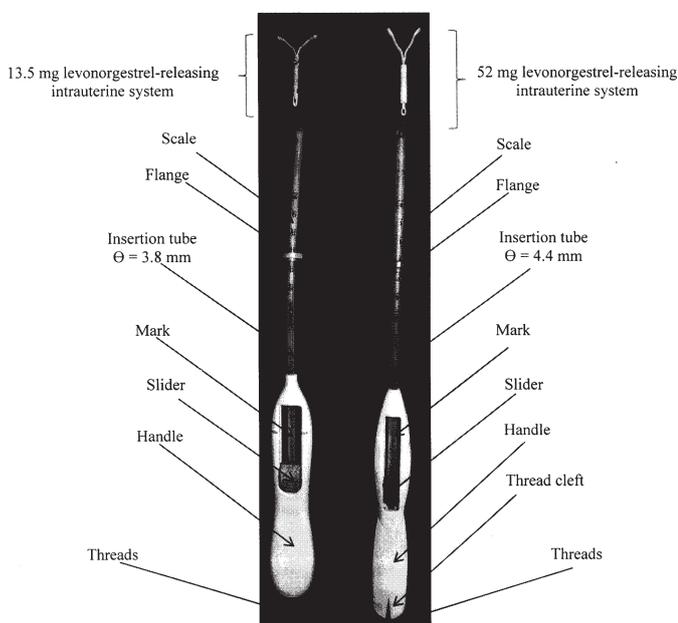


Fig. 2. Levonorgestrel-releasing intrauterine systems and mechanisms of insertion

ascertain uterine size and position. Next a speculum is used to gain clear visualization of the cervix. After the cervix and adjacent vagina are cleansed with povidone-iodine or chlorhexidine, a single-tooth tenaculum is used to grasp the anterior lip of the cervix. While performing gentle traction on the tenaculum, a uterine sound is inserted into the uterus, to assess the direction of the cervical canal and the direction and size of the uterine cavity. Afterwards the levonorgestrel-releasing intrauterine system is loaded into insertion tubing and the threads are then secured in the thread cleft. The flange on the insertion device is then set at the level to which the uterus sounds. The insertion tubing is placed into the vagina at the level of the external cervical orifice. The insertion tubing is then gently advanced until the flange is approximately 1.5-2 cm from the external cervical orifice. Next, the slider on the handle is pulled backward to the level of the raised mark on the insertion handle, expelling the IUD arms from the insertion tubing. The insertion tubing is then advanced until the flange is at

the external cervical orifice, thereby advancing the IUD to the level of the uterine fundus. Afterwards, the handle and insertion tubing are then gently retracted from the uterus and cervix. The strings of the intrauterine system that remain in place will then be trimmed, so that approximately 3 cm are visible, extending from the external cervical orifice [10,11,13].

The 52-LNG-IUS initially releases levonorgestrel at a rate of 20 ug/day, which decreases to 11 ug/day after 5 years [10-12]. The 13.5-LNG-IUS has a releasing rate of levonorgestrel of 14 ug/day in the first 24 h, but diminishes to 10 ug/day after 60 days and 6 ug/day at 1 year [13]. The release rate of 13.5-LNG-IUS after 3 years reaches 5 ug/day [13].

Although the hormonal concentration and releasing rates of the two levonorgestrel-releasing systems are different, the mechanism of action is similar. The levonorgestrel, is a powerful progesterone, that locally, inside the uterine cavity, causes glandular atrophy and stromal decidualization. The endometrium becomes very thin, preventing sperm, ovum and embryo migration and implantation. The levonorgestrel also modifies the viscosity of the cervical mucus blocking the ascend of the spermatozoa into the uterine cavity [12,14-17]. In addition, another local mechanism by which these two intrauterine systems prevent undesired pregnancy is the physical presence of the device inside the uterine cavity, that cause a foreign body reaction which destroys the spermatozoa, ovum or the fertilized embryo prior to implantation [10, 14-17].

These intrauterine effects have been well documented for 52-LNG-IUS [10, 14-17]. Although the 13.5-LNG-IUS has a decreased levonorgestrel-releasing rate it determines homonymous progesteronic effects on the endometrium and cervical function as 52-LNG-IUS [13,18].

However, although the hormone is delivered inside the uterine cavity it passes into the systemic circulation and according to serum concentration it may suppress ovulation [18]. Due to increased concentration and levonorgestrel-releasing rates, 52-LNG-IUS has a higher incidence of anovulation, in comparison to 13.5-LNG-IUS [18].

The most common adverse reactions of patients using the 52-LNG-IUS are headache, bleeding irregularities, and

pelvic pain [10,19,20]. The very common adverse reactions reported in the clinical trials of 13.5-LNG-IUS are headache, bleeding irregularities, acne/seborrhea, vulvo-vaginitis, ovarian cysts and pelvic pain [8,9,13].

