Ectopic pregnancy: spectrum of radiological findings from beginning to end

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Learning objectives

Learning objectives:

- Look over the pathophysiology and risk factors of ectopic pregnancy.
- Review clinical findings and radiological manifestations of ectopic pregnancy with special emphasis on US.
- Revise treatment, from surgery to expectant management.
- Illustrate the appearance of complications after treatment.
Background

Introduction:

Ectopic pregnancy (EP) occurs when a blastocyst abnormally implants outside the endometrium of the uterus. In EP, the gestation grows and draws its blood supply from the site of abnormal implantation. As the gestation enlarges, it creates the potential for organ rupture. Only the uterine cavity is designed to expand and accommodate fetal development. Without timely diagnosis and treatment, ectopic pregnancy can become a life-threatening situation with massive hemorrhage, or death. It remains the leading cause of maternal death in the first trimester of pregnancy and accounts for 9% of all pregnancy related deaths. The incidence of EP is increasing and affects about 2% of all pregnancies.

Risk factors:

Multiple factors contribute to the relative risk of ectopic pregnancy. Anything that hinders or delays the migration of the fertilized ovum to the endometrial cavity can predispose to EP. The following risk factors have been related Fig. 1 on page 6. Most patients presenting with an ectopic pregnancy have no identifiable risk factor.

Implantation sites:

Most ectopic pregnancies are located in the fallopian tube, approximately 98% Fig. 2 on page 6. Of tubal pregnancies, the ampulla is the most common site of implantation (80%), followed by the isthmus (12%), fimbria (5%), and interstitial (2-3%). Nontubal ectopic pregnancies are a rare occurrence, with abdominal pregnancies accounting for 1.4%, and ovarian and cervical sites accounting for 0.2% each. Some ectopic pregnancies implant in the cervix, in previous cesarean delivery scars, or in a rudimentary uterine horn (corneal pregnancies) although these may be technically in the uterus, they are not considered normal intrauterine pregnancies.

Diagnosis:

1-History:

Pregnancy status:

- Known pregnancy: The classic clinical triad of ectopic pregnancy is: first trimester bleeding, abdominal pain and amenorrhea, but only 50% of patients present with all 3
symptoms. These symptoms may also occur in intrauterine pregnancy and spontaneous abortion.

- **Unknown pregnancy:** Any woman of child-bearing age who presents with abdominal pain or abnormal vaginal bleeding should be evaluated for pregnancy as part of the initial examination. It is important to take into account that patient may present with abdominal pain without knowledge of pregnancy status.

2-**Physical examination:**

Physical examination should be used to detect peritoneal signs that may indicate hemoperitoneum. The presence of: abdominal rigidity, involuntary guarding, severe tenderness, or evidence of hypovolemic shock suggests a surgical emergency. Inspection of cervical os for bleeding and evidence of product of conception helps differentiate spontaneous abortion from EP.

3- **-hCG levels:**

Human chorionic gonadotropin is a glycoprotein hormone that contains both an alpha and a beta subunit. The beta subunit begins to ascend early in pregnancy and continues until it reaches a plateau at approximately 9-11 weeks. The plateau lasts for a few days and then starts to decline at 20 weeks. Standardized methods for measuring -hCG levels have been established. The clinician should be aware of the standard used at their institution. In this review international reference preparation (IRP) will be employed.

**Urine:**

Positive urine pregnancy test is present in 95% of cases. ELISA is sensitive to 10-50 mIU/ml of -hCG and can be detected on day 24 after the last menstrual period (LMP).

**Serum:**

Serum detection is more sensitive for assessment of pregnancy than urine detection. It becomes positive 23 days after LMP, before the first missed period.

The **discriminatory level of -hCG:** the level above which an imaging scan should reliably visualize a gestational sac within the uterus in a normal intrauterine pregnancy is:

- 2000 mIU/mL for transvaginal ultrasonography
- 6000-6500 mIU/mL for abdominal ultrasonography.

These values should be used as guidelines and not absolute threshold. In case of multiple gestates the discriminatory level can be higher, up to 2300 mIU/mL. It also depends on
equipment, sonographer experience and patient characteristics such as body habitus, abdominal bleeding and presence of fibroids. In general as the level increases the specificity of sonography also increases.

**Serial levels of #hCG:** no single serum #hCG level is diagnostic of an ectopic pregnancy. Serial serum #hCG levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated. Serial measurements can be used to evaluate pregnancy of unknown location. In 99% of normal intrauterine pregnancies (IUP), the #hCG level doubles every 48-72 hours. Failure to increase at this rate suggests ectopic pregnancy or nonviable intrauterine pregnancy. Likewise 1% of IUP may not increase at this rate and 20% of EP may increase by more than 50% over 48 hours. This uncertainty highlights the need to consider all available data and if the patient is stable perform follow up evaluation with both #hCG testing and sonography to determine the location of a pregnancy of unknown location.

