CLINICAL PRACTICE

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Tubal Ectopic Pregnancy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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CME

A 34-year old woman who had recently and happily discovered that she was pregnant seeks care for worsening right lower abdominal pain and daily vaginal bleeding. On the basis of her last menstrual period, she is at approximately 7 weeks' gestation. She has no history of surgery and has had one previous vaginal delivery, one previous induced abortion, and a remote history of chlamydia. In the emergency department, she is visibly uncomfortable. Her vital signs are normal. She has diffuse tenderness in her lower abdomen that is worse in the right lower quadrant. Pelvic examination reveals scant blood in the vaginal vault, a closed cervix, and right adnexal tenderness. Her hemoglobin level is 11.2 g per deciliter, and her beta human chorionic gonadotropin (hCG) level is 3627 mIU per milliliter. Pelvic ultrasonography shows no free fluid in the pelvis, and her uterus does not contain a gestational sac. In the right adnexa, a gestational sac with a mean sac diameter of 3.5 cm is seen containing a yolk sac and no embryo. What would you advise?

THE CLINICAL PROBLEM

Tubal ectopic pregnancy is the implantation of a fertilized egg in the fallopian tube and is a time-sensitive condition that can result in tubal rupture and life-threatening hemorrhage. Ectopic pregnancy accounts for approximately 2% of all pregnancies in Europe and North America[1-3] and 2.7% of pregnancy-related deaths in the United States; mortality may be higher in low- and middle-income countries where deaths are underreported.[4] In the United States, Black women are nearly 7 times as likely as White women to die from the condition, which underscores racial health disparities and the need for improved access to early pregnancy care and equitable clinical management.[3] The risk of hemorrhage in untreated ectopic pregnancy is 50% or more.[5-7] As recently as the 1970s, 15% of patients with ectopic pregnancy presented in hypovolemic shock.[8] However, techniques for diagnosis and management have improved, and many tubal ectopic pregnancies are now detected early enough to be managed in the ambulatory setting.

Conditions that result in tubal inflammation and scarring, such as previous ectopic pregnancy, pelvic inflammatory disease, and previous tubal surgery, increase the risk of ectopic pregnancy.[9] Patients with a previous ectopic pregnancy have an 8 to 15% risk of another ectopic pregnancy.[10-12] Cigarette smoking, which may affect oviductal motility or tubal epithelial-cell turnover, is another risk factor.[13] Although pregnancy is rare after tubal ligation or with the use of an intrauterine device, when pregnancies do occur in patients using these contraceptive methods, the

KEY POINTS

TUBAL ECTOPIC PREGNANCY

- Tubal ectopic pregnancy is a time-sensitive medical condition that can be life-threatening.
- Risk factors include previous ectopic pregnancy, a history of pelvic inflammatory disease, tubal surgery, and cigarette smoking.
- The diagnosis is most commonly made by means of transvaginal ultrasonography showing the absence of an intrauterine pregnancy and the presence of adnexal mass.
- Management strategies include surgical treatment (salpingectomy or salpingostomy), medical treatment (methotrexate), or, in selected cases, expectant management.
- Post-treatment care should include attention to family planning and mental health.

risk of ectopic implantation is increased.[14-19] Approximately half the patients with ectopic pregnancy have no known risk factors.

STRATEGIES AND EVIDENCE

EVALUATION

Although vaginal spotting and lower abdominal pain are common in pregnancy, these are also typical presenting symptoms of tubal ectopic pregnancy and are indications for ultrasonography in persons with a positive serum test for beta hCG. Ultrasonographic visualization of a gestational sac containing a yolk sac, an embryo, or both outside the uterus is diagnostic (Fig. 1). However, many ectopic pregnancies do not progress to a visible stage or do not have normal developmental structures.[20] In these cases, ultrasonography may show an inhomogeneous adnexal mass or an extrauterine saclike structure (Fig. 2). Although the diagnostic usefulness of ultrasonography is greatest when the evaluation is completed by experts with specialized equipment,[21,22] these ultrasonographic findings in a patient with a positive pregnancy test and no intrauterine pregnancy are suggestive of ectopic pregnancy.[22] A normal pregnancy should be seen on transvaginal ultrasonography by approximately 5 or 6 weeks after the last menstrual period but may not be seen until the serum beta hCG level reaches approximately 2500 mIU per milliliter. If the beta hCG level is greater than 3500 mIU per milliliter, no intrauterine pregnancy is visualized on transvaginal ultrasonography, and clinical history does not suggest recent miscarriage (i.e., substantial vaginal bleeding), ectopic pregnancy is also highly likely. Free fluid in the peritoneal cavity should raise suspicion for a ruptured ectopic pregnancy with hemoperitoneum if no intrauterine pregnancy is seen on ultrasonography.

