REVIEW ARTICLE

DIAGNOSIS AND MANAGEMENT OF ECTOPIC PREGNANCY: A COMPREHENSIVE REVIEW FOR THE OSTEOPATHIC PHYSICIAN

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ABSTRACT

Ectopic pregnancy (EP) is a serious obstetric complication that can be life-threatening. Age-adjusted incidence of ectopic pregnancy is roughly 15.8 pregnancies per 1000.[1] Despite this seemingly low value, EP remains one of the largest contributors to maternal mortality in the first trimester. While some patients require urgent surgery, there is a role for medical and conservative management in patients who are hemodynamically stable. In cases where medical or conservative management is appropriate, family physicians can choose to manage this condition with collaboration from the patient's obstetrician. Particularly for residents in the 50% of US counties with no obstetrician,[2] it is imperative for family doctors to diagnose EP quickly and accurately.

BACKGROUND

Ectopic pregnancy (EP) is defined as any pregnancy in which a fertilized ovum implants outside of the uterus.[3] Most EPs implant in the fallopian tube, accounting for over 90% of EPs. Implantation can occur outside the fallopian tube as well. Roughly 3% of EPs implant on an ovary, 2% to 4% are classified as interstitial, and the remaining 1% are classified as abdominal, cervical, intramural, or cesarean section scar EPs.[4] Heterotopic pregnancy is an extremely rare cause of EP in which intrauterine pregnancy and EP occur simultaneously; this accounts for an estimated 1 in 30,000 pregnancies.[5] Due to the lack of national surveillance in the United States, prevalence data are difficult to ascertain; however, according to the American College of Obstetricians and Gynecologists (ACOG), it is estimated that EPs account for 2% of pregnancies in the United States. Despite only representing a small percentage of pregnancies, ruptured EPs are a major health concern and a leading contributor to maternal mortality.[6] Currently, EPs are responsible for up to 10% of pregnancy-related deaths and are the number one contributor to maternal mortality in the first trimester.[7]

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The most significant risk factors for EP include previous tubal surgery, sterilization, previous EP, history of pelvic inflammatory disease, and current use of an intrauterine device.[8] History of EP is one of the strongest risk factors, as patients with a previous EP have a 10% to 20% increase in risk of recurrent EP in future pregnancies.[9,10] Those with previous tubal surgeries are more likely to go on to develop a future EP with an odds ratio of 8.8.[11] Lack of risk factors should not be considered reason to exclude EP as a diagnosis, as up to 50% of patients presenting with EPs have no clinical risk factors.[12] Classic symptoms of EP are not sensitive or specific for EP alone, and patients may present with a variety of signs and symptoms. The most common presenting symptoms include abdominal pain and vaginal bleeding, while other symptoms such as amenorrhea, breast tenderness, nausea, syncope, or frequent urination may also be seen.[13-15] A syncopal episode in a patient with a possible EP could indicate the ectopic has ruptured and that the patient may need urgent surgical intervention.[7] The symptoms are not specific to EP, thus the differential may be large. The differential diagnosis includes appendicitis, urinary tract infection, ovarian torsion, normal intrauterine pregnancy (IUP), implantation bleeding, spontaneous abortion, or tubo-ovarian abscess.

In the primary care setting, the key differentiation among patients with a possible EP is hemodynamic stability. Those that are hemodynamically stable and at minimal risk for rupture may be worked up and treated in the outpatient setting by a primary care provider. Unstable patients with signs such as hypotension and tachycardia potentially need surgical intervention, will require urgent inpatient care, and should be transferred to the emergency department.

DIAGNOSIS

A hemodynamically stable female patient of reproductive age presenting to their primary care physician with signs and symptoms of an EP should first receive a urine pregnancy test in the office. If the urine pregnancy test yields a positive result, stable patients in whom there is suspicion for EP may continue to be worked up in the outpatient setting. The next step is to obtain an urgent quantitative beta-human chorionic gonadotropin (β-hCG) and perform transvaginal ultrasonography.