**4-Blood type and Rh status:**

They should be determined in case transfusion needed, in order to prevent from Rh alloimmunization
Ectopic Pregnancy Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>Tubal damage from previous infection</td>
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<tr>
<td>Salpingitis isthmica nodosum</td>
<td>Multiple sexual partners</td>
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<tr>
<td>Diethylstilbestrol exposure</td>
<td>Maternal age highest rate in women aged 35-44 years.</td>
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<td>History of previous ectopic pregnancy</td>
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<td>Smoking</td>
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**Fig. 1**

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**ECTOPIC PREGNANCY LOCATIONS**

- Interstitial 2-3%
- Isthmus 12%
- Ampulla 80%
- Ovarian 0.2%
- Fimbria 5%
- Cervical 0.2%
- Abdominal 0.2%

**Fig. 2**

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Findings and procedure details

Imaging

Ultrasonography

When an abnormal pregnancy is suspected pelvic ultrasound should be done to determine the location of the pregnancy. The sonogram should be performed both transabdominally and transvaginally the former to assess for a mass or fluid high in the pelvis and the latter to obtain a detailed view of the uterus and adnexa. Transvaginal US (TVUS) is the preferred method to assess an early IUP as it can detect pregnancy about 1 week earlier than transabdominal US. Cases have been reported of EP detected transabdominally that were missed with vaginal scan. The goal of US is to demonstrate an intrauterine pregnancy be normal or abnormal.

Normal sonographic appearance of first trimester pregnancy:

a- Gestational sac:

During the first 3 weeks after conception the gestational sac (GS) is too small to be detected. Pregnancy is not generally visible on US before a gestational age of 5 weeks.

4.5- 5 weeks: when the GS is first identifiable on TVUS it appears as a round or oval intrauterine fluid collection 2-3mm diameter:

- Excentrically located within the endometrium surrounded by a thin white echogenic ring that has been termed the intradecidual sign. Some authors refer this sign to appear at 4.5 weeks after LMP. The echogenic ring is important to be differentiated from decidual cysts that can be seen in normal IUP and EP.
- Located in the central echogenic portion of the uterus and surrounded by 2 concentric echogenic rings that has been termed the double sac sign or doubledecidual sign.
- It can appear as a small featureless saclike with either of these signs. As a decidual cyst can be mistaken for a very early pregnancy the prudent option is to follow up symptomatic patients.

5.5 weeks: when the GS reaches 6-10 mm the yolk sac is seen within the GS as a small thin walled circular structure.
6 weeks: the embryo is visible in TVUS when the GS reaches 10 mm. It is visible as a small structure at the edge of the yolk sac, measuring 1-2 mm in length and usually demonstrating motion of cardiac activity Fig. 3 on page 13. Embryonic cardiac activity can be detected at 5-6 weeks, when the gestational sac measures more than 18 mm or when the embryonic pole is more than 5 mm.

b- Adnexa:

Corpus luteum cyst is a normal feature of pregnancy. It can have variable sonographic appearance: simple cyst, thick walled cyst, complex cyst or homogeneous solid appearance, at times similar to EP Fig. 4 on page 13. It can show a hypervascular ring, "ring of fire", when color Doppler is employed. To determine if a mass depends from the ovary gentle pressure can be applied to the adnexa. If the mass moves with the ovary it is more likely to be a corpus luteum as ovarian EP is very rare (1%). If the mass moves separately from the ovary it is extraovarian and probably an EP.

**Sonographic findings in abnormal early IUP:**

Spontaneous abortion is common in pregnant women with pain and bleeding. Any substantial deviation from the normal sonographic appearance of first trimester pregnancy should raise concern that the pregnancy has already, or will soon, fail. Current criteria for definitive pregnancy failure on TVUS are:

- No cardiac activity in an embryo whose CRL is 7 mm.
- No embryo in a GS whose mean diameter is 25 mm
- No embryo at least 2 weeks after a scan that detected a GS without a yolk sac.
- No embryo 11 days after a scan demonstrated a GS with a yolk sac.

