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Proposed Updated Guidelines for Diagnosis of Pregnancy of Unknown Location (PUL)

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ABSTRACT

Early diagnosis of an extra-uterine pregnancy is important for safe and effective management. However, a pregnancy's location often cannot be easily determined with abnormal implantations or prior to 5-6 weeks' gestation. Multiple testing strategies exist to diagnose an abnormal pregnancy when location is unknown, but caution needs to be used to avoid a false diagnosis. Medical treatment is optimal when an abnormal pregnancy is diagnosed early. Because most of these pregnancies are intrauterine, additional testing to localize the pregnancy will allow the correct choice of therapy and avoids unnecessary exposure to a toxic therapy should be reserved for patients with significant concern for ectopic pregnancy, based on either risk factors or clinical findings.
Updating guidelines, to include MRI and new biomarkers, is required to define early location of pregnancy (intrauterine or extra uterine) and condition (healthy and unhealthy) pregnancy.

Keywords: (Ectopic pregnancy; MRI, Ultrasonography; Biomarkers; B-hCG; Progesterone).

INTRODUCTION

Implantation of the zygote outside the uterine cavity occurs in 2% of all pregnancies. The rate of ectopic pregnancies has increased from 0.5% in 1970 to 2% today. The prevalence of ectopic pregnancy (EP) in all women presenting to an emergency department with first-trimester bleeding, lower abdominal pain, or a combination of the two is between 6% and 16%.

Epidemiology of Ectopic Pregnancy

Usually the oocyte and the sperm meet in the ampullary part of the fallopian tube, and impregnation takes place. The growing morula moves slowly toward the uterus cavity while differentiating into the embryoblast and trophoblast. Implantation in the uterine cavity usually takes place after 6 or 7 days.

Etiology and Risk Factors

Theoretically, anything that impedes migration of the conceptus to the uterine cavity may predispose a woman to develop an ectopic gestation. These may be intrinsic anatomic defects in the tubal epithelium, hormonal factors that interfere with normal transport of the conceptus, or pathologic conditions that affect normal tubal function. The hormonal interference effects that estrogen and progesterone show on the growth and the motility of the epithelial ciliae, and estrogen stimulates the growth and differentiation of the fallopian tube including the generation of the epithelial ciliae. [(1)]

Diagnosis

Usually the earliest appearance of symptoms occurs in the sixth week after the last period. Patients with ectopic pregnancy can show all symptoms of a normal early

pregnancy, such as interruption of the normal menstrual period, nausea, vomiting, breast fullness, and fatigue. Typical symptoms of ectopic pregnancies are lower abdominal pain and abnormal uterine bleeding, ranging from spotting to severe bleeding, Involuntary guarding and peritoneal signs are indicative of intraperitoneal blood collection; there may be tenderness on cervical motion. [(2)]

Serial Serum Human Chorionic Gonadotropin

In a normally developing pregnancy, B-hCG starts secretion on days 5 to 8. A serum array detects levels as low as 5 mIU/mL, whereas the detection limit in urine is 20 to 50 mIU/mL.

The B-hCG levels double every 1.5 days in the first 5 weeks of a regular gestation. After 7 weeks, the sequence for double titers is 3.5 days.

In comparison, only 30% of ectopic pregnancies show a normal B-hCG course, In 70% of ectopic pregnancies, the B-hCG levels rise more slowly and reach a plateau or show a decrease in serum levels. An abnormal B-hCG pattern is highly suggestive of an ectopic gestation or a no longer intact gestation. [(3)]

Progesterone

Single serum P doses have been used together with serum B-hCG doses in the follow-up of ectopic pregnancy.