The term "pregnancy of unknown location" applies when a patient with pain, bleeding, or both has a positive pregnancy test but no pregnancy visualized on transvaginal ultrasonography. The differential diagnosis includes an early normal intrauterine pregnancy, early intrauterine pregnancy loss, and ectopic pregnancy. In such cases, if the pregnancy is undesired, diagnosis can be expedited by emptying the uterus procedurally or medically, and if the pregnancy is desired, clinicians should follow patients closely with serial beta hCG testing every 2 days, frequent symptom assessment, and repeat imaging to reassess pregnancy location.[23] Ectopic pregnancy is suggested by a failure of beta hCG levels to double in 48 hours or by the development of worsening pain or hemodynamic instability.[24] For patients in a clinically stable condition with desired pregnancies, careful assessment of pregnancy viability and location is required before any presumptive intervention.[25]

MANAGEMENT

Management strategies for ectopic pregnancy include surgical, medical, or expectant (Fig. 3). Patients present to a range of clinical settings for assessment and management of ectopic pregnancy, including primary care and prenatal care clinics, emergency departments, and, where available, early pregnancy assessment centers. Data are lacking to inform patient outcomes according to the site of care.[2,26]

SURGICAL MANAGEMENT

Surgery is indicated for patients whose condition is hemodynamically unstable and those who prefer expedited treatment or wish to avoid methotrexate (see below). Laparotomy for tubal ectopic pregnancy is occasionally warranted in cases of

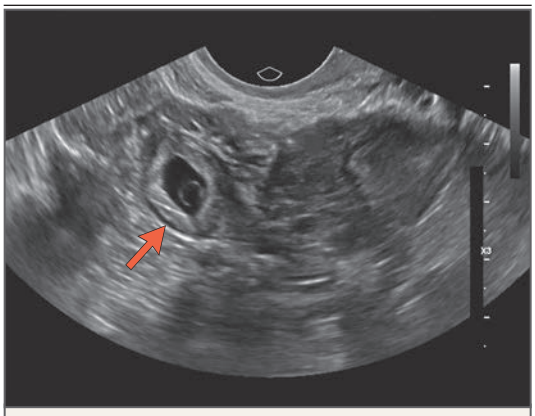

Figure 1. Transvaginal Ultrasonogram of Definitive Tubal Ectopic Pregnancy.
A gestational sac and yolk sac (arrow) are visible.

massive intrabdominal hemorrhage or if adhesive disease precludes the laparoscopic approach. The procedure generally involves either laparoscopic salpingectomy (removal of the affected fallopian tube) or salpingostomy (removal of the pregnancy through a tubal incision while the tube is preserved, sometimes referred to as salpingotomy); both can be performed on an outpatient basis. Recovery is relatively rapid with a minimally invasive approach, and patients typically return to usual activities within 2 weeks. Although salpingectomy is considered to be the standard procedure and is preferred if the tube is ruptured, certain factors — including the degree of damage to the contralateral fallopian tube and plans for future fertility — may favor salpingostomy. Patients who undergo salpingostomy have a small risk of retained trophoblastic tissue, so this procedure typically requires verification that beta hCG levels return to zero postoperatively and treatment with methotrexate for evidence of persistent trophoblast.

The European Surgery in Ectopic Pregnancy randomized trial compared salpingostomy with salpingectomy. Among the 446 participants, the cumulative incidence of subsequent pregnancy within 36 months did not differ significantly between the two groups (61% and 56%, respectively; rate ratio, 1.06; 95% confidence interval [CI], 0.81 to 1.38; P=0.68). Of 215 patients assigned to undergo salpingostomy, 43 (20%) had conversion to salpingectomy owing to persistent tubal bleeding, 2 (1%) underwent repeat laparoscopy owing to postoperative bleeding, and 5 (2%) underwent repeat laparoscopy to treat persistent trophoblast. Adverse events included conversion to laparotomy (1% in each group), blood transfusion (7% in the salpingostomy group and 3% in the salpingectomy group), and readmission (5% and 1%, respectively). These findings support salpingectomy as the preferred surgical treatment for patients with ectopic pregnancy and a healthy contralateral tube.[27,28] A systematic review and meta-analysis including both randomized trials and observational studies confirmed advantages of salpingectomy over salpingostomy.[29] However, the largest randomized trial included only participants who had a normal contralateral tube.[27] After this trial had been excluded from the analysis, a subgroup analysis involving patients with risk factors for infertility undergoing salpingectomy (as compared with salpingostomy) showed a lower odds of subsequent intrauterine pregnancy (odds ratio, 0.30; 95% CI, 0.17 to 0.54) and a higher odds of repeat ectopic pregnancy (odds ratio, 1.96; 95% CI, 0.88 to 4.35). These observations suggest that salpingostomy may be

