

PRIMARY OVARIAN PREGNANCY

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Ectopic pregnancy, where the gestational sac is located outside the uterus, is the most common life-threatening emergency in early pregnancy [1]. Although recent reports have shown a continuous increase in its incidence, mortality from ectopic pregnancy declined by almost 90% from 1979 to 1992 [2]. This reduction was primarily the result of earlier diagnosis, i.e. before the occurrence of hemoperitoneum and/or more severe conditions such as hypovolemic shock. Earlier diagnosis is made possible by the availability of sensitive and specific radioimmunoassays for human chorionic gonadotropin (hCG), serum progesterone screening, high-resolution transvaginal ultrasonography (TVS), and most importantly, laparoscopy. The most common extrauterine site for embryo implantation is the fallopian tube, but the conceptus may implant in the ovaries, cervix, abdomen, or at interstitial or cornual sites. The latter are considered to be unusual ectopic pregnancies [3] and often result in a more complicated clinical course, including difficulty in making an early and accurate diagnosis, an inconsistent therapeutic approach, and an unpredictable outcome, leading to a risky, life-threatening status.

In this issue, Su et al [4] reports on a rare case of a primary ectopic pregnancy that took place in the ovary (primary ovarian pregnancy) in a woman aged 22 years, who subsequently received treatment with methotrexate (MTX). This patient's condition fulfilled the following strict criteria: (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, and no contraindications to MTX treatment [3]. Although fixed, multiple-dose MTX was given, the patient failed to respond to treatment and eventually underwent laparoscopic surgery to allow for an accurate diagnosis of the primary ovarian pregnancy, which was followed by

wedge resection of the ectopic pregnancy. The authors claimed that MTX was not suitable for first-line treatment of ovarian pregnancy, and that an accurate pre-operative diagnosis of primary ovarian pregnancy might help in the decision-making process. Early surgery and avoidance of other useless and possibly harmful therapeutic strategies, such as conservative observation or medical treatment by systemic MTX injections, could thus be avoided [4].

We fully understand the key points emphasized by the authors, but many controversial issues require further attention. First, why did the authors select multiple-dose MTX treatment in place of single-dose MTX treatment to manage the ectopic pregnancy, which was originally thought to be an uncomplicated case? A recent report based on a systematic review and meta-analysis found that single-dose MTX might be more acceptable for the management of tubal ectopic pregnancies, since there was no significant difference in the treatment success rates between single-dose and multiple-dose MTX [5]. Two trials involving 159 women compared single-dose and the fixed multiple-dose MTX regimens [6,7] and showed no significant difference in treatment success (relative risk, 0.99; 95% confidence interval, 0.89–1.10) [5]. Mean serum hCG concentrations varied between 2,230–2,973 and 2,180–2,244 IU/L, respectively [5]. In addition, another report highlighted the potential for tubal damage associated with multiple-dose MTX therapy [8], since free passage through the ipsilateral tube (examined by hysterosalpingography) was observed in 17 of 30 cases (56.7%) after multiple-dose treatment, compared with 26 of 31 cases (83.9%) after single-dose MTX therapy. The patency of the contralateral tube was higher after single-dose than multiple-dose MTX treatment. Although the main cause of tubal damage is still under debate, and the definitive mechanism of tubal obstruction induced by multiple-dose MTX has yet to be clarified, a possible mechanism was proposed [8]: in terms of the trophoblastic repair and damage cycle found at tubal ectopic pregnancy sites [9], a single dose of MTX may disrupt cell division in highly mitotic placental cells, and then initiate the repair process, whilst



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repeated doses over time, as in multiple-dose regimens, could have a negative impact on both the placental bed and the initial repair process in the tubal epithelium [8]. The risks and benefits should be carefully weighed when deciding whether to use single- or multiple-dose MTX for the management of an ectopic pregnancy.

Second, we presume that the authors initially considered this to be a case of tubal pregnancy, and they, therefore, treated the patient as a low-risk tubal pregnancy and thus suitable for medical (rather than surgical) treatment [4]. Unfortunately, multiple-dose MTX treatment did not achieve the intended results, therefore raising the concept, mentioned by the authors, that primary ovarian pregnancy is not a medical illness. We do not completely agree with this concept. From the scientific point of view, this case would have been better considered as a pregnancy of unknown location (PUL). A PUL occurs when there is a positive pregnancy test with no signs of intra- or extrauterine pregnancy on TVS. In addition, the woman should have no signs of intra-abdominal bleeding or evidence of hemoperitoneum on an ultrasound scan [10]. A recent issue of the journal *Ultrasound Obstetrics and Gynecology* (2006) published a consensus statement on PUL [10]; the important conclusions included: (1) using modern imaging tools (TVS), the incidence of PUL is less than 15%; (2) clinically stable women with a PUL should initially be managed expectantly; (3) the initial serum hCG level is not predictive of PUL outcome, but mathematical models based on the hCG ratio have been developed to predict PUL outcome; (4) in most cases, uterine curettage should not play a role in the classification of PULs; and (5) although a single-visit approach to the management of PULs is not appropriate, visits at too frequent intervals might also be inappropriate [10]. The number and interval of visits for the optimal clinical management of women with PULs is still unknown.

In conclusion, we would like to use the consensus statement from The Practice Committee of the American Society for Reproductive Medicine as our final opinion on the medical treatment of women with primary ovarian pregnancies [6]; that is, a primary ovarian pregnancy can only be diagnosed definitively at the time of surgical exploration, including laparoscopy, and MTX is, therefore, not a suitable first-line treatment for this condition. Laparoscopy is considered to be the gold standard for the diagnosis of ectopic pregnancies and seems to be superior to other diagnostic and therapeutic methods, because it is minimally invasive, cost-effective, useful in treatment, and only takes a short time [11–13]. However, it is necessary to bear in mind that there is no consensus on appropriate intervention rates in women with PUL because of the difficulty in

accurately distinguishing between primary ovarian pregnancy and PUL. A clinical audit should be regularly carried out to determine the rate of emergency surgery carried out because of undetected ectopic pregnancies, and the rate of unnecessary interventions, such as negative laparoscopic examinations [10].

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