**Sonographic findings of ectopic pregnancy:**

An adnexal mass that is separated from the ovary and the tubal ring sign are the most common findings of a tubal pregnancy. Although many of US findings are not specific by themselves when several of them are seen the specificity of US improves.

a- Tubal findings: An adnexal mass that is separate from the ovary is the most common finding of tubal pregnancy. The tubal ring sign is the second most common sign Fig. 5 on page 14. It describes a hyperechoic ring surrounding an extraterine GS. It can appear as a tubal ring with a yolk sac and embryo, a tubal ring with a yolk sac only, a tubal ring without central identifying features or a complex adnexal mass separate from the ovary. When a GS is detected it is important to measure it’s larger diameter as it will affect treatment choice. A related sign is the "ring of fire sign" which relates to the hypervasculature of the periphery detected in Doppler US.
b- Ovary: in the adnexa the most common finding is the corpus luteum. About 80% of ectopic pregnancies are found on the same side as the corpus luteum, contralateral implantation occurs in up to one-third of cases.

c- Uterus:

- Decidual cysts are thin walled cysts usually located at the junction of the endometrium and myometrium, they are usually multiple and do not have echogenic rim. They are associated with EP but can also be seen in IUP and nonpregnant patients.
- Intrauterine fluid collection: centrally located within the endometrial cavity that can be very heterogenous due to the presence of blood, generally irregular shaped with pointed edges and filled with debris. When scanning the fluid can be seen to move.

With modern equipment these fluid collections are clearly distinguishable from a GS. When it is unclear no adnexal mass is seen, and the patient is stable it is reasonable to correlate with #-hCG and obtain a follow up sonography.

d- Color Doppler ultrasound: corpus luteum cysts, mature follicles and EP may show hipervascular ring on color Doppler assessment, "ring of fire" Fig. 6 on page 15 . When present it is important to determine whether it is inside or outside the ovary.

e- Abdomen: free fluid accumulates in the cul de sac. If it has a complex appearance with floating echoes it is consistent with hemoperitoneum. It is important to scan up by the kidneys, Morrison pouch, to assess for the amount of hemoperitoneum Fig. 7 on page 16 . If large amount of free fluid is detected US must be performed as fast as possible in order to have the patient treated as soon as possible. In this case differentiating ruptured EP from ruptured corpus luteum cyst will not be necessary as both will require immediate surgery. If no signs of IUP, EP or hemoperitoneum are found other causes of abdominal pain may be searched for.

f-Special location sites:

- Interstitial EP: located in the interstitial portion of the tube partially surrounded by myometrium. They have higher mortality and morbidity because they can have later presentation and massive hemorrhage. The diagnosis is suggested when an IUP is visualized high in the fundus, in a very superolateral location, and is not surrounded in all planes by 5mm of myometrium. Another sign is the interstitial line sign which represents an echogenic line that extends into the upper regions of the uterine horn and borders the margin of the intramural GS.
• **Cornual EP:** although it is used interchangeably with interstitial pregnancy it specifically refers to the implantation within the cornua of a bicornuate or a septate uterus. The gestational sac is surrounded by less than 5 mm of myometrium.

• **Cervical pregnancy:** it centers in the cervix enlarging the endocervical canal. It can be differentiated from an abortion in progress as a miscarriage will show a flattened and irregular sac and absence of cardiac activity.

• **Scar ectopic pregnancy:** most common in the site of prior cesarean scar. It can be diagnosed when the GS develops in the anterior part of the lower uterine segment and no myometrium is seen between the bladder wall and the GS.

• **Heterotopic pregnancies:** The incidence of heterotopic pregnancy is very low. (1 in 4000 conceptions) but is much higher after assisted reproduction treatments (1-3%). Particular care should be taken in these patients even if IUP is documented.

• **Intrabdominal pregnancy:** implantation occurs within the abdominal cavity. It is very rare and more common after assisted reproduction. Maternal mortality higher than in other EP.

**CT and MR**

Although CT and MR are not commonly used in the imaging of patients with positive hCG test, this pathology may occasionally be imaged by these modalities. EP should be considered when hemoperitoneum or a pelvic mass is seen in a woman of childbearing age.

CT is usually performed in the evaluation of abdominal or pelvic pain of unknown cause. CT findings are not well recognized because pregnant woman generally should not undergo abdominal or pelvic CT, particularly for a condition that can be diagnosed by other techniques. If pregnant status is unknown and the patient is not adequately screened CT may be inadvertently performed Fig. 8 on page 17.

In stable patients MR can serve as a problem solving tool. It should be reserved for situations in which patients are stable and for whom additional information is needed to guide patient care decisions Fig. 9 on page 18.

Sonographic findings have MR or CT correlates; cystic structure surrounded by a thick wall, hemoperitoneum, hematosalpinx, heterogeneous mass, tubal dilatation and wall enhancement can be found.