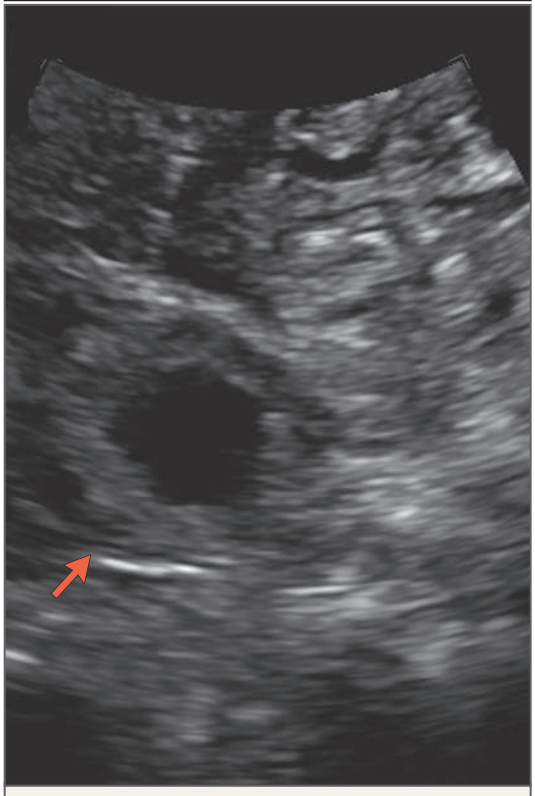

Figure 2. Transvaginal Ultrasonogram of Probable Tubal Ectopic Pregnancy.
Shown is an adnexal mass containing a cystic structure (arrow).

preferred for patients at high risk for tubal disease in the contralateral tube who desire future fertility. Bilateral salpingectomy is an option for patients who want permanent contraception after treatment of ectopic pregnancy.

MEDICAL MANAGEMENT

Methotrexate (administered intramuscularly) is the standard of care for medical management of tubal ectopic pregnancy. Methotrexate inactivates dihydrofolate reductase, which causes depletion of tetrahydrofolate, an essential cofactor for DNA and RNA synthesis; rapidly dividing cells such as trophoblastic cells are susceptible to its action. Methotrexate should not be used if the pregnancy is desired, before definitive confirmation of ectopic pregnancy. Eligibility for medical management, which is provided in the ambulatory setting, requires hemodynamic stability, no evidence of tubal rupture, and an ability to follow up for care, including no difficulty with transportation. Patients who have a serum beta hCG level of less than 5000 mIU per milliliter, absent embryonic cardiac activity, and a size of ectopic pregnancy of less than 4 cm are eligible for methotrexate therapy as an alternative to surgical treatment.[30] However, the time to pregnancy resolution can be prolonged. In a recent retrospective study involving 216 patients, the median time to pregnancy resolution was 22 days in cases in which medical management was successful; 20% of these patients received a second dose of methotrexate, and 24% underwent surgery.[31]

Methotrexate can be administered in single-dose, two-dose, or multidose protocols[24] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The single-dose regimen is most commonly used, and although most patients will have pregnancy resolution with one dose, patients should be made aware of the possibility of additional dose administration and the resulting increased likelihood of side

