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Early Pregnancy Failure: Beware of the Pitfalls of Modern Management

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Abstract

The evolution of the diagnosis and management of women with an early pregnancy loss has been a success story. The mortality from ectopic pregnancy has objectively been decreased in the past few decades. However, modern management has resulted in a new set of issues. Over-interpretation of a single ultrasound, misunderstanding of the utility of serial hCG values and inappropriate use of methotrexate can result in iatrogenic complications. Modern management has successfully improved the diagnosis of ectopic pregnancy before rupture; it should now also focus on ensuring that an intrauterine pregnancy is not interrupted as a result of diagnosis and treatment. This article reviews some of the pitfalls of the modern management of early pregnancy failure and introduces a series of articles on the subject.

Keywords

early pregnancy failure; methotrexate; ectopic pregnancy; miscarriage

Introduction

In little more than a generation, the diagnosis and management of a woman with an early pregnancy failure have changed dramatically. Treatment has moved out of the hospital and into outpatient clinics, away from the surgical suite and toward medical or expectant management. Cases of management of shock and catastrophic bleeding are rare, while diagnosis and treatment before symptoms are experienced has become common. Technological advances and consideration of the risks associated with ectopic pregnancy have resulted in prompt, safe care (1). Modern management has, however, resulted in new pitfalls and dilemmas. In this series of articles, we will explore how modern management of early pregnancy failure has increased iatrogenic complications, concomitantly to reducing morbidity and mortality associated with ectopic rupture.

A woman who presents with vaginal bleeding and pain is at risk for early pregnancy failure. By far, the most common complication is that of miscarriage. However, EP accounts for 1 to

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2% of all pregnancies in the United States (2). Ectopic pregnancy can compromise a woman's health and future fertility, and is still a leading cause of maternal morbidity and mortality accounting for 6% of pregnancy deaths (1, 2). A ruptured EP presents with intraperitoneal hemorrhage and should be treated emergently. Currently most patients present before rupture and with non-specific symptoms, raising new questions: who needs aggressive diagnosis and how should those patients be managed?

The most recent mortality data available (estimated between 2003 and 2007) demonstrates that mortality resulting from EP has declined significantly to a five-year US national average of 0.50 per 100,000 live births. This translates to an average of 21 deaths from EP annually (2). There has also been a dramatic change from open surgical procedures, transitioning through laparoscopic procedures, now shifted towards a predominance of medical management or even expectant management. These historical trends are well demonstrated in the article by Dr. van Mello (3). Today, women not initially diagnosed with ultrasound are followed with algorithms involving serial hCG values, follow up ultrasounds, and, at times, laparoscopy or uterine curettage. As more women undergo such surveillance, it should be recognized that these algorithms and decision aids are not without error (4). An error can result in false reassurance that a woman does not have an ectopic pregnancy, or conversely, interruption of a desired intrauterine pregnancy (IUP) during diagnosis and management.

Ultrasound findings need to be put into clinical context

One common error resulting in misdiagnosis is the reliance on ultrasound findings without full consideration of the clinical circumstances. Ultrasound is a very accurate diagnostic test, however, ultrasound does have quantifiable false positive and false negative rates (5, 6). Errors in ultrasound are far more common when the presenting hCG value is low (below 1500 mIU/mL) (7) and when diagnostic criteria do not include the finding of a yolk sac or embryo in the identification of an intrauterine or extra uterine gestation (6). Importantly, because such a high number of women undergo ultrasound, even when the rate of misdiagnosis with ultrasound is low, the number of errors can become clinically important. Today, almost all women who conceive with ART, almost all women with first trimester vaginal bleeding and/or pain, and many asymptomatic women undergo a transvaginal ultrasound as soon as they are determined to be pregnant. The prevalence of ultrasound in early pregnancy increases the total accumulation of error in the scans. As an example, if the error rate of ultrasound is only 1%, but a practice performs 500 scans a year, five women will likely be misdiagnosed, potentially resulting in a missed EP or the interruption of a desired IUP.

hCG Surveillance

An important adjuvant to ultrasound is the use of serum hCG concentrations. How hCG values can and cannot aid in diagnosis of a women at risk for EP, or with a PUL, is thoughtfully discussed by Dr. Seeber (8). While hCG values can inform clinical management, they can also be misinterpreted. A single measurement of hCG is neither diagnostic of pregnancy location nor viability. A single hCG value, however, can be used as a surrogate marker for gestation using the concept of an hCG discriminatory zone. An hCG series can help determine if the gestation is potentially viable and/or if the trend is expected for a normal growth or spontaneous resolution (9-11).

The Discriminatory Zone

One reason a pregnancy is not visualized is that the ultrasound was performed too early and the gestational sac has not yet developed. To address this issue, we use the concept of a

discriminatory zone (12, 13). The discriminatory zone is the hCG value at which, if no IUP is visualized with ultrasound, one can be confident that a healthy singleton intrauterine gestation is not present. However, this concept is not always applied correctly. If no intrauterine gestation is visualized when the hCG is above the discriminatory zone, it does not diagnose an ectopic pregnancy, but only suggests the pregnancy is not viable, i.e. miscarriage or EP. The hCG discriminatory zone is not the lowest level at which an intrauterine pregnancy can be detected with ultrasound. A clinical practice should use a high discriminatory zone to reduce the error of missing an intrauterine pregnancy.