Serum P levels are a satisfactory marker of pregnancy viability, but they are unable to predict the location of a pregnancy. P levels below 5 ng/mL are associated with nonviable gestations, whereas levels above 20 ng/mL are correlated with viable intrauterine pregnancy, however, a considerable proportion of EPs present with P doses between 5 and 20 ng/mL, which limits its use in clinical practice to exclude the possibility of EPs [(4)]

Role of ultrasound in ectopic pregnancy

Ultrasound remains the first-line imaging modality for the evaluation of pregnant patients with abdominal or pelvic pain. In almost all cases of suspected ectopic pregnancy, ultrasound in combination with clinical data and laboratory tests is sufficient for making a correct diagnosis. Advantages include the ability of ultrasound to assess for fetal heart activity to confirm the presence of an embryo and the ability to differentiate ectopic pregnancy from a corpus luteum by pressing down on the ectopic pregnancy to separate it from an ovary. The most specific sonographic feature of ectopic pregnancy is the presence of an extra-uterine gestational sac [(5)]

Role of MRI in ectopic pregnancy

As previously described, ultrasound is the first-line imaging modality for obstetric imaging and diagnosis of ectopic pregnancy.

In addition to the aforementioned limitation of operator dependence, ultrasound is also limited by bowel gas interference, obesity or large body habitus, and small field of view. Another important limitation relative to diagnosis of ectopic pregnancy is ultrasound's inability to differentiate hemorrhage from other fluids.

As such, MRI plays an important role in the early diagnosis and management of ectopic pregnancy. MRI is now increasingly being used in complicated cases, in cases with unusually located ectopic pregnancy, and as a supplementary problem-solving imaging modality, MRI requires no specific patient preparation or premedication. Other advantages of MRI include no ionizing radiation, multi-planar imaging, and excellent soft tissue contrast [(6)]

The major roles of MRI are to identify fresh hemorrhage, to accurately localize the abnormal implantation site with superb spatial resolution, and to identify associated congenital uterine anomalies or Mullerian abnormalities. The fallopian tubes, round ligaments, and other adnexal structures are easier to identify in the presence of pelvic fluid or hemorrhage. Other important roles of MRI include planning of the surgical approach in abdominal pregnancy, differentiation of

some forms of ectopic pregnancy from incomplete abortion, and differentiation of ectopic pregnancy from other acute conditions, such as ovarian torsion, pelvic inflammatory disease, and acute appendicitis. [(7)]

Non-contrast technique should be used since gadolinium crosses the placenta and is relatively contraindicated in pregnancy. [(8)] MRI scan time is prohibitively lengthy, and these cases most often require urgent surgical management. [(9)]

MicroRNAs

MicroRNAs (miRNAs) are short, single-stranded RNA (19-25 nucleotide long) non-protein coding genes able to recognize complementary messenger RNAs (mRNAs), acting as master gene regulators by repressing mRNA translation or by mRNA degradation. [(10)]

Previous studies demonstrated dysregulation of miRNA expressions in early embryonic tissues and in the fallopian tube of women with EP, including Lin28b, let-7, miR-132, miR-145, miR-149, miR-182, miR-196, miR-223, miR-424, and miR-451 [(11,12,13)]

Circulating miR-323-3p has a high sensitivity for ectopic pregnancy diagnosis, when used as a single marker [(14)] miR-873 could be a valuable noninvasive and stable biomarker for the early detection of EP [(15)]

DISCUSSION

Early diagnosis of ectopic pregnancy is essential, because ruptured ectopic pregnancy in a hemodynamically unstable patient requires urgent or emergent surgical intervention.

Laboratory investigations in ectopic pregnancy with negative serum B-hCG level virtually exclude the possibility of live pregnancy.

Serum B-hCG is secreted by the placenta and can be detected in the blood stream about 9 days after conception or approximately 3 weeks after last menstrual period (LMP). A gestational sac should be visible on trans-vaginal sonography if the serum B-hCG level is 1800-2000 mIU/ml. In normal healthy pregnancies, the B-hCG level should double about every two days, if no intrauterine pregnancy is detected, knowledge of the B-hCG level is crucial. A B-hCG level of <2000 mIU/ml (IRP) suggests three diagnostic possibilities, including early intrauterine pregnancy, ectopic pregnancy, or abnormal intrauterine pregnancy, such as spontaneous abortion. Work-up reveals no abnormality at both adnexa, the patient should be followed-up with a repeat ultrasound in 5 to 7 days with serial monitoring of B-hCG levels. If follow-up scans show abnormality in the adnexal region, ectopic pregnancy should be considered. If the B-hCG level is >2000 mIU/ml (IRP), the intrauterine gestational sac should be identified. [(16)]

The discriminatory zone indicates the value of serum B-hCG above which an intrauterine gestational sac should be visible on ultrasound.