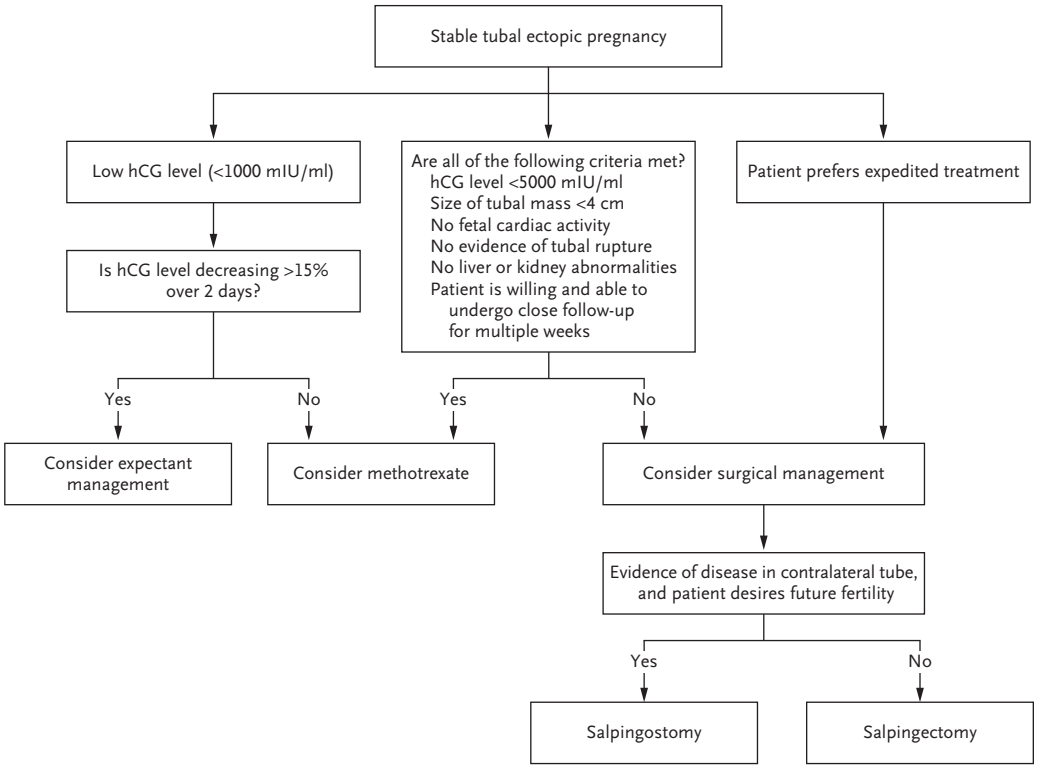

Figure 3. Approach to Treatment of Tubal Ectopic Pregnancy.

This general guidance may be adjusted on the basis of clinical judgment and available resources. Dose regimens for methotrexate are described in Table S1 in the Supplementary Appendix. The term hCG denotes human chorionic gonadotropin.

effects.[32] For each protocol, serum beta hCG levels are measured at baseline, during treatment, and weekly in surveillance after treatment. Treatment success is most conservatively defined by resolution of the beta hCG level to less than 5 mIU per milliliter, although some researchers have defined success as a decrease of hCG levels to less than 15 mIU per milliliter[33-36] or less than 200 mIU per milliliter.[37] Additional, or fewer, doses than initially planned may be given, depending primarily on the progression of beta hCG levels during the treatment course. In a meta-analysis of randomized, controlled trials comparing the two-dose with the single-dose protocol (four trials, involving 243 participants),[32] treatment was successful in 89% and 81% of participants, respectively (odds ratio, 1.84; 95% CI, 1.13 to 3.00); the difference between the two regimens in time to resolution was −7.9 days (95% CI, −12.2 to −3.5). Surgery for ruptured ectopic pregnancy occurred in 5% receiving the two-dose protocol and 6% receiving the single-dose protocol. The relative effectiveness of the two-dose protocol appears to be greater than that of the single-dose protocol in patients with beta hCG levels greater than 3000 mIU per milliliter and in those with larger adnexal masses (>2 cm). Adverse events, most commonly stomatitis and conjunctivitis, were reported in 31% receiving the two-dose protocol and 23% receiving the single-dose protocol. Similarly, studies comparing the multidose protocol with the single-dose protocol have shown a higher incidence of adverse effects with the former. In three studies (involving 298 participants) comparing the multidose protocol with the single-dose protocol, no significant differences were found in treatment success or time to resolution, nor were there significant differences in the incidence of surgery for tubal rupture in the two studies in which this outcome was reported.[32]

Ultimately, patients who opt for methotrexate therapy can expect a median time to pregnancy resolution of 28 days (interquartile range, 21.0 to 36.5).[38] For those wishing to conceive again, fertility outcomes for 207 participants randomly assigned to salpingostomy plus methotrexate or salpingectomy alone and 199 participants randomly assigned to salpingostomy plus methotrexate or methotrexate alone showed no significant between-group differences in the incidence of pregnancy over the subsequent 2 years.[39]

