



## **Ectopic Pregnancy**

The diagnosis and management of ectopic pregnancy have been revolutionized by early improved ancillary testing and new management advances. The lecturer will review the most recent research associated with the emergency department evaluation and treatment of pregnant women who have a possible ectopic pregnancy.

- List the etiology and common sites of ectopic pregnancy.
- Discuss the current research in the evaluation and management of ectopic pregnancy.
- Discuss the role of bedside emergency department ultrasound in diagnosing an ectopic pregnancy.

TH-240  
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## **FACULTY**

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## **Ectopic Pregnancy**

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### **The Basics**

**Ectopic pregnancy:** A pregnancy that occurs elsewhere than in the uterus

**Heterotopic pregnancy:** The coexistence of an intrauterine and ectopic gestation. These are rare with reports ranging from 1 in 3,000 to 1 in 30,000 pregnancies. However, it is much more common in the patient receiving fertility drugs with rates of 1% to 3%. A heterotopic pregnancy is very difficult to establish in the patient using fertility agents.

### **Epidemiology**

- Continues to be common in the United States constituting 2% of all pregnancies
- An estimated 88,400 ectopic pregnancies in 1989
- Occurs in 4-5% of pregnancies in patients undergoing in-vitro fertilization
- Accounts for 9% of all pregnancy related deaths
- The most common cause of maternal death in the 1<sup>st</sup> trimester

### **Pathogenesis and risk factors**

- Ectopic pregnancy commonly occurs in women with impaired tubal function from any cause
- Risk factors
  - Tubal surgery: ligation or other surgery
  - Tubal scarring from endometriosis
  - Pelvic infections: PID, gonorrhea, chlamydia
  - Previous ectopic pregnancy
    - 10% chance of recurrence of ectopic
    - Only a 50% chance of bearing a live infant in the future with one ectopic pregnancy
  - Use of IUD
  - In-vitro fertilization
  - History of infertility

### **Sites of ectopic pregnancy**

- Fallopian tubes – the majority (97%) of ectopic pregnancies are located here
  - Interstitial portion (1%) – that segment within the wall of the uterus. These types can grow larger than those in the true fallopian tube can because the endometrial tissue is more expandable. These can be misdiagnosed as an IUP due to the partial endometrial implantation and increased size
  - Isthmus (25%)– the narrow nonmobile section lateral to the interstitial portion
  - Ampullary (55%) – the widened portion of the tube
  - Fimbriated (17%)– the area of the tube with the fimbria
- Cervix
- Angular portion of the endometrial cavity
- Ovary
- Peritoneal cavity

## **History and Physical Examination**

***There is no combination of historical and/or physical findings that will confirm or exclude the diagnosis of ectopic pregnancy with a high degree of certainty.***

### **History**

- Classic triad: amenorrhea, abdominal pain, and vaginal bleeding. This is more commonly seen with spontaneous abortion than ectopic pregnancy
- Risk factors
  - **Not helpful to rule out ectopic** because unfortunately, around 45% of ectopic pregnancies occur in women without any risk factors
  - Although, a previous history of ectopic pregnancy, intrauterine device use, and prior pelvic surgery or tubal ligation increase the probability of ectopic pregnancy
- Abdominal or pelvic pain in almost all patients
  - Moderate to severe
  - Sharp
  - Lateral
- Vaginal bleeding and passage of tissue
  - Abnormal bleeding occurs in 50-80% of cases
  - Usually vaginal bleeding does not occur until the corpus luteal influence on the endometrium ceases
  - The passage of tissue may represent a spontaneous abortion, but a *decidual cast* of ectopic pregnancy may be mistaken for fetal tissue
  - The amount of vaginal bleeding, a history of passing tissue are not predictive of ectopic pregnancy

### **Physical Exam**

- Neither tachycardia or hypotension are predictive of ectopic pregnancy
- The presence of peritoneal signs, although not commonly present, is predictive of ectopic pregnancy
- Cervical motion tenderness, and lateral or bilateral abdominal tenderness are also predictive of ectopic pregnancy
- The presence of a unilateral adnexal mass is more commonly seen in normal IUP (corpus luteum cyst)

## **Hormonal Markers in Diagnosing Ectopic Pregnancy**

### **Beta-hCG**

- The trophoblasts begin producing hCG very early in normal and ectopic pregnancy
- The production of  $\beta$ hCG is detectable in the serum as early as one week before an expected menses is missed

