

# Role of MRI and biomarkers; in early ectopic pregnancy diagnosis

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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.

**Keywords:** (Ectopic pregnancy, MRI, Ultrasonography, Biomarkers, B- hcg, Progesterone).

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## 1. INTRODUCTION

### Background;

Implantation of the zygote outside the uterine cavity has increased from 0.5% in 1970 to 2% of all pregnancies 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 2 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, with the hormonal interference effects that estrogen and progesterone show on the growth and the motility of the epithelial ciliae, estrogen stimulates the growth and differentiation of the fallopian tube including the generation of the epithelial ciliae .

### 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, hCG starts with secretion on days 5 to 8. A serum assay 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 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, and an abnormal 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 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, and the most specific sonographic feature of ectopic pregnancy is the presence of an extrauterine 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, which requires no specific patient preparation or premedication, and other advantages of MRI include no ionizing radiation, multiplanar 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).

However, gadolinium contrast media imaging is sometimes performed in pregnant patients when neither the prescribing physician nor the patient have any clue or suspicion of the patient's pregnancy. Gadolinium injection may help to identify the precise implantation site of the gestational sac, even in the presence of hematosalpinx or hemoperitoneum, Subtraction image maybe helpful in this setting (9)

. Of note, if a viable intrauterine pregnancy has not been conclusively ruled out, administration of gadolinium should not be performed.

However, the role of MRI may be restricted in hemodynamically unstable patients, particularly in cases with ruptured ectopic pregnancy. MRI scan time is prohibitively lengthy, and these cases most often require urgent surgical management.

### MicroRNAs

MicroRNAs (miRNAs) are short, single-stranded RNA (19–25 nucleotide long) nonprotein 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)

## 2. 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;

A negative serum beta hCG level virtually excludes the possibility of live pregnancy, which 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 transvaginal sonography if the serum beta hCG level is 1800-2000 mIU/ml.

In normal healthy pregnancies, the beta hCG level should double about every two days, if no intrauterine pregnancy is detected, knowledge of the beta HCG level is crucial. A beta 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 beta HCG levels. If follow-up scans show abnormality in the adnexal region, ectopic pregnancy should be considered. If the beta HCG level is >2000 mIU/ml (IRP), the intrauterine gestational sac should be identified. (16)

The discriminatory zone indicates the value of serum hCG above which an intrauterine gestational sac should be visible on ultrasound, and most services consider a discriminatory zone between 1,500 and 2,000/2,500 mIU/mL of hCG while using TVUS (17).

When the 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 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 hCG values above 2,000 mIU/mL (18)

Serum Plevel are useful in cases of PUL(pregnancy of unown location) to identify patients with PULF(pregnancy of unown 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 faisure of 98.2% (19).

Concentration of serum miR-323-3p was higher, in women with EP, and among these miRNAs, circulating miR-323-3p has the highest sensitivity when used as a single marker, furthermore, the combined 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 (21)

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 (22).

One great concern of PULs is that they are cases of ectopic pregnancy whose diagnosis might be postponed, and 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 (23).

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 (24).

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, and 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 that is located within the fallopian tube(25) .

The wall shows high signal intensity on T2-weighted MR images, and hemorrhage adjacent to the wall is frequently observed

-Hematosalpinx with tubal dilatation occurs after implantation of the embryo into the epithelium of the fallopian tube. This process can lead to bleeding and subsequent hematosalpinx (26).

It typically demonstrates as dilated fallopian tube with high signal intensity fluid on T1-weighted MR images, with 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 fetoplacental 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 (27)

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, and 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.(28)

Angular pregnancy refers to implantation of the embryo in the endometrium of the lateral edge of the uterus, medial to the uterotubal junction, with angular pregnancy can be confused with both normal pregnancy and interstitial pregnancy, and 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 (29)

Incidence of cervical pregnancy is less than 1% of all ectopic pregnancies, and diagnosis can be made when the gestational sac is discovered within the cervix.

MRI is helpful for making 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 (30).

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, while 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 (31).

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 reimplanted 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(32).

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 (33).

### 3. 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 nontubal 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.

#### 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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