

# IS OVARIAN PREGNANCY A MEDICAL ILLNESS?

## METHOTREXATE TREATMENT FAILURE AND RESCUE BY LAPAROSCOPIC REMOVAL

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Primary ovarian pregnancy is a rare form of ectopic pregnancy. Preoperative diagnosis is extremely uncommon, and our knowledge of the use of methotrexate (MTX) therapy in such cases is, therefore, limited to sporadic case reports. MTX therapy has recently achieved good results in the treatment of ectopic pregnancies when the following criteria were met: (1) hemodynamic stability, (2) no severe or persistent abdominal pain, (3) commitment to follow-up until the ectopic pregnancy resolved, and (4) normal baseline liver and renal function tests, as well as an absence of contraindications to MTX treatment [1]. The Practice Committee of the American Society for Reproductive Medicine recommended that ovarian pregnancy should be definitively diagnosed by surgical exploration, and MTX is, therefore, not a first-line treatment for this condition [1]. However, it is extremely difficult to make an accurate preoperative diagnosis of ovarian pregnancy; thus, medical treatment with systemic MTX injection, or expectant observation using high-resolution transvaginal ultrasound (TVS) and serial serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) monitoring is often suggested in patients with an ectopic pregnancy at an unknown site, who meet the above-mentioned criteria. We report a case of suspected ovarian pregnancy diagnosed by TVS, which met all the criteria, but failed multiple-dose systemic MTX therapy. This suggests that systemic MTX treatment might not be appropriate for the management of ovarian pregnancies.

A woman aged 22 years visited our emergency department because of lower abdominal pain and



**Figure 1.** A small sac-like shadow, 0.8 cm in size, over the right ovary near the posterior surface of the cortex, with some fluid nearby.

abnormal spotting. She had a 2-year history of primary infertility. Her last menstruation had been around 5 weeks earlier, and a pregnancy test was positive. TVS examination revealed an empty uterus and some fluid accumulation in the cul-de-sac. Her initial serum  $\beta$ -hCG level was 944 mIU/mL. She had stable vital signs and symptom relief, and was, therefore, discharged for subsequent observation on day 1, despite the possibility of an ectopic pregnancy.

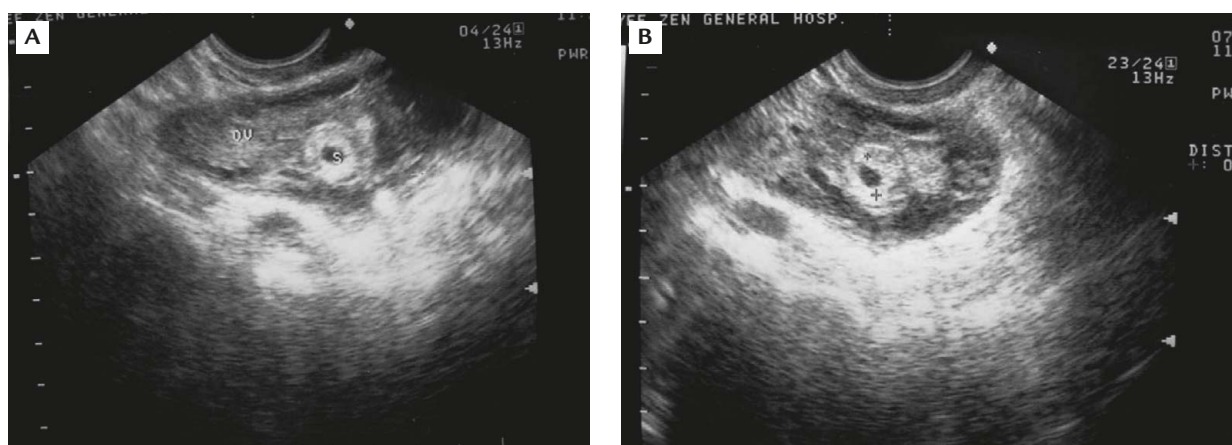
Two days after the initial diagnosis of a possible ectopic pregnancy (day 3), her  $\beta$ -hCG level was 1,755 mIU/mL and TVS showed an empty uterine cavity with suspected right adnexal sac-like tissue and a nearby ovarian shadow (Figure 1). The patient refused invasive management and was, therefore, advised to receive an alternative therapy, such as single- or multi-dose MTX treatment. A multidose MTX regimen (MTX with leucovorin rescue) was initiated. The first dose of MTX 50 mg/m<sup>2</sup> intramuscular injection was given on day 3. On day 4, her  $\beta$ -hCG was 2,238 mIU/mL and the right ovarian sac-like shadow was enlarged. A second



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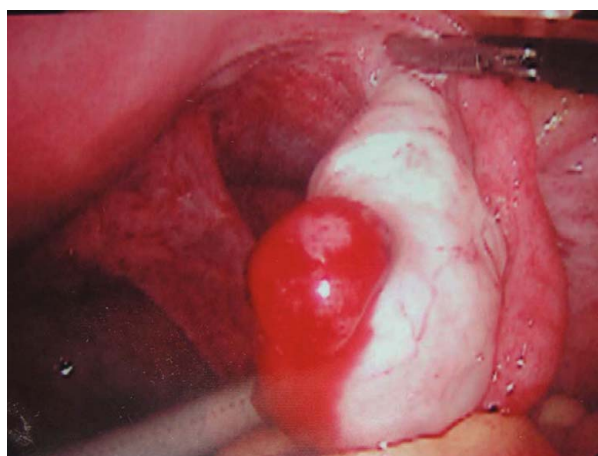
**Figure 2.** (A) The sac became larger with a halo sign and an echogenic shadow over the 2 o'clock position of the sac. (B) From another angle, the echogenic shadow connecting to the sac showing the appearance of a corpus luteum.