### **Urine $\beta$ hCG testing**

- Urine  $\beta$ hCG assays are sensitive down to 20-50mIU/ml
- Various investigators have found urine  $\beta$ hCG tests to be 95-100% sensitive and specific when compared with serum assays
- However, in one study, 1% of ectopic pregnancies manifested with a serum  $\beta$ hCG < 25mIU/ml
  - Assuming a 5% false negative rate at these levels only one ectopic per 2,000 cases would be missed
  - This is within an acceptable failure rate due to the time and cost saved with the urine test, although when in doubt about a negative urine  $\beta$ hCG obtain a serum  $\beta$ hCG

***Thus, urine  $\beta$ hCG tests are acceptable screening alternatives for possible pregnancy***

### Serum $\beta$ hCG testing

- Most serum assays measure down to  $\geq 5$  mIU/ml
- A negative serum  $\beta$ hCG assay can rule out pregnancy in virtually 100% of cases
  - There are rare case reports of ectopic pregnancy with negative serum  $\beta$ hCG levels
  - The cases are much more rare when utilizing the newer, more sensitive tests
- A single quantitative serum  $\beta$ hCG level is not sufficient to rule in or rule out ectopic pregnancy or to determine whether an ectopic has ruptured
  - Ruptured and unruptured ectopics are seen at  $\beta$ hCG levels  $< 100$  and  $> 50,000$  mIU/ml
  - In one series 10% of ectopic pregnancies with  $\beta$ hCG levels  $< 100$  mIU/ml were ruptured
  - In this same series, **7% of all ruptures** occurred at  $\beta$ hCG  $< 100$  mIU/ml

### Serial Serum $\beta$ hCG testing

- Normal  $\beta$ hCG dynamics
  - 50-100 mIU/ml at 4 weeks from last menstrual period
  - Doubling time of 1.9  $\pm$  0.5 days when  $< 10,000$  mIU/ml
  - Reaches a maximum of 100,000 mIU/ml at 12 weeks gestation
- **Normal dynamics:  $\geq 66\%$  rise in  $\beta$ hCG over 48 hours**
  - In 85% of normal IUPs
  - May occur in early asymptomatic ectopic pregnancy
- **Abnormal dynamics:  $< 66\%$  rise in  $\beta$ hCG over 48 hours**
  - May occur in 15% of normal IUPs
  - Suggests an abnormal gestation – 75% sensitive and 93% specific in one study (for abnormal gestation of any cause)
  - 85% of ectopic patients did ultimately manifest abnormal  $\beta$ hCG dynamics  $\rightarrow$  this is less reliable in symptomatic patients
  - Nonviable IUP – blighted ovum, impending abortion
- **Declining  $\beta$ hCG values**
  - Indicates nonviability
    - $\rightarrow$  Complete abortion
    - $\rightarrow$  Tubal regression/abortion
  - These declining levels are useful to monitor success of therapy

*The best way to employ serial  $\beta$ hCG testing is in conjunction with ultrasonography in the follow-up of those patients with suspected abnormal pregnancy or possible ectopic pregnancy with a negative initial evaluation*

### Progesterone

- Serum progesterone levels are produced by the corpus luteum in response to a *viable* pregnancy
- As opposed to  $\beta$ hCG levels, the serum progesterone levels remain **stable** over the first 8 to 10 weeks with very little change, except as a pregnancy fails
- Several studies have demonstrated a low serum progesterone level in abnormal pregnancy  $\rightarrow$  without distinction of spontaneous abortion or ectopic pregnancy
- The difficulty in utilizing this measurement is the lack of a clearly defined level at which a pregnancy is either normal or definitely abnormal

### Application of serum progesterone measurement

- A single level of  $\geq 25$  ng/ml **excludes** ectopic pregnancy with 97.5% sensitivity
- A single level of  $\leq 5$  ng/ml
  - This identifies a nonviable pregnancy with 100% sensitivity
  - The pregnancy may be either ectopic or due to some other nonviable etiology
  - This will allow a diagnostic uterine evacuation to be performed when ectopic pregnancy can not be otherwise distinguished from spontaneous abortion
- A level of between 5 and 25 ng/ml is not helpful and pregnancy viability must be established by other methods  $\rightarrow$  Unfortunately, a lot of patients will fall into this gray zone

