



Ectopic Pregnancy Following Levonorgestrel Emergency Contraception: Report of Two Cases

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Abstract

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BACKGROUND: Ectopic pregnancy (EP) is likely to occur as an unwanted complication after unprotected intercourse in spite of levonorgestrel emergency contraception (LNG-EC). Its incidence has been increasing recently.

CASE REPORTS: We present two cases of tubal EP after the oral use of levonorgestrel, treated by laparoscopy. The first unruptured EP with unclear ultrasound findings, because of uterine ventrofixation after the caesarean section (CS). The second case is a ruptured EP after LNG –EC on day 24 of the period with mild hemoperitoneum with severe peritoneal irritation. The fundamental question is whether levonorgestrel participates in the etiology of EP.

CONCLUSION: The etiology of EP involves many factors. Levonorgestrel mechanisms of action give us grounds to believe theoretically that it increases the risk of EP and participates as an etiological factor.

Introduction

Ectopic pregnancy (EP) is likely to occur as an unwanted complication after unprotected intercourse in spite of levonorgestrel emergency contraception (LNG-EC). Its incidence has been increasing recently.

Case Presentation

Case report 1

This is the case of a 30-year-old patient with 1st day of last menstrual period May 27, 2020, of normal duration and amount, no delay in the menstrual cycle, with a positive pregnancy test. Because of an unprotected intercourse around the time of ovulation, she had taken postcoitally one dose of 1.5 mg LNG-EC.

Family history, concomitant diseases, and general surgical interventions – not reported. Gynecological interventions – two CS. Births – two; Abortion – one. The microbiological investigation of vaginal discharge was sterile.

At the first examination (June 18, 2020), the patient reported mild pain in the hypogastrium, predominantly on the right, as well as nausea. B-HCG levels were 2406 mIU/ml.

Transvaginal ultrasonography (TVS) findings: Uterine endometrium 15 mm and no intrauterine gestational or pseudogestational sac. Adnexae: On the right – echonegative rounded mass and sized 30 mm; on the left – suspected heterogeneous ultrasound mass not visualized and ovary normal in size. Pouch of douglas (POD) – no detection of free fluid.

On June 21, 2020, B-HCG levels were 3786 mIU/ml. No alteration was found in the ultrasound image from June 18, 2020. A decision was taken to keep the patient under observation because of the B-HCG levels bordering on the discriminatory ones and the lack of clinical evidence of peritoneal irritation.

On June 24, 2020 B-HCG value was 6374 mIU/ml. The patient reported mild pain in the hypogastrium, predominantly on the left. No clinical evidence of peritoneal irritation was observed.

TVS: Uterine endometrium 20 mm and no intrauterine gestational or pseudogestational sac. Adnexae: On the right – echonegative rounded

mass and sized 35 mm; on the left – Heterogeneous ultrasound mass of irregular shape and approximately 20 mm in size. POD – no detection of free fluid.

On June 25, 2020, the patient was admitted to *Selena* University Ob-Gyn Hospital for diagnostic laparoscopy on the basis of the following indications:

1. Lack of intrauterine pregnancy at B-HCG values exceeding the discriminatory ones.
2. Presence of adnexial mass on the left, clinically and echographically evaluated to be approximately 5 cm suspected of an EP, most likely in the left tube.
3. Clinical, ultrasound, and laboratory evidence showed that conservative treatment involving methotrexate was not appropriate; the patient also refused conservative treatment.

Gynecological status on admission: external genitalia of a nulliparous woman; vagina – non-erythematous walls; ectocervix – conical; external orifice of cervical canal – oval, without bleeding; retroverted uterus, mildly enlarged; adnexae on the right – rounded mass, mobile, and sized 3 cm; adnexae on the left – tender adnexial mass and 5 cm in diameter. POD – tender.

TVS – Uterine endometrium 20 mm and no intrauterine gestational or pseudogestational sac. Adnexae: on the right – echonegative rounded mass and sized 35 mm; on the left – heterogeneous ultrasound mass of irregular shape and 50 mm in size. POD – no detection of free fluid.

Excerpt from the operative report: Laparoscopy (June 25, 2020).