Most services consider a discriminatory zone between 1,500 and 2,000/2,500 mIU/mL of B-hCG while using TVUS. [(17)] When the B-hCG value is above the discriminatory zone and no intrauterine gestation is visible on TVUS, an EP should be suspected; however, it is possible to have a viable intrauterine pregnancy, even if the ultrasound does not show an IUP, and the B-hCG value is above the discriminatory zone.

Several studies have documented the appearance of embryos with cardiac activity in the follow-up of pregnancies where the gestational sac was not visible on TVUS with B-hCG values above 2,000 mIU/Ml. [(18)]

Serum P doses are useful in cases of PUL (pregnancy of unknown location) to identify patients with PULF (pregnancy of unknown location failure) and thereby minimize the examinations and days of follow-up because they are considered low risk, regardless of the location of the pregnancy. P<10 nmol/L was found a

positive predictive value for Pregnancy failure of 98.2%. [19]

Concentration of serum miR-323-3p was higher, in women with EP. Among these miRNAs, circulating miR-323-3p has the highest sensitivity when used as a single marker. Furthermore, the combined B-hCG, progesterone, and miR-323-3p show even higher sensitivity and specificity when compared to each use alone, suggesting that miR-323-3p might be a useful biomarker to improve the diagnosis of EP. [20]

As a single marker, miR-873 has a high sensitivity at 61.76 % (at a fixed specificity of 90%), suggesting its potential as a biomarker for the early detection of EP. [15]

Ultrasonography is the best examination method for identifying the location of an early pregnancy. TVUS identified the location of the pregnancy in 91.3% of pregnant women. Of these women, 89.6% were diagnosed with intrauterine pregnancies (IUPs), 1.7% were diagnosed with ectopic pregnancies (EPs), and 8.7% were diagnosed with PUL. [21]

One great concern of PULs is that they are cases of ectopic pregnancy whose diagnosis might be postponed. TVUS is able to identify an EP with a sensitivity ranging from 87% to 94% and a specificity ranging from 94% to 99% when multiple exams are performed.

With a single examination, TVUS identifies EPs with 73.9% sensitivity and 98.3% specificity. [22]

Regarding PULs, a common mistake is to perform TVUS alone. The adnexa might be located in a higher region, and only a pelvic abdominal ultrasound enables visualization and identification via a suggestive image to diagnose EP. [23]

In addition to the aforementioned limitation of operator dependence, ultrasound is also limited by bowel gas interference, obesity or large body habitus, and small field of view. Another important limitation relative to diagnosis of ectopic pregnancy is ultrasound's inability to differentiate hemorrhage from other fluids.

As such, MRI plays an important role in the early diagnosis and management of ectopic pregnancy.

MRI is now increasingly being used in complicated cases, in cases with unusually located ectopic pregnancy,

On MR imaging, the features of tubal pregnancy include:

- Sac-like cystic tubal lesion with a thick wall [24] that is located within the fallopian tube. The wall shows high signal intensity on T2-weighted MR images, and hemorrhage adjacent to the wall is frequently observed
- Hemato-salpinx with tubal dilatation occurs after implantation of the embryo into the epithelium of the fallopian tube. This process can lead to bleeding and subsequent hemato-salpinx. [25] It typically demonstrates as dilated fallopian tube with high signal intensity fluid on T1-weighted MR images.
- Hemorrhagic complex adnexal mass that is separate from the ovary when non-contrast images are equivocal, post-contrast images may be helpful.

