Early ovarian pregnancy diagnosed by ultrasound and successfully treated with multidose methotrexate. A case report

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Summary

A case report of a primary interstitial ovarian pregnancy is presented. A 37-year-old married woman with two children after two Cesarean sections and a spontaneous abortion, with a contraceptive intrauterine device (IUD) inserted three years before, presented at five weeks plus five days amenorrhea with a positive pregnancy test and lower abdominal pain but with no vaginal bleeding. Her previous menstrual cycles had been regular. She was hemodynamically stable. On bimanual examination, the uterus was of normal size, and there was an approximate four-cm tender right adnexal mass. Serum beta-human chorionic gonadotropin (b-hCG) was confirmed positive. Ultrasound revealed a well-positioned IUD in the uterus and a right adnexal mass with normal vascular flow on Doppler, that contained a well-defined gestational sac, well-distinct from the quiescent hemorrhagic corpus luteum. There was no fetal node or cardiac activity or free fluid. The patient received four injections of methotrexate intramuscularly using the multidose regimen that involves the administration of methotrexate calculated according to body weight, alternated with 0.1 mg/kg of leucovorin calcium per os after 30 hours until the values of β-hCG had decreased by 15%. The patient's post-treatment period was uneventful with a full restoration of ovarian morphology and the complete absorption of the gestational sac. This case is the first where diagnosis was made by endovaginal sonography and treatment was made by multidose methotrexate. Spiegelberg criteria for the diagnosis of ovarian pregnancy are obsolete; new ultrasound and laboratory criteria are needed for a diagnosis as early as possible without the need of surgery.

Key words: Ectopic pregnancy; Ovarian pregnancy; Pregnancy; Multidose methotrexate; MTX; Ultrasound.

Introduction

Ovarian pregnancy is a rare type of extrauterine pregnancy. Its incidence is about one in 7,000 to one in 60,000 pregnancies and accounts for about one to three percent of all extrauterine pregnancies. Recently there appears to have been an increase in ovarian pregnancy due to the improvement in diagnosis ability. Sonography and beta-human chorionic gonadotropin (b-hCG) have made it easier for the early preoperative diagnosis of ectopic pregnancy. In primary ovarian pregnancy the ovum is not guided into the tube but is fertilized in the peritoneal cavity and then implants onto the ovary. It causes the same symptoms as a tubal pregnancy and severe internal bleeding will eventually occur. Primary ovarian pregnancy is a rare entity; the reported incidence being one in 25,000 pregnancies, 0.5 - 3% of extrauterine pregnancies. The diagnosis is difficult and a continuous challenge to the gynecologist [1].

In the secondary type, there is a tubal abortion with secondary implantation of the embryo on the tubal surface. Ovarian pregnancy is probably an accidental event that occurs in fertile women in contrast to tubal pregnancy, which is more frequently associated with impaired fertility.

Early diagnosis of an ovarian pregnancy is perhaps the most difficult compared to all the other types of extrauterine gestations. The signs and symptoms of a ruptured ovarian pregnancy are similar to those of disturbed tubal pregnancy. Although an adnexal mass is palpable in many cases of ovarian pregnancy, the mass is frequently confused for a hemorrhagic corpus luteum cyst or ruptured tubal pregnancy [2]. With a few exceptions, the initial diagnosis is made on the operating table and the final diagnosis only with histopathology on the basis of the four Spiegelberg criteria described in 1878 [3]: the tube must be entirely normal, the gestational sac must be anatomically sited in the ovary, the ovary and the gestational sac must be connected to the uterus by the uteroovarian ligament, and placental tissue must be mixed with the ovarian cortex.

Until today, histology alone can confirm the diagnosis and distinguish the four forms: intrafollicular, juxtafollicular, juxtacortical, and interstitial pregnancy [4]. New ultrasound and laboratory criteria are needed for a diagnosis as early as possible without the need of surgery.

The present report concerns a primary interstitial ovarian pregnancy with an omolateral corpus luteum.