**Differential diagnosis:**

Numerous conditions may have a presentation similar to an extrauterine pregnancy. The most common of these include the following:

• **Appendicitis** Fig. 10 on page 19
• Salpingitis
• Ruptured corpus luteum cyst or ovarian follicle
• Spontaneous abortion or threatened abortion
• Ovarian torsion
• Urinary tract disease
• Intrauterine pregnancies with other abdominal or pelvic problems.

Treatment and management

After all the diagnostic process three scenarios can be expected:

• Intrauterine pregnancy: visualizing sonographic findings of normal or abnormal early IUP dramatically reduces the likelihood of EP. It is still important to perform a careful investigation of the adnexa since heterotopic pregnancies can occur. Absence of an intrauterine gestational sac should trigger a detailed search for an EP.
• Ectopic pregnancy: when ultrasound visualizes a gestational sac or embryonic pole in ectopic location treatment of EP should be initiated.
• Pregnancy of unknown location: the diagnostic challenge is when US does not determine a pregnancy as intrauterine (either viable or not viable) or ectopic. The approach to this situation requires a balance of benefits and risks. Early treatment reduces morbidity from a ruptured ectopic pregnancy but risks overtreating an evolving spontaneous abortion or interrupting a viable pregnancy. Conversely longer periods of observation, with serial #-hCG and US, improve the ability to determine location but may increase morbidity from a later diagnosis of EP.

Therapeutic options in ectopic pregnancy will depend on: patient stability, GS size, presence of cardiac activity, presence of hemoperitoneum and patient preference.

Expectant management:

Many small EP that previously went underdiagnosed are known to resolve spontaneously. Candidates for successful expectant management should be: asymptomatic or stable patients, with low or declining levels of #-hCG and a mass less than 4 cm. Close follow-up and patient agreement are of paramount importance Fig. 11 on page 20.

Medical treatment with methotrexate:

Methotrexate is a folic acid antagonist that inhibits DNA synthesis and cell replication. It is the standard medical treatment for unruptured ectopic pregnancy. A single IM dose injection is the more popular regimen. Dose can be repeated on day 7 if #-hCG values
do not decline appropriately (at least 15% from day 4). The ideal candidate should have the following: hemodynamic stability, no severe or persisting abdominal pain, the ability to follow up multiple times, normal baseline liver and renal function test results. Best treatment responses have been described if GS is less than 3.5cm, no embryonic cardiac activity and hCG level less than 2000-4000 mIU/mL.

Absolute contraindications to methotrexate therapy include: existence of an intrauterine pregnancy, immunodeficiency, moderate to severe anemia, leukopenia, or thrombocytopenia, sensitivity to methotrexate, active pulmonary or peptic ulcer disease, clinically important hepatic or renal dysfunction, breastfeeding, evidence of tubal rupture.

Patients may present some adverse effects such as gastrointestinal symptoms, neutropenia, alopecia and pneumonitis. Lower abdominal pain may occur several days after treatment due to tubal abortion or hematoma formation.

Sonography of patients after methotrexate treatment is difficult. Most patients show worsening appearance due to increased hemorrhage around the EP. An initial increase in size may be visible up to three months after treatment. Sonography is indicated if rupture is suspected, failure of hCG levels to decline, or increasing of plateauing after the first week of treatment. To evaluate adequate evolution sometimes performing MR is needed Fig. 12 on page 20.

**Sonographically guided treatment:**

Potassium chloride or methotrexate are most commonly used. It is the treatment of choice for unusual locations: cervical, interstitial, scar or heterotopic pregnancies.

**Surgical treatment:**

For patients who are medically unstable or experiencing life-threatening hemorrhage immediate surgical treatment is indicated. Surgical options include salpingectomy or salpingostomy performed by laparoscopy or laparotomy Fig. 13 on page 21 Fig. 14 on page 24. Surgery is being performed less often since alternative treatments are more available. It is indicated when positive cardiac activity, mass of more than 4 cm, desires sterilization and hemodynamically unstable patients. Some early and late complications after surgery may occur such as abscess formation or late hydrosalpinx Fig. 15 on page 22 Fig. 16 on page 23.
Images for this section:

Fig. 3

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Young female in the 7th week of gestational age with descending levels of βHCG. Ultrasound image of the pelvis shows a cystic lesion in the right ovary with heterogeneous internal echoes and a cobweb appearance that corresponds to the corpus luteum.

Fig. 4

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Young 28 year old female presented at the emergency room with vaginal bleeding and hypovolemic shock. A portable US was performed. Image shows extraterine gestational sac with embryonic pole (cursor) surrounded by a thick echogenic ring "ring sign" (arrow). Tubal pregnancy was found at surgery.