Experimental part

Clinical study

This study was undertaken in order to determine whether there is a different level of pain during the insertion of 52 mg levonorgestrel-releasing intrauterine system compared to 13.5 mg levonorgestrel-releasing intrauterine system, considering the mechanism of action and the structural and dimensional discrepancies between the two intrauterine devices.

Materials and methods

We evaluated 46 patients, admitted in the Bucharest Emergency University Hospital between the 28th of April 2014 to 4th of July 2014, to whom either the 52-LNG-IUS or 13.5-LNG-IUS was inserted as a long-acting reversible method of contraception. All participants were first counseled regarding alternative forms of contraception and the advantages, disadvantages and side effects of both levonorgestrel-releasing intrauterine systems. Also, all patients were apprised that the 13.5-LNG-IUS has just been launched in Europe and therefore it still needs to be tested in large clinical trials. An informed consent was then taken from all the subjects of the study.

At a visit prior to the levonorgestrel-releasing intrauterine system insertion, medical and sexual history was obtained and all patients underwent a physical examination, a pap smear, screening for common sexually transmitted infections and a trans-vaginal sonography (during examination cervical and total uterine lengths were estimated and recorded). Participants with significantly distorted uterine anatomy, unexplained vaginal bleeding or history within 3 months of treatment for pelvic inflammatory disease endomyometritis, chorioamnionitis, puerperal sepsis, or a septic abortion were excluded. Were also foreclosed patients with cervical or uterine neoplasia, breast cancer, renal insufficiency, hepatic tumors or hepatic insufficiency and hyper-sensibility to levonorgestrel or any of the excipients found in the structures of the two intrauterine devices.

During the visit for the insertion of one of the two levonorgestrel-releasing intrauterine systems, all patients underwent a urine pregnancy test – which was negative in all cases. No antibiotic prophylaxis was indicated.

All the levonorgestrel-releasing intrauterine systems were inserted by well-trained healthcare professionals, during the first 7 days of the follicular cycle, with no anesthesia or analgesia, following the technique described before in the introduction chapter.

The 13.5-LNG-IUS was inserted in 23 patients, who were enrolled in group A. Group B was composed of 23 patients who received the 52-LNG-IUS.

Participants from both groups recorded the level of pain by using a 10 point visual analog scale with the value of 10 meaning “worst imaginable pain” and 1 “absence of pain” immediately after the insertion of the intrauterine system. All subjects were also asked to report which phase of the levonorgestrel-releasing systems insertion is the most distressful.

Scanning electron microscopy

In addition to the clinical part of this study we analyzed if the structure of the components of the two levonorgestrel-releasing intrauterine systems and the

mechanism of interaction of the devices with the fluids inside the uterine cavity can influence the level of pain during insertion and in the first months of use.

Scanning electron microscope was used to evaluate four levonorgestrel-releasing intrauterine systems. Three of them were 52-LNG-IUS which were extracted after 3 months in two cases and one after a period of 36 months. We also evaluated a 13.5-LNG-IUS, which was extracted after 3 months, due to pelvic pain and prolonged dysfunctional bleeding. All the devices were investigated by SEM QUANTA INSPECT F (R=1.2 nm) equipped with FEG and EDAX, without any coatings.

The mean age of the 46 women enrolled in the study was 28.83 years, 29.23 years in group A and 28.43 in group B.

A comparison between the pain levels described by the subjects in the two groups immediately after insertion of one of the two levonorgestrel-releasing intrauterine systems has been made (see Table 1). Rank test statistics

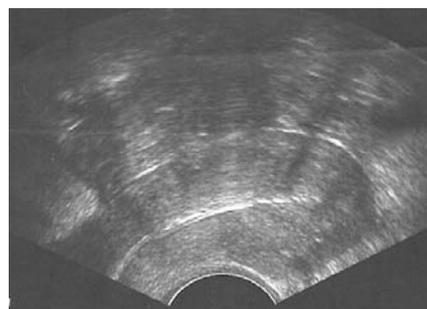


Fig. The 52 mg levonorgestrel-releasing intrauterine system (trans-vaginal sonography)

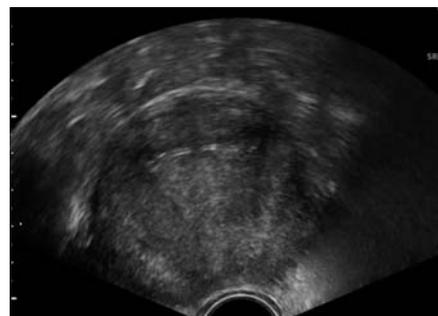


Fig. The 13.5 mg levonorgestrel-releasing intrauterine system (trans-vaginal sonography)

confirmed a lower level of pain voiced by the patients in group B, who received the 13.5-LNG-IUS than the ones to whom the 52-LNG-IUS was inserted.

