

## **Editorial**

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# **Recent Advances in the Management of Ectopic Pregnancy**

Ectopic pregnancy is a potentially life-threatening condition. While surgical approaches are the mainstay of treatment, recent reports affirm that ectopic pregnancy has become a medical rather than a surgical disease. Advances in early diagnosis facilitated the introduction of medical therapy with methotrexate (MTX) in the mid 1980s<sup>1</sup>. MTX is a folic acid antagonist. Folic acid normally is reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR), a step in the synthesis of DNA and RNA precursors. MTX inhibits DHFR, causing depletion of cofactors required for DNA and RNA synthesis. As a consequence treatment with (MTX) is highly toxic to rapidly replicating tissues and achieves results comparable to surgery for the treatment of appropriately selected ectopic pregnancies. The dosage of 1 mg/kg locally was determined by a previously reported pharmacokinetic study<sup>2</sup>. With evolving experience with methotrexate, the treatment of selected ectopic pregnancies has been revolutionized. In one report, approximately 35 percent of women with ectopic pregnancy are eligible for medical treatment<sup>2</sup>. Due to the routine use of early ultrasound among infertile patients who conceive, diagnosis of ectopic pregnancy can be established early and medical treatment can be administered in most cases. The overall success rate of medical treatment in properly selected women is nearly 90 percent<sup>3-5</sup>.

Early diagnosis is the key to effective non surgical treatment. The use of serial human chorionic gonadotrophin (hCG) levels and transvaginal ultrasonography (TVU) facilitate the early diagnosis of ectopic pregnancy<sup>6</sup>. A gestational sac should become visible by TVU between 5.5 and 6.0 weeks gestational age<sup>7</sup>. When gestational age is not known, hCG levels can provide alternate criteria for timing and interpretation of TVU. It now is widely accepted that when the HCG level is above the discriminatory zone of 1,500 IU/L a normal intrauterine pregnancy (IUP) should be visible by TVU. The absence of an intrauterine gestational sac when the hCG concentration is above the discriminatory zone implies

an abnormal Gestation. The specific cutoff value for hCG used will, of course, depend on clinical expertise with TVU and the specific characteristics of the hCG assay used. A more conservative discriminatory zone, that is, higher hCG level, may be used to minimize the risk of treating a viable pregnancy with MTX. In the case of a multiple pregnancy, hCG levels are higher at an early stage of development than in singleton intrauterine gestations, but the rate of increase remains similar.

If the initial hCG level is below the discriminatory zone, and TVU cannot identify definitively an intrauterine (IUP) or extrauterine gestation, then serial hCG measurements are needed to document either a growing, potentially viable pregnancy or a nonviable pregnancy. When the hCG levels have risen above the discriminatory zone, TVU should be used to document the presence, or absence, of an IUP. Declining hCG values suggest a failing pregnancy. However, a decline in hCG concentrations does not exclude entirely the possibility of a resolving ectopic pregnancy or its rupture and therefore hCG levels must be followed down until hCG <5 IU/L<sup>8</sup>.

The absence of a gestational sac with an hCG above the discriminatory zone, or an abnormally rising or declining hCG level, suggests an abnormal pregnancy but does not distinguish an ectopic pregnancy from a failed intrauterine gestation. The presumption of an ectopic pregnancy in such circumstances can be incorrect in up to 50% of cases. A uterine curettage and evaluation of uterine contents may be helpful to differentiate an abnormal IUP from an ectopic pregnancy. Alternatively, if hCG levels continue to rise after curettage, the diagnosis of ectopic pregnancy is established.

Effort should be made to diagnose ectopic pregnancy definitively before medical treatment with MTX. Candidates for successful expectant management should be asymptomatic and have no evidence of rupture or hemodynamic instability<sup>9</sup>. Furthermore, they should demonstrate objective evidence of resolution, such as declining beta-human chorionic

gonadotropin ( $\beta$ -HCG) levels. They must also be fully compliant and be willing to accept the potential risks of tubal rupture

Medical treatment for a suspected ectopic pregnancy without a definitive diagnosis does not reduce complication rates or cost because many women with undiagnosed miscarriage would otherwise be exposed to MTX and its side effects unnecessarily. Potential consequences of medical management of a presumed ectopic pregnancy include [1] subsequent pregnancies will be viewed as high risk for recurrent ectopic pregnancy resulting in repeated, costly, and anxiety-provoking diagnostic evaluations; [2] apparent efficacy of MTX to treat ectopic pregnancy will be artificially increased; and [3] an IUP may be exposed to a known teratogen and abortifacient. Exposure of a viable pregnancy to MTX may result in embryopathy, a very serious and avoidable complication that is unfortunately being reported with increasing frequency<sup>10</sup>.

Absolute contraindications to MTX treatment include: intrauterine pregnancy, immunodeficiency, known sensitivity to MTX, active pulmonary disease, active peptic ulcer disease, clinically significant hepatic dysfunction, clinically significant renal dysfunction and nursing. Relative contraindications include: fetal cardiac activity, high hCG (> 10,000-15,000), TVU evidence of an ectopic >4cm, refusal on the part of the patient to accept blood transfusion and anticipation of poor patient compliance with the necessary treatment protocol and follow-up.

Prior to the first dose of MTX, women should be screened with a complete blood count, liver function tests, serum creatinine and blood type and Rh typing<sup>11</sup>. Women having a history of pulmonary disease also should have a chest x-ray because of the risk of interstitial pneumonitis in patients with underlying lung disease. In addition the patient should discontinue any folic acid supplement that she is taking.

Medical therapy of ectopic pregnancy is appealing over surgical options for a number of reasons, including eliminating morbidity from surgery and general anesthesia, potentially less tubal damage, and less cost and need for hospitalization<sup>12</sup>.

Measures of current trends in the management of ectopic pregnancy in the United States from 2002 to 2007 indicated that the percentage of patients treated

with methotrexate increased from 11.1% to 35.1%, whereas surgical management decreased from approximately 90% to 65%<sup>13</sup>. In this study, the authors reported that more than 60% of surgical cases were done laparoscopically and that about 5% of surgical cases required medical therapy. In the medical treatment group, 15% of cases were categorized as failures and required surgery<sup>12</sup>. Use of transvaginal ultrasonography and quantitative measurement of the beta subunit of human chorionic gonadotropin ( $\beta$ -hCG) has led to a reduction in the need for diagnostic laparoscopy<sup>13,14</sup>.

Approximately one fourth of women presenting with ectopic pregnancies have declining  $\beta$ -HCG levels, and 70% of this group experience successful outcomes with close observation, as long as the gestation is 4cm or less in its greatest dimension. An initial low  $\beta$ -HCG titer also correlates with successful spontaneous resolution. Although data are limited on this matter, initial  $\beta$ -HCG titers below 1000 mIU/mL have been demonstrated to predict a successful outcome in 88% of cases managed expectantly<sup>11</sup> making close follow-up and patient compliance of paramount importance. It has, in fact, become the gold standard of treatment in properly selected cases.

**Prof. Nazneen Kabir**

ICMH, Dhaka

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