EXPECTANT MANAGEMENT

Although data are limited, a selected population of patients may be eligible for expectant management of tubal ectopic pregnancy. A meta-analysis including two randomized trials (involving 153 participants) compared single-dose intramuscular methotrexate with expectant management for tubal ectopic pregnancy. According to individual participant data, treatment was successful in 79% of the participants in the methotrexate group and 69% of those in the expectant-management group (risk ratio, 1.16; 95% CI, 0.95 to 1.40),[40] and surgical intervention was used in 10% and 19%, respectively (risk ratio, 0.65; 95% CI, 0.23 to 1.14). One trial compared a single dose of intramuscular methotrexate (50 mg per square meter of body-surface area) with placebo among patients with an hCG level below 1500 IU per liter,[41] and the other compared a single dose of methotrexate (1 mg per kilogram of body weight) with no treatment among patients with an hCG level below 2000 IU per liter.[42] These trials included hemodynamically stable patients with a low hCG level (often <1000 mIU), many of whom had declining levels of beta hCG.[40] Patients meeting these criteria can be counseled regarding expectant management, with the acknowledgment that data are limited to inform efficacy and risks; if elected, expectant management should be abandoned if symptoms occur or if hCG levels do not decrease. A prospective cohort study of expectantly managed tubal ectopic pregnancies,[43] which was conducted at a center that does not offer methotrexate therapy, showed that beta hCG levels became undetectable before resolution of the visualized ectopic pregnancy on ultrasonography and that in 5% of patients, disappearance of the pregnancy on ultrasonography took longer than 3 months; the consequences of a prolonged time to resolution of ectopic pregnancy, if any, are unknown.

POST-TREATMENT FOLLOW-UP AND COUNSELING

Data are lacking to inform recommendations for the optimal time to conceive a new pregnancy after resolution of tubal ectopic pregnancy with either surgery or methotrexate. In future pregnancies, monitoring is advised as soon as a pregnancy test is positive in order to provide an early diagnosis and treatment if ectopic pregnancy recurs. Patients not planning to conceive should re-

ceive patient-centered contraception counseling. In a prospective cohort study involving women with pregnancy loss that included 116 ectopic pregnancies, one fifth of patients who had ectopic pregnancy had post-traumatic stress and anxiety, and one tenth had moderate or severe depression that persisted 9 months after treatment.[44] Clinicians should assess mental health after treatment for ectopic pregnancy and offer resources if indicated.

AREAS OF UNCERTAINTY

The potential role of novel therapeutics for ectopic pregnancy warrants further study. Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, could disrupt the ectopic pregnancy implantation site owing to high expression of EGFR in placental tissue. Case series and an open-label trial suggested a high likelihood of successful resolution of tubal ectopic pregnancy with a course of gefitinib in addition to methotrexate.[45,46] However, a randomized trial comparing a 7-day course of oral gefitinib with placebo, combined with single-dose methotrexate,[38] showed little difference in the percentage of patients who underwent surgical intervention (30% and 29%, respectively); these percentages were higher than those in previous trials evaluating methotrexate alone. Whether gefitinib might improve the efficacy of methotrexate in a two-dose protocol is not known. An open-label trial suggested that mifepristone in conjunction with methotrexate may be more effective than methotrexate alone,[47] but larger trials are needed to better inform its efficacy. Both contemporary data and societal consensus are lacking to guide the use of anti-D immune globulin prophylaxis after treatment of ectopic pregnancy.[1,2,48,49]

GUIDELINES

The most recent guidelines for management of ectopic pregnancy have been published by the American College of Obstetrics and Gynecology (2018)[24] and the American College of Emergency Physicians (2017).[50] The recommendations in this article are largely in line with the published guidance.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has findings consistent with tubal ectopic pregnancy. Given her beta hCG level (3627 mIU per milliliter), we would use a shared decision-making approach and recommend either laparoscopic surgical management or medical management with a two-dose methotrexate protocol, in accordance with guidelines.[1] Although salpingectomy is definitive treatment and results in a faster time to resolution than methotrexate therapy, methotrexate therapy may enable the patient to avoid surgical risks and recovery time; however, it carries a risk of failure of 10 to 15% and requires prolonged follow-up with repeated laboratory testing. We would assess whether our patient had the necessary social support. If she does not wish to conceive soon, we would provide patient-centered contraceptive counseling.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CLINICAL TRIAL REGISTRATION

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