Also, a comparison between the most distressful phase during the insertion of levonorgestrel-releasing intrauterine systems has been made. 39 subjects enrolled in the study, (21 from group A and 18 who pertain to group B), affirmed that the most distressful phase of the levonorgestrel-releasing systems insertion is represented by the initial moment when passing of the insertion tube maneuver is handled.

The mean length of the cervix was 2.74 cm. However, the size of the cervix was higher than 4 cm in all 4 patients who recalled the highest levels of pain (between 7 and 10 on the visual analog scale). Among the 12 patients who described high levels of pain (between 5 and 10 on the visual analog scale) 10 were nulliparous women – 7 pertained to group A and 3 to group B.

9 patients from group A and 8 from group B were first-time users of a intrauterine device. All 4 patients who described the highest levels of pain (between 7 and 10 on

Level of pain (visual analog scale)	Group A (n=23)	Group B (n=23)
1-2	0	2
3-4	15	17
5-6	5	3
7-8	2	1
9-10	1	0
Group A – number of patients with the 52-LNG-IUS inserted Group B – number of patients with the 13.5-LNG-IUS inserted		

Table 1
THE PAIN LEVELS OF THE SUBJECTS IN THE TWO GROUPS IMMEDIATELY AFTER THE INSERTION OF AN INTRAUTERINE SYSTEM

the visual analog scale) – 3 from group A and 1 from group B were women who had never used an intrauterine system before. 39 participants in our study had university education. The other 7 patients voiced high levels of pain (between 5 and 10 on the visual analog scale). All 4 patients who described the highest levels of pain (between 7 and 10 on the visual analog scale) – 3 from group A and 1 from group B were women with a medium or low level of education.

The investigations performed using scanning electron microscope (figs. 5, 6) highlighted different levels of degradation of the polymeric component of the levonorgestrel-releasing intrauterine systems, proportional with the time spent inside the uterine cavity.

We evaluated and compared the two 52-LNG-IUS and the 13.5-LNG-IUS that were extracted after 3 months of use. In all cases we detected minor degradation signs on the surface of the polymeric component, with no discrepancies between the two types of intrauterine devices (fig. 5).

When analyzing the surface of the polymeric component of the 52-LNG-IUS that was used 36 months we encountered signs of severe degradation – numerous fissures and even cracks, that for sure affect the proper function of the device (fig.6).

Results and discussions

In the clinical part of our study, we evaluated and compared the level of pain during the insertion of 52-LNG-IUS compared to the placement of 13.5-LNG-IUS. All the 46 patients were enrolled in the study after we have eliminated the frequent causes of pelvic pain – pelvic inflammatory disease, distorted uterine anatomy, or abnormalities of the cervical-vaginal cytology or vaginal flora [21-28]. Usually the pelvic inflammatory disease is present before the insertion of an intrauterine device; therefore, it is important to assess patient risk for sexually transmitted infections prior to the insertion visit [11, 21-26]. No antibiotic prophylaxis was indicated, due to the fact that multiple studies have demonstrated it has no effect on the incidence of post-insertion pelvic inflammatory disease [11,29-31].

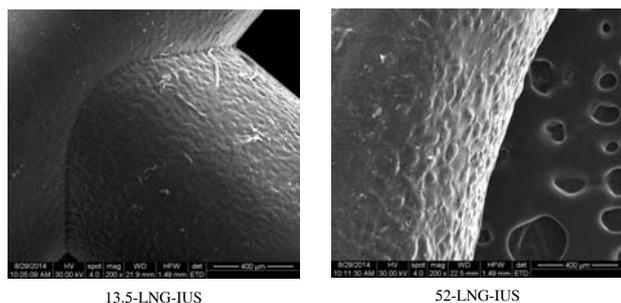


Fig. 5. SEM images of the levonorgestrel-releasing intrauterine systems after 3 months of use (note minor degradation signs on the surface of the polymeric component)

The pain experienced by the patient during the insertion of a levonorgestrel-releasing intrauterine system has multiple causes - placement of speculum, use of tuck on cervix, cervical and uterine irritation from passing the insertion tube and placement of the IUD [11].

Placement of a speculum in order to use a tenaculum on the cervix in order to insert either 52-LNG-IUS or 13.5-LNG-IUS is mandatory regardless dimensions, structure and insertion mechanism. However this is probably direct proportional with time spent with the placed speculum and tenaculum on cervix. Due to the high level of experience of the medical personnel enrolled in our study the time required for the insertion did not vary between the groups. However, although the insertion mechanisms of 52-LNG-IUS and 13.5-LNG-IUS are similar the healthcare professionals who inserted the intrauterine systems in this study stated that 13.5-LNG-IUS is easier to introduce.