Fig. 5

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Fig. 6

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Young woman with abdominal pain. Transabdominal US shows a cystic lesion in the left ovary with a thin septum. Doppler color depicts peripheral increase of vascularization. Patient also had free fluid (not shown). A ruptured ovarian follicular cyst was diagnosed.
Fig. 7

Young woman 7 weeks pregnancy. Presents at the ER for abdominal pain, hypotension and vaginal bleeding. Fast abdominal US was performed: an important amount of free fluid located in the pouch of Morrison is detected with echogenic content suspicious of hemoperitoneum. No other sonographic findings. Patient underwent surgery and a salpingostomy for a ruptured ectopic pregnancy was performed.

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30 year old patient presented at ER with abdominal pain and vomiting, pregnancy was not suspected. Transabdominal US was performed (a and b), a left adnexal heterogeneous mass and free fluid with echogenic content were observed (arrows). An abdomino-pelvic CT was performed (c and d): left adnexal mass and free fluid with high attenuation values suspicious of hemoperitoneum were observed. Pregnancy test was then obtained with a positive result. Urgent laparoscopic salpingectomy for a ruptured ectopic pregnancy was performed.

Fig. 8

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41 year old woman 12 week pregnancy that starts with abdominal pain. After US a cornuate pregnancy is suspected. MR is performed for better delineation of anatomy. Coronal and sagital T2 WI are shown. Adnexal mass is seen with a fetus inside (arrow). After MR the patient underwent laparoscopic salpinguectomy and a tubal pregnancy was demonstrated.

Fig. 9

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Pregnant patient, 12 weeks, starts with abdominal pain, fever and leukocytosis. Abdominal US shows normal intrauterine pregnancy and inflammatory changes in the appendix consistent of appendicitis. Appendectomy was performed and the patient evolved adequately.
Fig. 10

25 year old woman with recent gestation (3-5 weeks) and abdominal pain. Transabdominal US was performed: free fluid in the abdomen and pelvis (asterisk) and a complex right adnexal mass (arrows) were detected. β-hCG levels were low, 750 mIU/mL. The patient was stable and expectant management was decided. β-hCG levels 24 hours later were lower, 570 mIU/mL. A tubal abortion was diagnosed and the patient evolved adequately.

Fig. 11

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Pelvic MR of an ectopic pregnancy in the uterine isthmus after one month of Methotrexate treatment. The patient had a uterine scar due to a previous cesarean. Sagittal T2weighted image with fat saturation and sagittal T1 weighted image with fat saturation after contrast administration show a nodular heterogeneous mass in the uterine isthmus with heterogeneous enhancement that corresponded to the involuting pregnancy.

**Fig. 12**

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Hysterosalpingography after ectopic pregnancy surgery. The image demonstrates normal left Fallopian tube with contrast passage to the peritoneum. In the right side only the isthmic and proximal segment of the Fallopian tube are opacified due to prior salpingectomy.

Fig. 13

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Two weeks after surgical treatment of a right tubal ectopic pregnancy patient presents at the hospital with fever and abdominal pain. Abdomino-pelvic CT was performed. Right parauterine collection with peripheral enhancement was observed (arrows). A drainage catheter was placed inside the collection. Surgery was not needed.

**Fig. 15**

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Patient in study for infertility. 12 years before she had underwent left salpingostomy for an ectopic pregnancy. Histerosalpingography shows dilatation of the ampullary portion of the left fallopian tube (arrow) a finding consistent with hydrosalpinx. No contrast material spillage is seen on the left side. Right fallopian tube of normal size and permeable.

Fig. 16

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Uterine malformation. 2 years before patient underwent surgery for an ectopic pregnancy in the left hemiuterus. Histerosalpingography was performed as study for infertility. It depicts right hemiuterus with patent fallopian tube and extravasation of contrast to the abdominal cavity. Left hemiuterus and fallopian tube not visible were resected in prior surgery.

Fig. 14

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Conclusion

Conclusions:

• Ectopic pregnancy is an urgent pathology that without appropriate diagnosis and treatment can become a life-threatening situation. Radiologists should always consider ectopic pregnancy in the setting of hemoperitoneum or a pelvic mass in a woman of childbearing age and be aware of the different ultrasonographic signs to detect this pathology.
• Clinical data such as prior in vitro fertilization treatments, abdominal or pelvic surgeries, cesarean scar, gestational date and #-hCG levels are very important when evaluating these patients.
• Ultrasound is crucial not only for the diagnosis but also for the management and follow up of patients with EP.
References