### **Creatine kinase**

- The thought was that the CK would be elevated due to the erosion of the ectopic into the muscular layer of the fallopian tube
- Numerous studies failed to demonstrate utility of CK as a useful marker of ectopic due to a high degree of overlap between normal and ectopic pregnancies
- **NOT USEFUL**

## **Ultrasonography in Early Pregnancy**

### **Ultrasound Findings by $\beta$ hCG level and dates**

- $\beta$ hCG > 1000 mIU/ml → Gestational sac
- $\beta$ hCG ~ 2500 mIU/ml (6 weeks from LMP) → yolk sac
- $\beta$ hCG ~ 5000 mIU/ml (7 weeks from LMP) → fetal pole
- $\beta$ hCG ~ 17,000 mIU/ml → fetal heart beat

*Ultrasound findings diagnostic of a normal intrauterine pregnancy (IUP) are only rarely identified when the  $\beta$ hCG value is less than 1,000 IU/ml however...*

**13% of abnormal IUPs and 39% of ectopic pregnancies with  $\beta$ hCG values less than 1,000 mIU/ml can be identified at ultrasonography**

**Clinicians should not defer the ultrasound based upon the quantitative level**

### **Ultrasound diagnosis of ectopic pregnancy**

- **The diagnosis of ectopic pregnancy is made based on a serum  $\beta$ hCG level of  $\geq 1,500$  mIU/ml and an *empty uterus* on sonography**
  - This is 100% accurate for diagnosing ectopic pregnancy
  - Some studies used a cutoff of 1,300 mIU/ml
- Visualization of an adnexal mass in addition to a  $\beta$ hCG level of  $\geq 1,000$  mIU/ml is considered an ectopic pregnancy (97% sensitivity, 99% specificity, 98% positive predictive value)
- Ultrasound findings consistent with an ectopic pregnancy
  - Tubal ring
  - Cystic or complex adnexal mass
  - Cul-de-sac fluid
  - Observation of extrauterine fetal cardiac activity
- 20% of confirmed ectopics will have normal pelvic sonograms

### **Combination of sonography with $\beta$ hCG**

- $\beta$ hCG level of  $\geq 1,500$  mIU/ml is considered the discriminatory zone, although some studies use a lower level
- Non-diagnostic ultrasound when the  $\beta$ hCG level is below the discriminatory zone
  - Truly nondiagnostic
    - This may be an early normal pregnancy
    - This may be an abnormal pregnancy
    - This may be an ectopic pregnancy
  - This requires follow-up in 48 hours
    - May repeat  $\beta$ hCG level to check for 66% increase
    - May repeat US if  $\beta$ hCG level is above the discriminatory zone
  - One may consider using a serum progesterone to further stratify
- Non-diagnostic ultrasound when the  $\beta$ hCG level is above the discriminatory zone
  - This is abnormal and should be considered an ectopic pregnancy

