Adverse Reactions Due to Use of Two Intrauterine Devices with Different Action Mechanism in a Rare Clinical Case

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We report the case of a patient with simultaneously two intrauterine devices with different mechanism of action. By cumulating the effects and adverse reactions of the two intrauterine devices, the patient had severe dysfunctional bleeding and pelvic-abdominal pain. Using scanning electron microscope, we analyzed the surfaces of the two retrieved intrauterine devices in order to establish the physio-pathological mechanisms that occurred and lead to a local but also a hormonal disorder in the reported patient. We would also like to draw the alarm that a complete evaluation (clinical and imagistic) are mandatory prior to the insertion of an intrauterine device.

Keywords: intrauterine devices, mechanism of action, adverse reactions

Intrauterine devices are one of the most common contraceptive methods [1,2]. Intrauterine devices are sought to be efficient and increasingly popular when it comes to reversible contraception [1,2] .

Intrauterine devices are made of a solid material that is placed inside the uterus, with a contraceptive role, thus setting a borderline between sperm cells and the ovule, as well as limiting the implantation of the egg in case of fecundation [3].

Copper releasing intrauterine devices are *T* or *U* shaped plastic systems that present on their surface, a copper layer [4-6]. In Europe, there are various affordable copper releasing devices: Cu-380A T intrauterine device (T shaped) and Multiload 250 or Multiload 375 (horseshoe shaped) [4-6].

Classification of copper ions releasing intrauterine devices:

- Ist generation - Cu 7 and Cu-T 200
- IInd generation - Cu 250
- IIIrd generation- Cu 375 and Cu-380 A T (total surface covered by copper is 380 mm^2)

New generation devices contain a higher amount of copper ions, which significantly increases their efficiency and time of action [3,5].

Cu-T 380A is a T shaped intrauterine device, with a skeleton made of polyethylene, covered by copper on a 380 mm^2 surface, which can be effective 10 years after insertion, though it is recommended that the devices is renewed every 5 years [4]. Cu-T 380A is presented with a short arm of 32 mm (weights around 66.5 mg) and a long arm of 36 mm (weights around 176 mg) [5]. This intrauterine device is made of a stern covered with a 314 mm^2 copper line, each arm dealing with a 33 mm^2 copper bracelet, having thus a total of 380 mm^2 of copper [6].

Multiload is an intrauterine devices shaped like a horseshoe, covered by copper on a 375 mm^2 surface [7]. The arms are flexible and minimize the risk of expulsion, being made of high-density polyethylene. The role of these flexible arms is that of adapting to the extent inside the uterine cavity, decreasing the risk of affecting the integrity of the uterine walls [7]. The device is made of a plastic stern, formed from a mixture of polyethylene, ethylene vinyl acetate and barium sulphate in a 44/36/20 ratio. A copper line is enwrapped around the stern. A double headed nylon line is attached to the inferior end of the stern [7]. Depending on the contained copper quantity there are two types of Multiload devices: Multiload 275 (3 years of effective contraception) and Multiload 375 (5 years effective contraception) [7]. It has been proven that Multiload device, along with the Cu-T 380A have the same efficacy against an unwanted pregnancy.

Copper ions cyclically released by the intrauterine device have a spermicide effect, lowering the risk of fecundation [8-10]. Releasing the copper ions inhibits the capacitation phenomenon by inducing a severe inflammatory reaction, stimulates prostaglandins release by endometrial cells and has a chemotactic effect for leukocytes, by creating a hostile environment for implantation [8-12].

The first intrauterine device with progesterone releasing hormonal mechanism was first approved by FDA in 1976 [13]. This intrauterine system contains a reservoir with 38 mg of progesterone, releasing a dose of 65 μg per day. The vertical stern has a 36 mm length and it is made of an ethylene-vinyl-acetate copolymer, while the horizontal arms are 32 mm long and made of polyethylene [13]. The device contains minimum quantities of barium sulphate in order to be discovered during imagistic procedures. The progesterone quantity in this intrauterine device ensures a contraceptive effect for approximately 400 days, thus a yearly renewal being necessary [13]. It has been taken off the market starting with the summer of 2001 [13].