Case Report

A 37-year-old married woman with two children after two Cesarean sections and a spontaneous abortion, with a contraceptive intrauterine device (IUD) inserted three years before, presented at five weeks plus five days amenorrhea with a positive pregnancy test and lower abdominal pain but with no vaginal bleeding. Her previous menstrual cycles had been regular. She was hemodynamically stable and her hemoglobin was 11.8 g/dl.

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Fig. 1

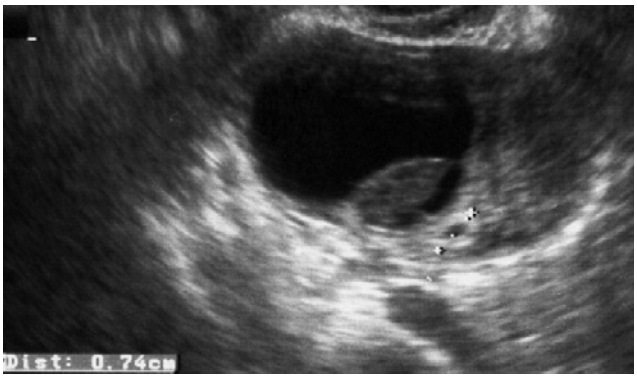

Fig. 2

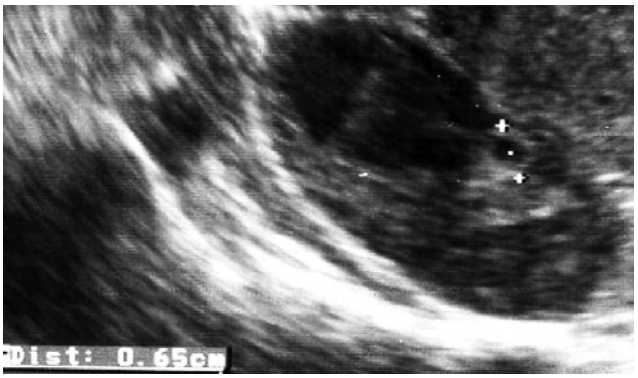

Fig. 3

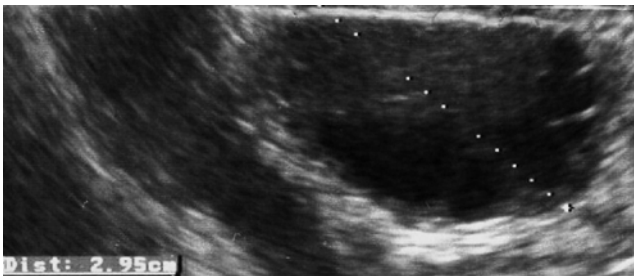

Figure 1. — Right ovary with a well-defined gestational sac of 0.74 cm, well-distinct from the quiescent hemorrhagic corpus luteum, with a more prominent echogenic ring surrounding an echolucent center.
Figure 2. — Gestational sac of 0.65 cm and a corpus luteum partially reabsorbed after the third dose of methotrexate.
Figure 3. — Full restoration of ovarian morphology and the complete absorption of the gestational sac after four cycles of methotrexate.

On bimanual examination, the uterus was of normal size, and there was an approximate four cm tender right adnexal mass. Serum b-hCG was 1,866 mIU/ml (reference value is < 5 mIU/ml). Ultrasound revealed a well-positioned IUD in the uterus with an atrophic endometrium and a right adnexal mass with normal vascular flow on Doppler, that contained a well-defined gestational sac of 0.74 cm, well-distinct from the quiescent hemorrhagic corpus luteum, with a more prominent echogenic ring surrounding an echolucent center (Figure 1). There was no fetal node or cardiac activity or free fluid. The gestational sac in the right adnexum was identified and confirmed by three observers.

This patient had nearly all the features that suggest successful medical management; ie, low b-hCG level, endometrial thickness < 12 mm, no cardiac activity, and no yolk sac. Her progesterone levels were not measured. Although her serum folic acid levels were also not estimated, she was not taking peri-conceptional folic acid supplementation.