The intraoperative findings were as follows: Retroverted uterus, mildly enlarged, adhered extensively to the anterior abdominal wall, and the apex of the urinary bladder. Left adnexae: Ovary – normal in shape and size. Cortex visualized as intact. No detection of trophoblast masses and/or macroscopic alterations suspected of ovarian EP. Five cm dilation of the left fallopian tube at the isthmus/ampulla borderline, no presence of rupture, with invasion of trophoblast tissue in the tubal muscles of the isthmic segment. Right adnexae: Ovary – a follicle about 3 cm in size. Cortex visualized as intact. No detection of trophoblast masses and/or macroscopic alterations suspected of ovarian EP. Right fallopian tube – normal in structure and length, non-dilated, no detection of hematosalpinx, and/or peritubal hematocele. No rupture was revealed along all segments of the right fallopian tube. No detection of trophoblast masses. Left and right accessory fallopian tubes were not visualized. POD – No detection of rectouterine hematocele.

In the free abdominal cavity, no masses resembling trophoblast elements were visualized macroscopically, which could be associated with primary and/or secondary abdominal pregnancy. The urinary bladder was coalesced at the apex to the anterior uterine

wall. The infracolic omentum had adhered extensively to the anterior abdominal wall. The visceral and parietal peritoneum was smooth. The abdominal organs accessible for inspection were normal in structure, without macroscopic alterations associated with malignancy.

The exploratory laparoscopy suggested an unruptured tubal pregnancy localized in the isthmic-ampullary segment and invading into the tubal muscles. Adhesiolysis and left salpingectomy were performed.

Pathoanatomical examination of the left fallopian tube revealed hemorrhage, chorionic villi, and decidual changes indicative of tubal pregnancy.

The difficulty in visualization was likely to be due to the fact that the uterus was fixed to the anterior abdominal wall; the presence of an ultrasound mass on the right, which was detected at the first examination but did not grow further misled us to look for right tubal pregnancy. The final diagnosis was established right before the operation.

Case report 2

History: This is the case of a 28-year-old patient, admitted to *Selena* University Ob-Gyn Hospital on July 28, 2020 because of clinical and ultrasound evidence suspected of ectopic, most likely right tubal pregnancy. Positive pregnancy test; ultrasound finding – hemoperitoneum. The patient experienced severe pain in the hypogastrium, on the right. She reported nausea and vomiting. Blumberg's sign was negative.

The patient had taken one dose of 1.5 mg Levonorgestrel in the second phase of her menstrual cycle around the 24th day because of an unprotected intercourse. On admission, her B-hCG value was 1510 mIU/ml.

Family history – parents with arterial hypertension. Concomitant diseases, general surgical interventions, and gynecological interventions – not reported. Last regular menstruation – June 17, 2020. Normal birth – one. Abortions – not reported. The microbiological investigation of vaginal discharge was sterile.

Gynecological status: External genitalia of a parous woman; vagina – scarce brownish bleeding; ectocervix – cylindrical; external orifice of cervical canal – oval, closed, with scarce brownish bleeding; anteverted uterus, mildly enlarged; adnexae on the right – tender, enlarged because of an adnexial mass with irregular walls, approximately 5 cm in size; right ovary – normal in size; on the left – pathologic masses not palpated. POD – tender and bulging.

TVS findings: No presence of intrauterine gestational or pseudogestational sac. The right ovary was 30 mm in size, with a heterogeneous ultrasound mass of irregular contours, approximately 5 cm in size visualized around it. The left ovary was 32 mm. Free

fluid was detected in POD, approximately 200–250 ml in amount.

The following procedures were suggested on July 28, 2020: Laparoscopy. Right salpingectomy indicated on the basis of suspected right tubal EP; hemoperitoneum.

The findings on laparoscopy were as follows: Anteverted mobile uterus, mildly enlarged; the right ovary was normal in shape and size. No detection of trophoblast masses and/or macroscopic alterations suspected of ovarian ectopic pregnancy. The right fallopian tube was severely dilated by a hematosalpinx larger than 5 cm in diameter, with a rupture in the ampullary segment, around which trophoblast masses and peritubal hematocele were visualized. The left ovary was normal in shape and size. No trophoblast masses and/or macroscopic alterations suspected of ovarian EP were detected. The left fallopian tube was normal in structure and length, non-dilated, no hematosalpinx, and/or peritubal hematocele were found. No rupture was revealed along all segments of the left fallopian tube. Trophoblast masses were not detected. The left and right accessory fallopian tubes were not visualized. POD – presence of rectouterine hematocele 200 ml.