Levonorgestrel releasing intrauterine system is T shaped and has a permeable membrane made of a polymer that releases in vivo 20μg daily for 5 years, out of a 52 mg reservoir of levonorgestrel [12]. The releasing ratio decreases to 11 μg after 5 years [12]. The system has a similar shape to that of the Copper T380 intrauterine device and it contains a 32 mm T shaped vertical polyethylene

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skeleton with a cylinder made of levonorgestrel and polydimethylsiloxane, a loop at the end of the vertical segment for extraction and two 32 mm horizontal arms [14-17]. The cylinder has a permeable membrane that regulates the hormonal releasing ratio. They are very flexible, reduced as scale and through a myometrium docking system present a minimal risk of spontaneous expulsion [16-18].

Both copper ions releasing intrauterine devices and hormonal ones induce an endometrial inflammation that has a chemotactic effect on neutrophils, turning the sperm cells inefficient [3]. A persistent endometrial inflammation may prevent implantation, though if the nidation already took place, the intrauterine devices do not cause abortion [19]. Nonetheless, fecundation can be prevented by other means, such as: altering the capacitation function of the sperm cells, inhibiting tubal transportation of the ovule and the ascension of sperm cells by thickening the cervical mucus, especially when it comes to non-hormonal uterine devices [3, 15].

Biochemical and vascular alterations appear, that are specific to the foreign-body reaction by increasing the local level of histamine, prostaglandins and some proteolytic enzymes [3, 15]. Copper stimulates the foreign body reaction by developing a toxic action over the gametes of the blastocyst and their mean of transportation [3, 8, 9, 15]. Levonorgestrel releasing intrauterine systems add a plus by thickening the cervical mucus in order to limit the ascension of sperm cells, inhibiting ovulation and deny the proliferation of the endometrium so that the zygote implantation does not take place [3, 15].

The efficacy of intrauterine devices is around 0.6 % for non-hormonal systems and 0.1 % for levornogestrel releasing intrauterine system [20]. Copper releasing intrauterine devices can be used as an emergency contraception as far as 5 days after an unprotected sexual intercourse [19, 21].

Experimental part

Case report

We report the case of a 33 years old female patient, known to possess an intrauterine device with 52 mg of levonorgestrel who was admitted in the Obstetrics and Gynecology Department of the University Emergency Hospital Bucharest, due to dysfunctional vaginal bleeding and pelvic-abdominal pain. Personal and family pathologic history were insignificant. The patient asserts that at a local Obstetrics and Gynecology Department, 6 months ago, she had a 4 year used intrauterine copper releasing device, extracted; after 2 months, the 52 mg levonorgestrel device was inserted.

The patient claimed that the symptoms appeared around 14 days after the new intrauterine devices was inserted and increased progressively, while the pain did not disappear with usual analgesics. During the standard vaginal examination, we encountered a cervix in a longitudinal position, covered in a white discharge, and through the external cervical orifice nylon fibers from an intrauterine device were exposed. The vaginal tact revealed that the uterine cervix was oriented in the axis of the vagina, the external cervical orifice was close, but the uterine body was slightly enlarged and sensitive at mobilization, while the annexes where enlarged and painful.

During the trans-vaginal ultrasound examination we observed that the uterus was in ante-version, with a homogenous myometrium, and we detected two intrauterine devices inside the uterine cavity. We also

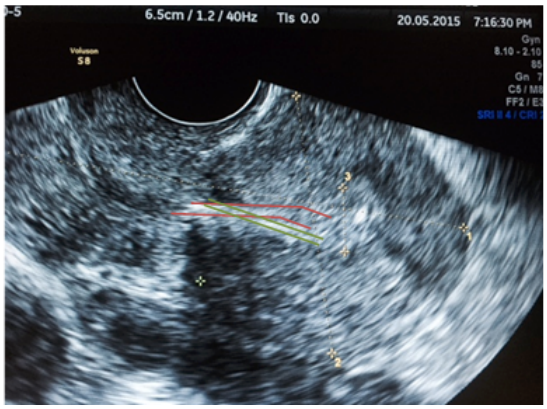


Fig. 1.Trans-vaginal ultrasound aspect of the uterus with normal dimensions (1) – longitudinal axis 75 mm (2) – sagittal axis 45 mm but note the distension of the uterine cavity (3) due to the presence of two distinct intrauterine devices inside the endometrial cavity – the red lines mark a Multiload intrauterine device– the green lines mark the lenorgestrel-releasing intrauterine system

encountered bilateral ovarian cysts - a transonic mass of 51/54/47 mm on the right ovary and another transonic mass of 43/42/37 mm on the left ovary (fig. 1).

By pulling the externalized fibres from the cervical area, we extracted a 52 mg levonorgestrel-releasing intrauterine system. Afterwards, we encountered other fibres at the level of the external cervical orifice and by pulling them we also extracted a Multiload intrauterine device (fig. 2).