Technological advances in ultrasound resolution should not result in a use of a lower discriminatory zone, but should only improve the accuracy of identifying early pregnancy failure. Because the concept of discriminatory zone is based on a singleton pregnancy, and multiple gestations have a higher hCG (at a given gestational age), the best “discriminatory zone” is gestational age and not hCG. A normal gestational sac should be seen at about 5 weeks and 5 days from last normal menstrual period (14, 15), regardless of whether the pregnancy is a singleton or a multiple gestation. The hCG discriminatory zone itself is a surrogate marker for gestational age only. Thus, gestational age should affect clinical decision-making more than a single value of hCG.

Pregnancy of unknown location

When the gestation is not seen in the uterus or in the adnexa, a woman is in a transient state called a pregnancy of unknown location (PUL). Management of a PUL can be a clinical conundrum, as one needs to balance the morbidity of a failed gestation with the morbidity of treatment or the procedures needed to make a diagnosis (16). The issue of diagnosing and classifying a PUL is also a relatively modern problem. A PUL is not a diagnosis, but instead a transient state. A consensus of the nomenclature for the outcome of women initially noted to have a PUL has been published (17). However, the need to diagnose the location of a pregnancy is still debated.

In the accompanying articles, the two sides of the debate are presented. Drs. Reid and Condous have taken the position that the location of an intrauterine pregnancy need not be identified in all cases for reasons of cost and time savings (18). Dr. Chung reviews the rationale in support of a definitive diagnosis of the location of a pregnancy (19). The rationale is to minimize incorrect diagnosis, to provide appropriate prognostic information for future pregnancies, and to limit over-treatment of women with a chemotherapeutic agent that is teratogenic and has side effects. As noted by Dr. Chung, it has been repeatedly demonstrated that up to 50% of women with a high hCG value and no evidence of an intrauterine pregnancy on ultrasound have an intrauterine gestation and not an ectopic pregnancy (20-22), and therefore, presumptive treatment with methotrexate will result in inappropriate treatment for many women. It should also be noted that a decision analysis attempting to quantify the number of visits necessary to treat a woman with a nonviable PUL demonstrates that the only advantage to presumptive methotrexate treatment is reduced clinician time. There are no cost savings or reduction of side effects, and there is an increase in number of visits required by the patient (23).

Premature surveillance can lead to errors

Because all diagnostic tests have false positive and false negative rates, as a large number of women undergo surveillance, the number of diagnostic errors will increase. This is particularly true when surveillance is started early in a gestation and when women are asymptomatic. Real world examples of diagnostic errors resulting from early intervention (perhaps too early) are demonstrated by Bottomley et al (24) and Morse et al (4). Bottomley et al demonstrated that when ultrasound is performed after 49 days of gestation, it reduces

the number of inconclusive scans without an associated increase in morbidity from missed ectopic pregnancies, thus decreasing false diagnoses (24). In other words, there is harm in performing an ultrasound in a woman without symptoms when one does not expect to see an intrauterine gestation. A clinician may be misled by non definitive and false findings, leading to more tests and potential diagnostic errors. Morse et al demonstrated that many of the cases where serial hCG values incorrectly suggested an abnormal gestation when, in fact, the pregnancy ultimately grew to be a viable gestation, occurred when hCG values were very low (around 500 mIU/mL) and very early in the gestation (4). This begs the question: when gestational age is known, such as in the case of ART, why is ultrasound performed prior to 5.5 weeks gestation and why are serial hCG values reflexively checked every two days? Unnecessary intervention will be initiated in a number of women due to over-surveillance.

Need for care in the use of methotrexate

An additional iatrogenic problem introduced by modern management of early pregnancy failure is inappropriate use of medical management. The use of methotrexate to treat ectopic pregnancy was first cited in 1982 (25). Since then, the use of methotrexate has revolutionized the treatment of EP. As medical management has become routine, new questions have arisen. For example, what is the optimal treatment regimen? Do all women need to be screened and monitored for serum measures of toxicity? Should the use of methotrexate be expanded to women with a presumed EP (but not definitively diagnosed)?

There are multiple published regimens for the use of systemic intramuscular methotrexate including a “single-dose” protocol, “multi-dose” protocol, and “two dose” protocol (26, 27). It has been demonstrated that the use of a “single-dose” protocol has a higher failure rate than that of a multi-dose protocol (odds of failure for a single dose administration was 1.96 times higher than that of multi-dose: 95% CI [1.07 to 3.60]) (28), yet the use of “single-dose” therapy remains the most widely used protocol. It seems that some clinicians are sacrificing therapeutic results for ease of administration. One possible explanation is because each individual clinician treats only a few patients a year, it is easy to attribute an occasional failure as anticipated, rather than recognize that a more effective treatment regimen will reduce the failure rate. A two-dose protocol was designed to provide a second dose of methotrexate at an earlier time point, without an increase in visits, to minimize this gap in success rates between single-dose and multi-dose (29).