MTX 50 mg/m<sup>2</sup> injection was administered on day 5. On day 6, her  $\beta$ -hCG level had fallen to 1,921 mIU/mL. A third MTX 50 mg/m<sup>2</sup> injection was prescribed on day 7. On day 8, the patient complained of increased vaginal bleeding and progressive abdominal pain, and her  $\beta$ -hCG level was 1,993 mIU/mL. TVS showed an increased mass and the presence of a halo sign with a sac-like shadow on the ovarian contour (Figure 2). Fluid accumulation in the cul-de-sac was not significantly different from that seen on day 1. Laparoscopy was advised, but the patient still refused to receive any surgical intervention. A final dose of MTX 50 mg/m<sup>2</sup> was, therefore, prescribed on day 9.

Acute onset of abdominal pain occurred on day 10. The patient's hemoglobin level dropped to 10.0 g/dL. An urgent laparoscopy was arranged, and it revealed a hemoperitoneum of almost 800 mL and a 1.5-cm swelling nodular lesion with active bleeding at the edge of the right ovary (Figure 3). Laparoscopic wedge resection was performed uneventfully and she was discharged the following day. The final pathology confirmed the diagnosis of ovarian pregnancy. Menstruation resumed 29 days after surgery.

Ectopic pregnancy is one of the main causes of pregnancy-related morbidity and mortality. Early diagnosis and treatment are vitally important for the handling of such cases. However, preoperative diagnosis remains challenging [2], especially in rare cases of ovarian pregnancy, which are almost always diagnosed after surgery [3].

Establishment of a diagnosis of primary ovarian pregnancy is strict and complicated. As with Spiegelberg's description in 1878, four criteria should be fulfilled, including: (1) the fallopian tubes are normal, (2) the gestational sac is anatomically sited in the ovary, (3) the ovary is connected to the uterus by the utero-ovarian ligament, and (4) the placental tissue is mixed with



**Figure 3.** Laparoscopy demonstrating the bleeding sac protruding from the right ovary.

ovarian cortex [4]. With the aid of careful TVS examination, the preoperative diagnosis of ovarian pregnancy in this case could be achieved at about 5–6 weeks of gestation (Figures 1 and 2). The embryo was just beside the corpus luteum and beneath the ovarian cortex (Figure 2B). This juxtafollicular and juxtacortical position would contribute to an early occurrence of hemoperitoneum at an early gestational age.

An increase in the early diagnosis of ectopic pregnancy has been paralleled by increased conservative medical treatment with MTX, especially in cases that fulfill the following criteria: an ectopic mass of <35 mm; absence of a yolk sac; embryo or fetal heart beat; and a  $\beta$ -hCG level <3,000–5,000 mIU [5–7]. Medical treatment in our case was reasonable but, nonetheless, failed. In a review of systemic MTX treatment for ovarian pregnancy (Table) [8–11], there were three successfully treated cases, but all of these received laparoscopic procedures before systemic MTX treatment. None were successfully treated with systemic MTX alone, even though all were suitable candidates

**Table.** Case reports of ovarian pregnancy treated by methotrexate therapy

Author (year of publication)	Preoperative diagnosis	Diagnosis tool	Biopsy	Medical treatment	Outcome	$\beta$ -hCG (mIU/mL)	Mass size (mm)
Shamma et al [2] (1992)	No	Laparoscopy	No (?)	MTX, IM	Success	5,000	20
Chelmow et al [9] (1994)	No	Laparoscopy	Yes	MTX, IM	Success	29	10
Habbu and Read [10] (2006)	No	Laparoscopy	Yes	MTX, IM	Success	10,000	24
Bagga et al [11] (2006)	Yes by TVS	Ultrasound	Yes	MTX, IM	Failure	400	8
Present case (2008)	Yes by TVS	Ultrasound	Yes	MTX, IM	Failure	1,755	8

$\beta$ -hCG =  $\beta$ -human chorionic gonadotropin; MTX = methotrexate 50 mg/m<sup>2</sup>; IM = intramuscular injection; TVS = transvaginal ultrasound.

for medical treatment. Based on these observations, it seems likely that successful outcomes in patients with ovarian pregnancies receiving MTX were attributable to the laparoscopy, rather than the MTX. The ectopic pregnancy could have been removed or destroyed during the laparoscopic procedures.

The value of direct injection of MTX, however, is less clear. Based on promising experiences in managing other similar diseases [12–15], a direct injection of MTX or other drugs, such as etoposide, directly over the ectopic pregnancy site under ultrasound or laparoscopic guidance might be a possible treatment option.

We agree with the opinion of the Practice Committee of the American Society for Reproductive Medicine, who has decided that MTX is not a suitable first-line treatment for ovarian pregnancy [1]. High-resolution TVS and sensitive serum  $\beta$ -hCG evaluation, together with a high index of suspicion, make early diagnosis of ovarian pregnancy feasible, so avoiding the use of a relatively ineffective treatment strategy such as systemic MTX treatment [16].

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