Scanning electron microscopy

Using scanning electron microscope we analyzed the surfaces of the two retrieved intrauterine devices in order to establish the physio-pathological mechanisms that occurred and lead to a local but also a hormonal disorder in the reported patient.

Scanning electron microscope was also used to evaluate the surface of two unused intrauterine devices (a levonorgestrel-releasing intrauterine system and a Multiload intrauterine device) in order to compare the results. All the devices were investigated by SEM QUANTA INSPECT F (R=1.2 nm) equipped with FEG and EDAX, without any coatings [22, 23].

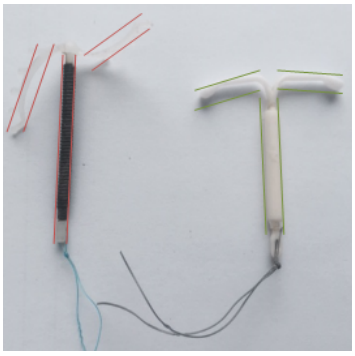
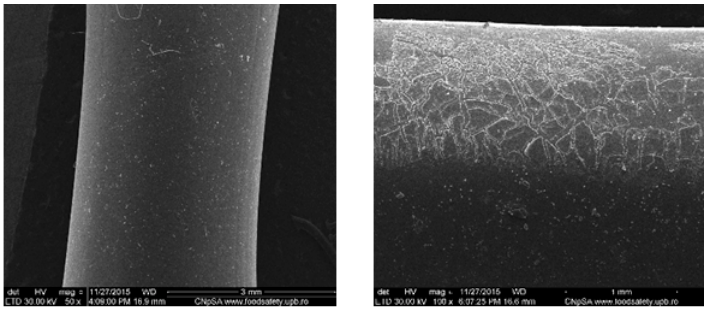


Fig. 2.Macroscopic aspect of the two extracted devices - on the left (marked with red lines) a Multiload intrauterine device - to the right (marked with green lines) a levonorgestrel-releasing intrauterine system

Results and discussions

Using scanning electron microscope we compared the surface of the retrieved specimen type levonorgestrel-releasing intrauterine system with an unused device in order to highlight the differences. Analyzing figure 3 and figure 4 it is clear that the polymeric surface of this type of intrauterine system modifies after implantation – note the presence of numerous organic deposits and minor degradation signs.

Although that initially the organic deposits on the surface of the explanted levonorgestrel-releasing intrauterine



unused levonorgestrel-releasing intrauterine system

retrieved levonorgestrel-releasing intrauterine system

Fig. 3 . SEM images after the surface analysis of the unused (left) and retrieved (right) specimen type of levonorgestrel-releasing intrauterine systems – note the presence of numerous organic deposits and minor degradation signs on the extracted device

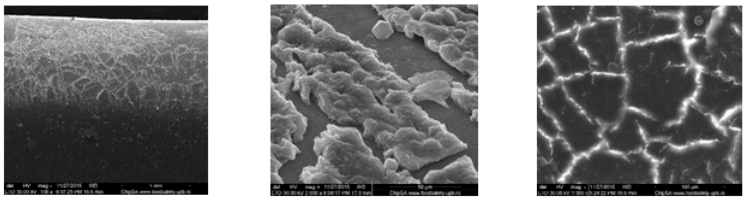


Fig. 4. SEM images of the retrieved type of levonorgestrel-releasing intrauterine systems – note the presence of numerous different organic deposits that are adherent to the polymeric surface of the device unused levonorgestrel-releasing intrauterine system

system do not appear to form a compact layer, they are quite adherent to the polymeric surface of the device (fig. 4).

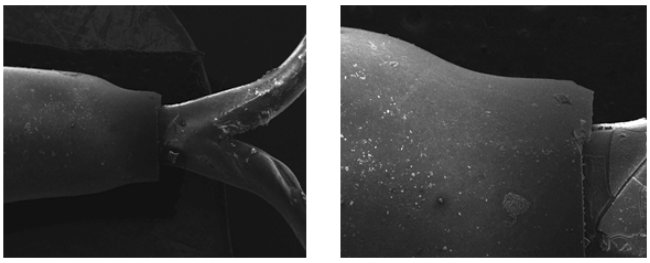


Fig. 5. SEM images of the retrieved type of levonorgestrel-releasing intrauterine systems – note the presence of a crack and deterioration of the hormonal reservoir in the superior part

Because the patient had a complex hormonal disorder we systematically analysed the surface of the reservoir of the extracted levonorgestrel-releasing intrauterine system (fig. 5).