The majority of subjects enrolled in the study, from both groups, affirmed that the most painful phase of the levonorgestrel-releasing systems insertion is represented by the initial moment when passing of the insertion tube maneuver is handled; this stage corresponds to the point when the insertion tube passes through the cervical canal. The main mechanism that is responsible for the augmented level of pain during the insertion of 52-LNG-IUS is represented by the fact that the outer diameter of the insertion tube of 13.5-LNG-IUS is 3.8 mm, while the outer diameter of the insertion tube of 52-LNG-IUS is 4.4 mm.

Prior to the insertion of the intrauterine system, a trans-vaginal ultrasonography and clinical examination was performed in all patients; therefore the total uterine length and cervical length were estimated. We have observed that patients with cervical length > 3 cm experienced

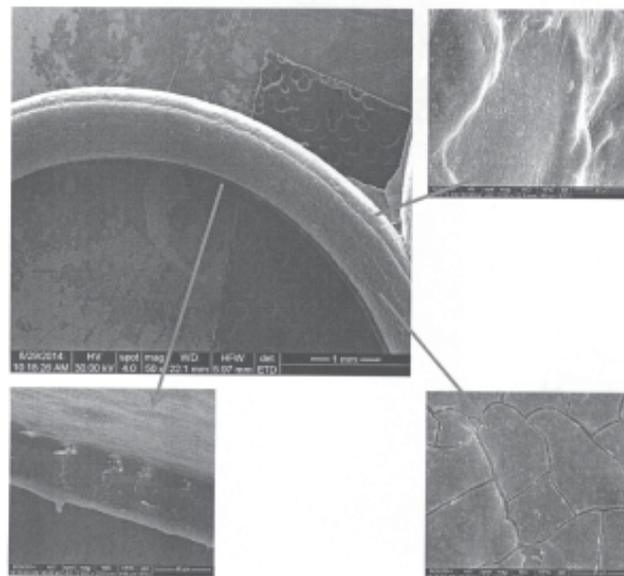


Fig. 6. SEM images of the 52-LNG-IUS after 36 months of use (note polymer aging – numerous fissures and even cracks can be seen on the surface of the intrauterine device)

higher levels of pain. This result is in contradiction with previous studies, which stated that the prediction of painful or difficult intrauterine device insertion cannot be anticipated [11,32].

Even though the structure of 52-LNG-IUS and 13.5-LNG-IUS is similar (they have the same excipients – as pointed before), so the index of elasticity is analogous, the 13.5-LNG-IUS has decreased dimensions (13.5-LNG-IUS - 28 x 30 x 1.55 mm Vs 52-LNG-IUS: 32 x 32 x 2.5 mm). Therefore the different dimensions of these two intrauterine devices influence the level of pain experienced by the patient during insertion (especially the passage through the cervical canal) in favor of 13.5-LNG-IUS, who's insertion is less hurtful than 52-LNG-IUS.

Another important matter that needs to be discussed is that the majority of patients that described high level of pain (between 5 and 10 on the visual analog scale) during the insertion of both levonorgestrel-releasing intrauterine systems were first-time users of intrauterine devices, nulliparous women, with a low level of education. The already demonstrated relation between parity and increased pain during the insertion of an intrauterine device, but also the degree of education and anxiety are conditions that can modify the pain levels during the insertion of levonorgestrel-releasing systems, regardless of the structure and dimensions of the two intrauterine systems [11,33].

In the experimental part of this study we evaluated and compared the surface of the polymeric component of the two levonorgestrel-releasing intrauterine systems, in relation to the time spent inside the uterine cavity, in order to determine if the structure of the components of the two devices influences the level of pain during the insertion and in the first months of use. The polymeric component plays a major role in anchoring the device into the uterine cavity, but also in the rate of delivering progesterone. The investigations performed using scanning electron microscope, revealed no structural discrepancies between the two types of intrauterine devices. However we can conclude that the degradation rate detected on the surface of the polymeric component of these two intrauterine devices is proportional with the time spent inside the uterine cavity, therefore it limits the long use of these intrauterine systems.

Conclusions

There is an augmented level of pain during the insertion of 52 mg levonorgestrel-releasing intrauterine system compared to the insertion of the 13.5 mg levonorgestrel-releasing intrauterine system, mainly due to dimensional discrepancies of the two intrauterine devices. No major interference was observed considering the structure of these two intrauterine devices.

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Manuscript received: 12.11.2014