Findings on post-gadolinium administration images include tree-like solid enhancement that represents feto-placental tissue within complex adnexal mass, peripheral enhancement of gestational cystic mass that corresponds with the sonographic tubal ring sign, and tubal wall enhancement that is thought to reflect increased vascularity in the tubal wall. Post-gadolinium images may facilitate more accurate detection of ruptured tubal pregnancy.

Although no specific MRI findings relating to tubal rupture have been fully described, disruption of tubal wall enhancement may be seen in ruptured tubal pregnancy, and the demonstration of acute or recent hematoma showing distinct low signal intensity on T2 weighted images located outside the enhancing implantation site may suggest tubal rupture in symptomatic patients. [26]

Interstitial pregnancy occurs when the embryonic tissue implants in the

intramural or interstitial portion of the fallopian tube, which is eccentrically located in the fundal region of the uterus. This location allows for painless growth, and the increased distensibility of this region facilitates a gestation period that can last as long as 16 weeks.

Given the proximity of this type of pregnancy to the uterine artery, rupture can cause life-threatening uncontrolled massive intraperitoneal bleeding. Early diagnosis of interstitial pregnancy is sometimes difficult to make on ultrasound since it can be misinterpreted as normal intrauterine pregnancy with eccentric location. [(27)]

Angular pregnancy refers to implantation of the embryo in the endometrium of the lateral edge of the uterus, medial to the utero-tubal junction. Angular pregnancy can be confused with both normal pregnancy and interstitial pregnancy.

Distinction between angular pregnancy and interstitial pregnancy can be difficult, but it is important because angular pregnancy can be carried to term. Angular and interstitial pregnancies may both appear as a heterogeneous mass of gestational sac with intermediate to high signal intensity on T2-weighted imaging and surrounded by myometrium.

However, if there is an intact junctional zone between the mass and endometrium, and the mass is lateral to the round ligament, then these findings are suggestive of an interstitial pregnancy. [(28)]

Incidence of cervical pregnancy is less than 1% of all ectopic pregnancies. Diagnosis can be made when the gestational sac is discovered within the cervix. MRI is helpful for making a diagnosis. MRI findings include, a heterogeneous mixed signal intensity lobulated mass that represents the gestational sac occupying the cervix, enlarged cervical canal, and normal endometrial stripe.

A cervical pregnancy may result in an hourglass-shaped or figure eight-shaped uterus that is formed by a distended uterine fundus at one end and the cervical canal at the other. [(29)]

Ovarian pregnancy is a rare form of ectopic pregnancy, being found in only 3% of all ectopic pregnancies. A gestational sac-like structure within the ovary that frequently contains acute hemorrhage with obvious low signal intensity on T2-weighted image and normal fallopian tubes are the suggestive imaging features of ovarian pregnancy on MRI [(8)]

Cesarean scar pregnancy, MRI, however, is able to demonstrate gestational sac localization and its relationship with adjacent organs, and it can assess for myometrial invasion and bladder involvement.

A key MRI finding is the absence or thinning of myometrium between the bladder wall and the gestational sac on T2-weighted imaging. Other imaging findings to support a diagnosis of cesarean scar pregnancy are an empty uterus and cervical canal, and gestational sac formation in the anterior part of the lower uterine segment. [(30)]

Abdominal pregnancy is categorized into primary and secondary types. Primary abdominal pregnancy is defined as pregnancy in which the embryo is directly implanted in the peritoneal cavity, and this type is extremely rare. Secondary abdominal pregnancy, the more common type of abdominal pregnancy, is defined as tubal pregnancy that ruptured and that then re-implanted in the abdomen. Blood supply can be recruited from the omentum and abdominal organs. Early abdominal pregnancy may mimic tubal pregnancy if located in the pelvic cavity. MRI may be helpful to establish diagnosis.

On MR imaging, a gestational sac associated with hematoma may be detected in the pouch of Douglas. There is an observable lack of myometrium surrounding the gestational sac.