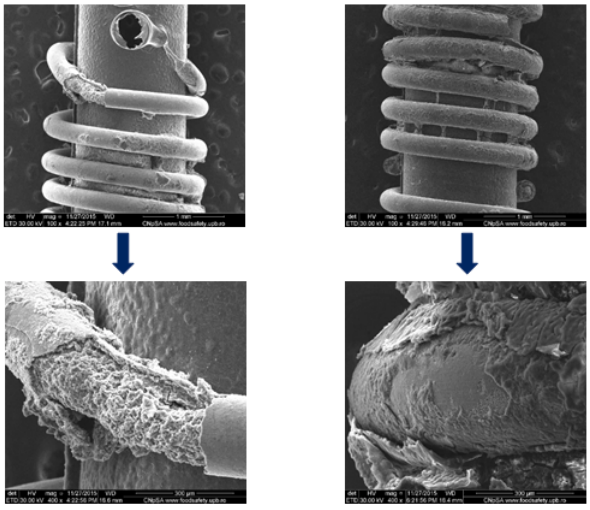


Fig. 6 . SEM images of the extracted Multiload intrauterine device – note the presence of numerous organic deposits on the surface and also strong deterioration of the copper wire

A complete surface analysis using scanning electron microscope of the extracted Multiload intrauterine device was also performed (fig. 6).

From our knowledge, there has been no previous case report of a patient with simultaneously two intrauterine devices with different mechanism of action (hormonal and non-hormonal).

We do not have an explanation as to why the patient initially affirmed that the Multiload intrauterine device was extracted and afterwards the 52 mg levonorgestrel-releasing intrauterine system was inserted. However, this patient did actually have two distinct intrauterine devices inside the endometrial cavity.

The symptoms (dysfunctional vaginal bleeding) and imagistic aspect (the presence of bilateral ovarian cysts) are highly representative for a malfunction of the 52 mg levonorgestrel-releasing intrauterine system that determined a systemic hormonal dysfunction.

Due to the fact that this hormonal type of intrauterine device releases levonorgestrel, a very powerful progesterone, it has both local (intrauterine) and systemic effects [14, 15, 24, 25]. The progesterone is released from the hormone reservoir at a constant rate [25]. This is why the serum levels are not sufficient to supress ovulation [14]. However in our case by a complete surface analysis using scanning electron microscope we detected a strong deterioration of the hormonal reservoir in its superior part that explains the explains the existence of functional bilateral ovarian cysts.

The dysfunctional vaginal bleeding may be explained be the mechanisms of action of both intrauterine devices. The progesterone, released inside the uterine cavity by the levonorgestrel-releasing intrauterine system, has androgenic properties and by attaching to progesterone receptors, it induces decidualization of the endometrial stromal cells and atrophy of the glandular epithelium by suppressing the formation of spiral arteries [14, 15, 26]. Therefore, a large quantity of levonorgestrel can dramatically reduce the size of the endometrium causing vaginal dysfunctional bleeding. In addition, the copper ions release by the Multiload intrauderine device determine a local inflammatory reaction that diminishes the endometrial blood flow and also induce decidualization predisposing to vaginal dysfunctional bleeding [10, 27]. The endometrial blood flow is also reduced by the physical presence of any intrauterine system inside the uterine cavity, by causing a foreign body reaction – thus explaining why in our case the patient had vaginal dysfunctional bleeding [10].

Analyzing figure 4 and figure 6 we can also note an interesting aspect – one can observe more organic deposits on the surface of the Multiload intrauterine device compared to the levonorgestrel-releasing intrauterine system. This may be explained in terms of mechanical adherence – the copper wire of the Multiload intrauterine device has an increased adhesion capacity compared to the polymeric

surface of the levonorgestrel-releasing intrauterine system. However, based on the conclusions of this clinical study, more research will be done in order to understand the adhesion of organic substance on different surfaces (polymeric versus copper) for understanding the exact mechanism of action of intrauterine devices.

Conclusions

We report adverse reactions due to use of two intrauterine devices with different action mechanism in a rare clinical case. By cumulating the effects and adverse reactions of the two intrauterine devices the patient had severe dysfunctional bleeding and pelvic-abdominal pain.

We would also like to raise awareness that a complete evaluation (clinical and imagistic) is mandatory prior to the insertion of an intrauterine device.

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