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Ectopic or Not?

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The Case

The patient is a 24-year-old woman, gravida 4, para 1, ectopic 1, at 6 weeks from her last menstrual period. She presents to the emergency department with a 3-day history of vaginal spotting and dull left lower quadrant pain. Her history is remarkable for pelvic inflammatory disease at the age of 22 followed by an ectopic pregnancy requiring right salpingostomy one year later. She is sexually active with one male partner and uses condoms inconsistently.

Examination shows normal vital signs, a benign abdominal exam, and a pelvic exam showing scant blood in the vagina, a closed os, a slightly enlarged uterus, and a minimally enlarged and mildly tender left adnexa. Rectal examination confirms these findings. Her hematocrit is 36%, hCG 12,206 mIU/ml, and her blood type is A positive. An ultrasound showed a thickened endometrial stripe but no fluid collection or gestational sac, and a 2-cm left adnexal cystic structure distinct from the left ovary with no fetal pole identified.

With the diagnosis of repeat ectopic pregnancy, the patient was given methotrexate 50 mg/m^2 IM and discharged home with precautions to return for increased pain, bleeding, or signs of hypovolemia. She returned 4 days later to the emergency department for worsening pain. Her follow-up hCG was 13,000 mIU/ml. The on-call gynecology team reviewed her work-up and decided to perform a uterine aspiration, which yielded copious tissue but no apparent villi. The patient was then offered surgical management of her ectopic pregnancy. Laparoscopy revealed a 3 x 4 cm left ampullary ectopic and 300 cc hemoperitoneum. The contralateral tube appeared normal and a left salpingectomy was performed. The patient was discharged home the next day and her hCG showed an appropriate decline.

The Commentary

This case raises several important issues. First, was the method used to diagnose an ectopic pregnancy adequate? This patient had an initial hCG of 12,206 mIU/ml with an ultrasound showing no intrauterine sac but instead demonstrating a 2-cm left adnexal cystic structure. In general, an hCG level of 2000 mIU/ml is considered the discriminatory zone at which a normal intrauterine pregnancy should be seen with

transvaginal ultrasound (TVUS). Most authorities would consider the absence of an IUP at this level to be highly suggestive of an ectopic pregnancy, as occurred in this case. Under these circumstances, it is not necessary to visualize an extra-uterine pregnancy to confirm the diagnosis. In fact, with current technology, ectopic pregnancy can be reliably diagnosed prior to the development of a visible mass. Accordingly, algorithms have been developed that rely on laboratory values, and in certain instances, D&C specimens, for the diagnosis of an ectopic pregnancy.(1) In our center, D&C is recommended only for patients with abnormally slowly rising (less than 50% in 48 hours) hCG levels that are below the ultrasound discriminatory zone. Local practices vary, and in some settings, D&C would also be offered to patients without a visible intrauterine pregnancy whose hCG levels are at or above the discriminatory level. Following D&C, patients without chorionic villi in the specimen or with rising or plateaued (less than 15% change) hCG levels may be considered to have an ectopic pregnancy. The most common adnexal finding on sonograms performed for suspected ectopic pregnancy is a complex cystic mass, which is not diagnostic and might instead represent a corpus luteum cyst. Definitive diagnosis by ultrasound requires the presence of an extra-uterine fetal pole, yolk sac, or cardiac activity.

Second, should this patient have been treated for an ectopic when she first presented? In stable patients with an hCG level above 2000 mIU/ml, it is our practice to obtain a second hCG level 12-24 hours later. A rapidly falling hCG level could indicate a failed intrauterine pregnancy, a completed abortion, or possibly, a spontaneously resolving ectopic pregnancy. At our institution, a third level is obtained 48 hours after the second to confirm continued falling levels. A decrease of 50% or more in 48 hours is highly suggestive of a completed abortion. If levels continue to fall, the patient may be followed with a weekly hCG level until it reaches a defined endpoint (15 mIU/ml in our protocol). On the other hand, if the hCG levels do not fall, or instead continue to rise, the diagnosis of ectopic pregnancy can be assumed with reasonable certainty. In the featured case, it can be argued that the administration of methotrexate (and the exposure to the side effects of a chemotherapeutic agent) prior to obtaining a second hCG level was premature, since the patient could have had a resolving pregnancy.

Third, once an ectopic pregnancy was diagnosed, what treatment should this patient have been offered? The criteria for treating an ectopic pregnancy with methotrexate vary from institution to institution. Generally accepted contraindications include size greater than 4 cm (3.5 cm if ectopic cardiac activity is seen) and free fluid outside the pelvis. Additional contraindications include hepatic dysfunction, blood dyscrasia or renal disease as evidenced by serum aminotransferase concentrations greater than twice the upper limits of normal, a white blood cell count less than 1500/mm,(2) a platelet count less than 100,000/mm,(2) or a serum creatinine concentration greater than 1.5 mg/dl. Serious active infection at any site, history of peptic ulcer disease or ulcerative colitis, and AIDS are other general contraindications for treatment with methotrexate. All patients considering methotrexate should be screened with a baseline hCG, Rh factor, complete blood count, SGOT, creatinine, and blood urea nitrogen. Furthermore, patients must have adequate access to medical care (including a reliable source of transportation) prior to treatment with methotrexate due to the possibility of rupture of the ectopic pregnancy.