MRI is better than sonography for clarifying anatomic relationship with surrounding structures, vascular supply, oligohydramnios, placental site, and unusual

fetal lie, and this can assist in preoperative planning and prediction of possible complications during surgical treatment. [(31)]

The benefits of MRI in abdominal pregnancy also include detection of unusual shape of gestational sac, location of implantation site, and presence of flattened placenta. MRI also provides details about potential vascular connections and placental adherence to surrounding structures. A rounded gestational sac and crescentic placenta are more likely to be observed in intrauterine and tubal pregnancy. Abdominal pregnancy can present at advanced gestational age, up to and including full term. Associated complications include massive hemorrhage, disseminated intravascular coagulation, gut obstruction, and fistula formation caused by fetal bones protruding through the thin amniotic sac. [(32)]

All guidelines for pregnancy of unknown origin recommended conservative period 7-14 days, with repeated B-hCG levels and TVS examinations.

RCOG GUIDELINES

Women with a pregnancy of unknown location could have an ectopic pregnancy until the location is determined. Do not use serum B-hCG measurements to determine the location of the pregnancy, and place more importance on clinical symptoms than on serum B-hCG results, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments. Use serum B-hCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management, and take 2 serum B-hCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management of a pregnancy of unknown location.

Regardless of serum B-hCG levels, give women with a pregnancy of unknown location written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care 24 hours a day. Advise women to return if there are new symptoms or if existing symptoms worsen, and for a woman with an increase in serum B-hCG levels greater than 63% after 48 hours, inform her that she is likely to have a developing intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded) and offer her a transvaginal ultrasound scan to determine the location of the pregnancy between 7 and 14 days later. Consider an earlier scan for women with a serum B-hCG level greater than or equal to 1500 IU/litre. [(33)]

ACOG recommendations

Here may be a role for expectant management of ectopic pregnancy in T specific circumstances. Candidates for successful expectant management of ectopic pregnancy should be asymptomatic; should have objective evidence of resolution (generally, manifested by a plateau or decrease in hCG levels); and must be counseled and willing to accept the potential risks, which include tubal rupture, hemorrhage, and emergency surgery. If the initial hCG level is less than 200 mIU/mL, 88% of patients will experience spontaneous resolution; lower spontaneous resolution rates can be anticipated with higher hCG levels [(34)]

Irish guidelines recommendations

Extended observation of women who have an uncertain prognosis in early pregnancy has shown that many EPs resolve spontaneously. Expectant management is an option in selected women with probable EP provided they have minimal symptoms and are compliant with follow-up. In the presence of a non homogenous adnexal mass, it has been shown that expectant management may have a success rate of over 80% provided that the initial B-hCG is less than 1,000 IU/L and falling by at least 13% over 48 hours.

Continuing outpatient observation is appropriate if the woman is clinically stable. She should be given written information explaining her condition and the possible complications of EP. She should understand

the importance of compliance with follow-up and have easy 24 hour access to emergency hospital gynecological care. Women managed expectantly should be followed at least weekly with serial B-hCG measurements and TVS Considering the potentially serious risks of tubal rupture and hemorrhage and the established safety and effectiveness of medical and surgical treatment of EP, it seems prudent that expectant management should be reserved for asymptomatic patients with very low and falling B-hCG levels. Any plateau or rise in the B-hCG measurements should prompt medical or surgical treatment. [(35)]

CONCLUSION

As a supplementary imaging modality to ultrasound, MRI can provide information that improves physician ability to diagnose ectopic pregnancy. MRI also plays an important role in identifying the implantation site in tubal and non-tubal ectopic pregnancy (with or without rupture) and in differentiating ectopic pregnancy from other diseases. miR-323-3p and miR-873 are potential markers for early ectopic pregnancy diagnosis, adding MRI, miR-323-3p and miR-873 to early ectopic pregnancy diagnosis guidelines will decrease maternal morbidity and mortality.

It is time to update guidelines, changing our practice, using combined diagnostic modalities, including MRI and new biomarkers, improving our management and prognosis.

Conflict of interest

All authors declare no conflicts of interest.

Authors' contribution

Authors have equally participated and shared every item of the work.

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