QUANTITATIVE β-HCG

Quantitative measurements are used to evaluate β-hCG growth trends and determine if the baseline value is above or below the discriminatory value. The discriminatory zone is a serum hCG value at which an IUP can be visualized. Each institution may have slight variations in their exact definition of discriminatory value, but in most cases, it is a β-hCG level between 1500 and 2000 mIU/mL.[7,12,16] If the quantitative β-hCG level is below the discriminatory level, the recommendation is to follow up with a repeat quantitative β-hCG in 48 hours. In normal IUP, the β-hCG level will typically double every 48 hours, but viable pregnancy can see β-hCG increase as little as 35% in 2 days.[17] In 2 days, if the repeat β-hCG results are now >1500 mIU/mL, a transvaginal ultrasound can be completed. If the level is still <1500 mIU/mL and declining, spontaneous abortion should be considered. If β-hCG is <1500 mIU/mL and increasing, the serum β-hCG should be repeated in another 48 hours.[18]

ULTRASONOGRAPHY

Following ACOG guidelines, any reproductive-aged female showing signs and symptoms of EP with positive serum β-hCG requires a diagnostic transvaginal ultrasound.[5] Generally, ultrasound cannot be used to rule out an EP, but results can confirm the diagnosis.[19,20] There are three possible results of transvaginal ultrasonography: confirmed EP, indeterminate IUP, or normal IUP.[8,12,18] Early in the course of an IUP, an ultrasound finding referred to as the "double ring sign" may be appreciated, which refers to the decidua parietalis and decidua capsularis forming around the gestational sac.[21] While this cannot rule out an EP, it does provide supportive evidence favoring an IUP. Detection of ectopic cardiac activity is the most accurate result for confirming an EP, with a likelihood ratio >100.[18]

It is best to use the results of both quantitative β-hCG and transvaginal ultrasonography rather than relying on one test independently. A quantitative β-hCG >1500 and transvaginal ultrasonography showing no IUP has a sensitivity ranging from 67% to 100% and specificity of 100% for diagnosing EP.[18]

MANAGEMENT

Once an unruptured EP has been identified, there are three potential methods to manage the EP: expectantly, medically, or surgically. Options become limited with additional complications such as ruptured EP, clinical instability, or hemodynamic instability—all situations which would require emergent surgical intervention. Assuming no complications exist and that the patient is stable, the decision to treat the patient medically or surgically should be made by the patient with information provided by their physician.[12]

Additionally, it is important to note that consideration of patient preferences and limitations may play a role in treatment options. Medical management with methotrexate is less expensive than surgery; in addition to being less invasive. A retrospective review found the direct costs of methotrexate-treated EPs were roughly 24% of the direct costs for treatment using laparoscopy.[22] However, β-hCG levels typically fall faster with surgical intervention.[23] Some studies indicate a higher success rate with surgical management as well.[18] Surgery may be a better option for patients who have little access to medical facilities for lab testing or for those with financial insecurity, and especially when there is concern regarding patient compliance for follow-up.

Expectant Management

Despite the limited patient population eligible for expectant management, this treatment option should not be overlooked as some EPs may resolve on their own.[24] Expectant management has been shown to be effective only in those patients with a low or decreasing β-hCG level.[25,26] However, the exact cutoff has been debated, with some studies citing a safe level of <1000 mIU/mL,[25] and others reporting efficacy as high as 3000 mIU/mL.[26] Patients who present with an initial β-hCG level of 200 mIU/mL or less have spontaneous resolution of the EP 88% of the time.[12] Most importantly, there should be a measured plateau or decline of β-hCG levels to safely consider expectant management.[27,28] Patients should be educated on the risks of expectant management and the warning signs of EP rupture; the treating physician should ensure the patient has access to emergency medical treatment and knows how to access this care in the case of an emergency.[27]

To ensure patient safety, the patient must be willing to return for close follow-up monitoring to confirm resolution of the EP. Follow-up appointments with the patient managed expectantly should begin at the 48-hour mark to reassess β-hCG levels and patient symptoms. If β-hCG levels are declining from baseline and the patient remains asymptomatic, expectant management may be continued. Once β-hCG decline has been proven, expectant management can continue as weekly quantitative β-hCG measurements.[27] Each week, measurements are expected to decline by at least 15%. If this is not seen, the patient should undergo follow-up in 48 hours and cessation of expectant management should be considered.[26] These weekly follow-up appointments should continue until β-hCG is no longer detectable.[18] At any point during expectant management, if the β-hCG level has risen or the patient is now experiencing symptoms of potential rupture, expectant management should no longer continue.[26]

Medical Management

Medical treatment of an EP can be managed by many specialties, including a primary care or family physician.[12] Those patients who do not qualify for expectant management as described above can often be medically managed using methotrexate.[28] Patients should be treated with methotrexate if they have a positive pregnancy test and a confirmed extrauterine pregnancy. These patients should be hemodynamically stable and should not show signs of imminent decline, impending or active fallopian tube rupture, or other complications that can be seen with EPs.[12] Other relative contraindications include embryonic cardiac activity, size greater than 4 cm, and maternal liver disease.[29] A baseline complete blood count (CBC) and comprehensive metabolic panel (CMP) should also be acquired to rule out contraindications to methotrexate such as renal insufficiency, liver disease, anemia, or leukopenia.[12,29] Rh D factor status for the patient should be determined and, if the patient is Rh D-negative, administration of Rh D immune globulin is required.[30] As always, a complete medical history should be taken to ensure safe use as described by the Food and Drug Administration (FDA) drug label.[29]