Some practitioners prefer surgical therapy to treatment with methotrexate in patients with more than trace amounts of peritoneal fluid, more than minimal pain, or the presence of ectopic cardiac activity regardless of ectopic size. At our institution, the presence of blood in the pelvis is not considered a contraindication to medical therapy since approximately 50%-60% of unruptured ectopics have blood in the pelvis on pelvic

ultrasound. In addition, this blood may produce mild peritoneal signs (ie, rebound) on abdominal examination. Although there are no data to indicate the amount of blood in the pelvis above which it is unsafe to treat medically, we empirically consider blood in the upper abdomen a strong relative contraindication to medical therapy. Stable patients with smaller amounts of blood confined to the pelvis can be safely treated medically. If there is concern that this blood is the result of active bleeding, observation in the hospital with the monitoring of serial hematocrits is indicated.

Was her hCG too high for methotrexate? The largest published study to date that evaluated risk factors for methotrexate failure found that neither ectopic size (up to 4 cm) nor the presence of free fluid confined to the pelvis were predictive of failure.(3) While cardiac activity was associated with increased failure using univariant analysis, logistical regression showed only hCG level to be truly predictive. Only a level of greater than 15,000 was associated with a marked increase in failure.(Table) We do not advocate using hCG levels alone to exclude patients from methotrexate therapy. However, the level should be used during counseling of the patient. For this patient, the success rate that should have been quoted during the informed consent process is 81.8% (with an hCG level of 10,000 to 14,999). This success rate is still quite acceptable for many patients wishing to avoid surgery.

If methotrexate is chosen as the best option, the safe administration of this drug is extremely important. After giving methotrexate, a repeat hCG is performed on days 4 and 7. If the hCG level declines 15%, hCG titers are then followed weekly until less than 15 mIU/ml. If the hCG level declines 4) but may take as long as 109 days. Tubal rupture also may be delayed: the longest time from initial treatment to rupture in our database was 32 days.(4) During treatment, patients should be counseled to avoid sexual intercourse, pelvic exams, alcohol, folate containing vitamins, and gas-producing foods.

When this patient returned with increased pain, it appears she was offered only surgery. It should be noted that most patients have at least one episode of increased pain after the use of methotrexate. Lipscomb and colleagues have shown that, even when pain requiring hospitalization, most patients can successfully avoid surgery.(2) Although many physicians would proceed to surgery in any women with significant pain, particularly if free fluid was noted in the pelvis, most of these patients will resolve without surgery.

Three randomized studies compared single-dose methotrexate to laparoscopic salpingostomy.(5-7) If failure of medical therapy was defined as requiring more than one dose of methotrexate, then salpingostomy was significantly more successful in treating ectopic pregnancy. However, if success in the medically managed group was defined as avoidance of surgical intervention, the groups were equally successful. Following treatment, ipsilateral tubal patency could be assessed in 77 patients. No significant difference was found between the two groups.(8) There was also no difference between the two groups with respect to subsequent intrauterine pregnancy rate and repeat ectopic pregnancy rate.

No randomized prospective trials have compared fertility rate or recurrent ectopic rate after salpingectomy versus salpingostomy. Only a few small retrospective studies are available.(9-12) Since there is no perceived disadvantage to salpingostomy over salpingectomy, salpingostomy is generally the procedure of choice when possible, with the intention of avoiding sterility.

In summary, several patient safety issues must be addressed when caring for patients with ectopic pregnancies. Practitioners need to rely on a standardized diagnostic algorithm to ensure that the patient

actually has an ectopic pregnancy. If the diagnosis is unsure, methotrexate should not be given. Before treatment with methotrexate is initiated, patients must be counseled extensively about the risks and benefits of treatment, the expected course and duration of treatment, as well as the importance of follow-up.

Take-Home Points

- Practitioners must follow a standardized and valid diagnostic algorithm to ensure that a patient actually has an ectopic pregnancy.
- If methotrexate is chosen, standard institutional protocols should be in place for assessing whether the patient has contraindications to its use and for counseling the patient.
- Follow-up is critical and should be arranged prior to treating with methotrexate.
- Physicians should be aware that most patients will experience at least one episode of increased pain following treatment with methotrexate; such pain does not necessarily represent failure of medical therapy.

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Table

Table. Single-dose Methotrexate Success Rates By HCG Levels

HCG Level*	% Success
	98.3
1000-1999	93.0
2000-4999	91.8
5000-9999	86.7
10,000-14,999	81.8
>15,000	68.2

* HCG expressed as mIU/mL

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