The selection of appropriate candidates for medical management is well published in guidelines, including the American Society for Reproductive Medicine (26) and the American College of Obstetricians and Gynecologists (27). It has recently been suggested that because the use of methotrexate is no longer experimental, and the vast majority of women who are treated are healthy, it is neither necessary, nor cost effective to routinely screen and monitor all women for evidence of elevated liver enzymes given that the vast majority return to normal without clinical consequence (30). Perhaps a larger debate is if methotrexate should be used when the diagnosis is presumed and not confirmed.

The inappropriate use of methotrexate is on the rise

There is real danger in administering a chemotherapeutic agent, known to be abortifacient and teratogenic, if a viable pregnancy has not been ruled out. Improper administration of methotrexate to a woman who has an intrauterine pregnancy is more common than may be suspected (31). The prevalence is likely increased because of the increase in use of methotrexate in general, and the expanded use to women with a pregnancy of unknown location. Because methotrexate is so easy to administer, it is often given to women when an ectopic pregnancy is suspected or when there is simply no evidence of an intrauterine

pregnancy based on ultrasound. Inappropriate use of methotrexate is most common in two clinical scenarios. The first is that methotrexate is administered on first presentation for care when hCG values are relatively high or above a defined discriminatory zone. The second situation is when serial hCG values are determined to be “abnormal” (20).

There is almost no reason to give methotrexate on first encounter with a patient. If a patient is symptomatic with severe pain or signs of rupture, a surgical approach is indicated and methotrexate is contraindicated. If the patient is clinically stable and the ultrasound is not definitive, repeat ultrasound can provide confirmation of diagnosis. Importantly, follow-up of nonspecific findings like “a sac like object” in the uterus (or in the adnexa) will increase accuracy of diagnosis. Moreover, a repeat hCG value will provide evidence of progression, resolution or plateau. If no adnexal mass is visualized by ultrasound, it is unlikely that an EP (if present) has started to hemorrhage. Thus, it is unlikely to rupture before scheduled follow up.

Consequences of inappropriate use of methotrexate

Administration of methotrexate because of its convenience can result in disastrous complications. There are numerous reports that have later documented intrauterine pregnancy after a woman has been treated with methotrexate. Methotrexate administration often results in miscarriage, but in some instances women treated for a suspected ectopic pregnancy have been diagnosed with an ongoing intrauterine pregnancy. In some instances, live born infants with malformations have been delivered. Wrongful treatment with methotrexate has become a common reason for medical liability. Awards for cases of children born with malformations due to methotrexate have been in excess of 20 million dollars.

It is understandable that such inappropriate administration of methotrexate is not often reported in the medical literature. Despite likely underreporting, there are numerous case reports of methotrexate resulting in craniofacial, skeletal, cardiovascular and gastrointestinal anomalies (32-34). Other documented abnormalities have included intrauterine growth retardation, hypertelorism, facial nerve palsy, scoliosis, and cardiovascular abnormalities (32-35). Non punitive reporting mechanisms are necessary to obtain a reliable assessment of how often a patient's pregnancy location is misdiagnosed and/or inappropriately treated with methotrexate.

When an intrauterine gestation is visualized there should be no rush to declare miscarriage

An additional clinical conundrum is the management of a woman with a first trimester pregnancy of uncertain viability. When a miscarriage is suspected (and ectopic pregnancy is not suspected), there should be no rush to diagnosis and treatment. Many medical societies are currently attempting to define ultrasound criteria defining a non-viable gestation based on a single ultrasound. As demonstrated by Drs. Bourne and Bottomley, such a strict use of measurements is likely unwise (36). There is very little harm in delaying the diagnosis of non-viability until it is absolutely assured. Comparison of serial ultrasounds and/or serial hCG values can enhance the diagnosis of non-viability, limiting false diagnoses based on the measurement of expected anatomical findings at a single ultrasound.

Conclusion

The evolution of the diagnosis and management of women with an early pregnancy loss has been a success story. Because clinicians are now well aware of the presence and potential

morbidity of an ectopic pregnancy, despite persistent racial disparities, most ectopic pregnancies are treated early with minimal morbidity (2). In fact, because the risk of a ruptured ectopic pregnancy during evaluation treatment is so small, some clinical trial networks, such as the Reproductive Medicine Network, are considering no longer classifying an unruptured ectopic pregnancy (treated conservatively) as a serious life threatening adverse event. However, despite advances in management, mistakes are still made, often from rush to judgment. These iatrogenic complications need to be understood and minimized. Perhaps the next breakthrough will be adjuvant diagnostic markers to help identify either the location of a pregnancy, the viability of a pregnancy, or the aggressiveness of its growth. Until then, diligence is required to minimize missing the diagnosis of an EP and especially in the elimination of potential interruption of a desired intrauterine pregnancy.

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