The patient received an injection of methotrexate intramuscularly the next day (60 mg, ie, 1 mg/kg), using the multidose regimen that involves the administration of methotrexate calculated on body weight, alternated with 0.1 mg/kg of leucovorin calcium per os after 30 hours until the values of b-hCG had decreased by 15% (maximum four cycles of administration). The serum b-hCG measurement was repeated on day three, as per standard protocol, (amenorrhea six weeks plus one day). The result, available the same day, indicated b-hCG was 4,162.8 mIU/ml, but repeated ultrasound scanning showed the same findings without hemoperitoneum. She showed no clinical and laboratory signs of toxicity, so a second dose of methotrexate was administered. The serum b-hCG measurement was repeated on day five (amenorrhea six weeks plus three days), the result was 5,201.8 mIU/ml, the vaginal ultrasound did not show a worsening of the clinical status and low-abdominal symptoms of the patient appeared in remission, despite the rising titers of b-hCG, it was decided to proceed with the third dose of the drug. On day seven serum b-hCG values had decreased to 3,584.6 mIU/ml and the ultrasound showed a smaller gestational sac of 0.65 cm and a corpus luteum partially reabsorbed (Figure 2). Despite the decline in values by over 15%, it was decided to proceed to the fourth administration and complete all four treatment cycles to reinforce the therapeutic response. After two days the patient experienced a massive metrorragia and the IUD was removed ambulatorially. The patient's post-treatment period was uneventful, she did not exhibit any side-effects to methotrexate, which has also been shown to predict treatment failure. After a week, the b-hCG values were 500 mIU/ml, and after another two weeks they were completely negative (1.28 mIU/ml), with a full restoration of ovarian morphology and the complete absorption of the gestational sac (Figure 3). The patient has been recommended to monitor monthly b-hCG values for at least six months.

Discussion

Environmental conditions favouring tubal ectopic gestation, such as pelvic inflammatory disease, previous surgery, and history of infertility are very rare in ovarian pregnancies [5, 6]. Recurrence is also exceptional and as the fertility of these women is conserved, the next pregnancy is usually intrauterine. However, a few risk factors seem to be present for ovarian pregnancies: endometriosis and IUD usage are reported to contribute in the majority of cases. If the patients have an IUD and a positive pregnancy test, an ectopic ovarian pregnancy must be suspected [7].

The literature shows a strong association between multiparity and IUD usage in cases of ovarian gestations [8]. An IUD is effective in preventing intrauterine and tubal pregnancies in 99.5% and 95%, respectively. However it has little effect on the prevention of an ovarian pregnancy [9].

The rate of IUD use in reported ovarian pregnancies is 17% to 25% [10].

Raziel *et al*. reported that 90% of ovarian pregnancies occured in IUD users [11].

Several theories have been suggested to explain ovarian implantation, such as reflux of the conceptus following a normal fertilization from the Fallopian tube along with blood from the uterus [10] or fertilization occurs within the follicule following defective ovum release at ovulation [12]. Since ovarian pregnancy may result from in vivo fertilization (IVF) of unrecovered oocytes, patients should be informed to avoid intercourse near the time of ovulation [13].

The incidence of ectopic pregnancy per se is on the rise owing to evolution in assisted reproductive techniques (ART). Ovarian pregnancy accounts for 0.5% - 3% of all ectopic pregnancies [11] and the incidence after IVF has been reported to be 0.3% [14].

The diagnosis of an ovarian ectopic pregnancy is seldom made before surgery. The recent advances in b-hCG determination and transvaginal ultrasound have aided the diagnosis. Ultrasound, especially transvaginal scanning has proven to be an invaluable tool in the diagnosis of this condition. Even then, it can be mistaken for a hemorrhagic corpus luteum or ovarian cyst. The presence of a hemorrhagic lesion on the ovaries should arouse the suspicion of the surgeon of an ovarian ectopic pregnancy. If a concomitant corpus luteum is seen as in this case, then the diagnosis becomes easier.