Once the decision to pursue medical management has been made, the physician must decide between a single- or multiple-dose regimen of methotrexate.[12] A single dose of methotrexate has been shown to be more effective in patients with an initial β-hCG level <5000 mIU/mL, with increased treatment failure rates above this β-hCG threshold.[31,32] Linear increase in risk of treatment failure is seen with increasing β-hCG, as risk of failure increases by 0.12% for each unit increase in β-hCG.[32] Women who received single-dose methotrexate treatment reported fewer side effects compared to those who received multiple-dose methotrexate treatment.[28] Additionally, better fertility outcomes were reported when women received a single dose as opposed to a multidose regimen.[33]

While there are several medications used to medically terminate pregnancies, methotrexate is the only medication approved by the FDA for treatment of EPs.[34] Methotrexate works as a folate antagonist, which prevents the rapidly dividing cells of the embryo from synthesizing new DNA, thereby preventing growth. The cells are no longer able to divide, so the pregnancy will not progress.[29] Methotrexate should be administered intramuscularly, with the hope that this is a one-dose treatment, with a dosing of 1.0 mg/kg or 50 mg/m^2.[30] The patient should return for β-hCG measurement in 2 to 4 days; if the level has risen, or has fallen <15% by day 4, an additional dose of methotrexate should be administered at the same dose.[30] If a second dose is needed, patients should return for β-hCG on days 7, 11, and 14.12 If a β-hCG decline >15% is noted at any point, no further methotrexate doses are indicated and the patient should return for weekly monitoring as described with expectant management.[12,30] Alternative to intramuscular delivery, oral methotrexate may also be used as a 4-day treatment course on days 0, 2, 4, and 6 at 1.0 mg/kg.[30] Patients should return for weekly monitoring until the EP has fully resolved, demonstrated by a nondetectable β-hCG.[18] This typically occurs in 4 to 6 weeks but can take up to 8 weeks to confirm success.[14,18]

Successful treatment with methotrexate is not guaranteed, and the success rate is estimated to range from 70% to 95%. The factor that most significantly indicates likelihood of methotrexate failure is higher baseline β-hCG level.[5,35] In the case that β-hCG does not diminish appropriately by day 7, surgical management should be considered and discussed with the patient. Conversion to surgical management of the EP should always be considered as an alternative and should be pursued if the patient shows signs of decline, hemodynamic instability, or new symptoms.[23]

Surgical Management

With most EPs, surgical intervention is not necessary for successful treatment. Typically, only 10% of patients will need surgical management.[36] However, it may be critical in saving the patient's reproductive function and potentially their life. Typically, surgical management of an EP is implemented when the patient fails medical management or is unable to complete medical management due to other medical contraindications such as hemodynamic instability.[37]

There are, however, certain situations that may indicate immediate surgical referral for patient safety. If an ultrasound demonstrates a visualizable embryo outside of the uterus with clear cardiac activity, the patient should receive urgent surgical management to prevent potential morbidity.[12]

Surgical management typically involves a salpingectomy (complete removal of the fallopian tube) or a salpinx-sparing salpingotomy (removal of gestational sac only). The latter is preferred, especially in cases in which preservation of fertility is a concern.[2] Despite surgical management, there is a chance of persistent EP; it is estimated that in nearly 8% of salpingostomy cases, patients still have the EP postoperatively.[2,11] Surgical management also requires follow-up to monitor β-hCG levels to confirm decline until no longer detected. However, β-hCG levels typically return to undetectable levels after surgery.[37]

OSTEOPATHIC PERSPECTIVE

Providing care to rural and underserved communities is a mainstay of osteopathic values and many patients may experience barriers to receiving proper maternity care. Data from ACOG show there are only 5.39 residency-trained ob-gyns per 10,000 reproductive-aged women, and almost one-half of counties in the United States do not have any ob-gyns.[2] Family physicians are essential in bridging gaps in care in these underserved areas. Family doctors practicing in rural areas provide 42% of total healthcare and, despite decreasing numbers, also provide the majority of obstetrical care.[38] Women in small rural towns have an 80% higher maternal mortality rate than those in urban locations. With EP continuing to be a top cause of maternal death, the role of family physicians in diagnosing and medically treating EPs is imperative.[39]

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