In the free abdominal cavity, no masses resembling trophoblast elements were visualized macroscopically, which could be associated with primary and/or secondary abdominal pregnancy. The abdominal organs accessible for inspection showed no macroscopic pathological alterations, or changes associated with malignancy. Following the exploratory laparoscopy, the hemoperitoneum consisting of blood and trophoblast elements was evacuated by means of an aspiration cannula. For the purposes of hemostasis, the bleeding source of the ruptured tube was visualized and coagulated, followed by right salpingectomy, since organ-conserving surgery was not possible. The histologic examination showed decidual changes and trophoblast elements.

Discussion

Levonorgestrel is a synthetic derivative of progestogen. Bastinelli recommends intake of 1.5 mg in one dose instead of two 0.75 mg doses [1].

Levonorgestrel impairs tubal peristalsis, which results in inversion of tubal motility. This leads to a delayed arrival of the conceptus in the endometrial cavity and implantation of the fertilized ovum in the tubes. The increased pharmacologic levels of progesterone are likely to relax tubal myoelectrical activity, reducing ciliary functions, and fimbrial beating, so that the conceptus does not reach the endometrial cavity, thus increasing the risk of tubal EP [2], [3], [4], [5], [6], [7], [8], [9], [10].

The exact mechanism of action of LNG as a postcoital contraceptive has not been fully clarified. It is believed that periovulatory LNG use inhibits follicular rupture or interferes with the formation and function of the corpus luteum, thus influencing ovulation as a result of gonadotropin suppression in the preovulatory period which has a negative effect on tubal motility and fertilization. LNG efficacy is higher in the follicular phase than in the luteal phase and before the 72nd h after an unprotected intercourse [2], [3], [11], [12], [13].

LNG-EC mechanism of action occurs predominantly during fertilization and not during blastocyst implantation [14].

LNG-EC transforms endometrial function by modifying integrin molecules and steroidal receptors, reducing blastocyst nidation capacity, and impairing implantation [2], [6], [11], [15], [16].

LNG-EC alters cervical mucus and consistency, which results in change in sperm fertilization capacity [17], [18].

Pelvic inflammatory disease (most frequently salpingitis, for example, caused by Chlamydia trachomatis, etc.), endometriosis or previous EP treated conservatively may cause tubal mucosal damage and dysfunction, and influence tubal motility, thus changing the efficacy of the hormonal method and may result in tubal EP [4], [5], [19], [20], [21], [22].

The previous tubal or uterine surgery (e.g., CS), adnexal or pelvic surgery, or the use of intrauterine contraceptive devices may also contribute to an increased risk of EP following LNG oral intake.

Various cases of EP following LNG-EC have been reported in specialized publications.

PanAfrican studies have found that the incidence of EP following LNG failure was 1.6%, which is about the same as the incidence in the general female population. Studies conducted in China have shown 5 and 4 times increased risk of developing EP in women who had used LNG, as compared to non-users [23]. In 2003, Trussell *et al.* published a clinical study on patients correctly using EC and reported a pregnancy rate of 5.2% [22]. There have been reports of increased risk (6.4%) of EP after oral LNG intake [24]. A study conducted in Kenya found that LNG-EC was associated with EP, the occurrence of the latter being more than nine times higher, as compared to other contraceptive methods [25]. Specialists may have come across numerous cases of EP following LNG-EC, which have not been reported.

Conclusion

The likelihood of EP occurrence following LNG administration is well known but controversial.

The number of reported cases is constantly increasing, but the cause-effect relationship between LNG and EP remains unclear, as well as the exact mechanism by which LNG impairs conception.

A series of epidemiological investigations are needed to establish EP after LNG use but up to this moment research has found that this risk has increased from 6.4 to 9.34%, which shows that the relationship between the LNG and EP is not only theoretical.

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