As for other ectopic locations, the combination of symptoms, such as abdominal pain with or without vaginal bleeding, with a history of antecedent amenorrhoea, raised b-hCG levels, and an ultrasonographically empty uterus, should trigger an investigation for ectopic pregnancy. The diagnosis is usually suggested after ultrasound. A more echogenic wide ring on the ovary, compared with the ovarian tissue, with a yolk sac or fetal parts are key ultrasonographic indicators for ovarian pregnancy [5, 15, 16]; however, an embryo is relatively infrequently seen within the cyst.

Both sonographically and at the time of surgery, the clinical challenge is to distinguish an ovarian ectopic pregnancy from a corpus luteum or hemorrhagic cyst [1, 17, 18], because a cystic adnexal mass with a positive pregnancy test without clear intrauterine gestation could also indicate a corpus luteum in an early or failing intrauterine or tubal pregnancy. Decreased wall echogenicity compared with the endometrium and an anechoic texture suggest a corpus luteum [17]. Color or spectral Doppler sonography do not seem to fulfill additional diagnostic expectations, yet *Atriv* [19] found that a resistive index of < 0.39 had a specificity of 100% and a positive predictive value of 100% for diagnosing ectopic pregnancy, but was present in only 15% (confidence interval 7% - 23%) of ectopic pregnancies. He concluded that both low- and high-resistive indices discriminate ectopic pregnancy from a corpus luteum cyst.

Hallat [20], in his study of 25 cases of ovarian pregnancies, reported that the most significant finding was the inability to distinguish an ovarian pregnancy from a hemorrhagic ovary or ruptured corpus luteum. A correct surgical diagnosis was only made in 28% of the cases. In the remaining cases the pathologist made the diagnosis [21].

Ruptured ectopic pregnancy with circulatory collapse [22] or wrong diagnosis of malignant ovarian tumours producing b-hCG [23] may also decrease the accuracy of diagnosis.

Early preoperative diagnosis based on vaginal ultrasonographic findings has resulted in conservative treatment in singleton ovarian cases [24].

There are two possible therapeutic approaches to ovarian pregnancy: surgical (partial or total ovariectomy) and pharmacological (methotrexate, etoposide, and prostaglandins).

Conservative treatment in the ovarian pregnancy, as in tubal pregnancy, is of the utmost importance if the patient is young and desires to bear children. Methotrexate is an effective therapeutic option in the management of unruptured ovarian ectopic pregnancy. It permits to avoid more invasive interventional surgery, with possible complications such as hemorrhage, ovariectomy, or later pelvic adhesions [25].

For selected ovarian pregnancies, an alternative therapy using methotrexate or prostaglandin may possibly minimize adhesion formation and optimize future fertility. The first successful case of treatment of unruptured ovarian pregnancy by prostaglandin was reported in 1990 by Koike *et al*. [26]. It is followed by the first successful case of treatment of unruptured ovarian pregnancy by methotrexate by Shamma and Schwarts in 1992 [27]. Mittal *et al*. [25] reported the third case of successful treatment of an ovarian pregnancy with methotrexate. Similiarly Chelmow *et al*. treated an ovarian pregnancy diagnosed by laparoscopy with methotrexate [28].

Medical treatment options are reported with etoposide [29] and methotrexate if b-hCG levels are still raised after surgery, indicating persistent trophoblastic tissue [30]. Some authors treated ectopic pregnancies by sonographically-guided injection of methotrexate or potassium chloride into the ectopic gestational sac or fetus and thus see the advantage of the continuation of a concomitant intrauterine pregnancy, and preservation of the uterus for subsequent pregnancies [31-33] by avoiding surgical intervention.

Conclusion

This case report is the first to demonstrate the usefulness of a multidose methotrexate protocol in the treatment of ovarian pregnancy. It is extremely important to select patient candidates according to a pharmacological approach and make a diagnosis as early as possible to improve the therapeutic success and preserve future fertility. Spiegelberg criteria are obsolete; new ultrasound and laboratory criteria are needed for a diagnosis without the need of surgery.

Do not be discouraged if you get an initial increase in the values of the b-hCG during the first cycles of treatment; it must be remembered that the possible number of treatment cycles with methotrexate is four.

Following monthly b-hCG concentrations for six months is important since remaining pregnancy cells may be able to grow post-treatment.

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