## Treatment Modalities for Ectopic Pregnancy

### Surgery

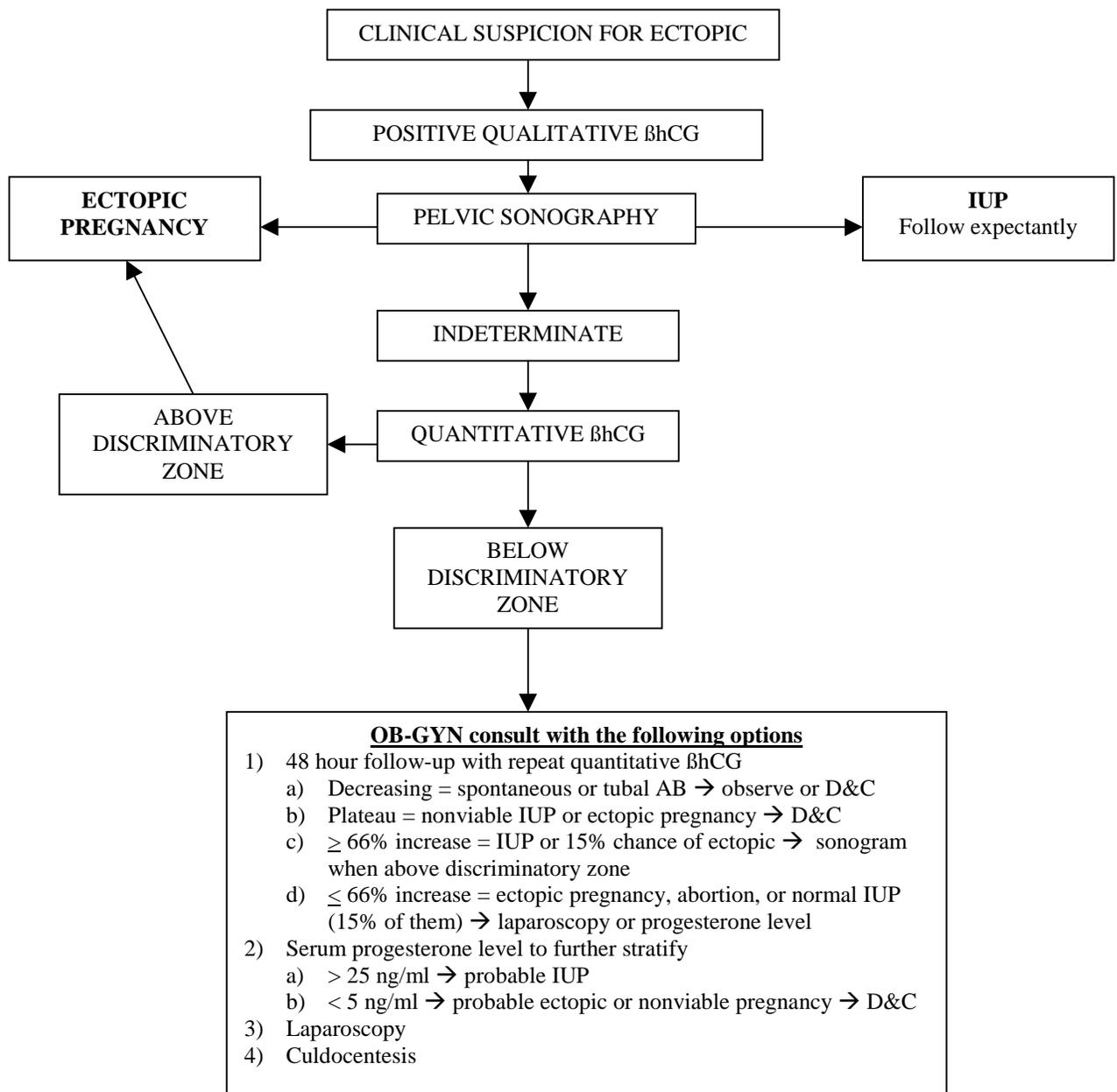
- The gold standard treatment for ectopic
- Laparoscopy is the usual method utilized
- Indications
  - Rupture
  - Hypotension
  - Anemia
  - Ectopic sac diameter (if visualized) greater than 4 cm
  - Pain greater than 24 hours → this indication is variable on the source

### Medical therapy

- This accounts for approximately one-third of all patients treated for ectopic pregnancy
- Indications
  - Unruptured
  - Ectopic sac diameter (if visualized) less than 4 cm
- Primary treatment is methotrexate
  - Generally dose QOD until the  $\beta$ hCG level drops by 15% or more in 48 hours
  - Variable dosing as above is 93% effective
- Safeguards for the patient being treated medically for ectopic
  - The patient is examined by only one examiner, and only once
  - Transient pain is common
    - This occurs 3 to 4 days after the start of the methotrexate treatment
    - The pain normally lasts 4 to 12 hours
    - It may be consistent with a rupture if orthostatic tachycardia, hypotension, or falling hematocrit

## APPROACH TO THE PATIENT WITH SUSPECTED ECTOPIC PREGNANCY

- 1) Positive qualitative serum or urine  $\beta$ hCG and clinical suspicion
- 2) Pelvic sonography
  - a) Positive for IUP → follow expectantly
  - b) Indeterminate → Measure a quantitative serum  $\beta$ hCG
  - c) Consistent with ectopic pregnancy → GYN consult for further treatment
- 3) Quantitative serum  $\beta$ hCG **above** the discriminatory zone → ECTOPIC PREGNANCY  
Quantitative serum  $\beta$ hCG **below** the discriminatory zone → OB-GYN consult  
Consider the following options:
  - a) 48 hour follow-up with repeat quantitative  $\beta$ hCG
    - i) Decreasing = spontaneous or tubal AB → observe or D&C
    - ii) Plateau = nonviable IUP or ectopic pregnancy → D&C
    - iii)  $\geq 66\%$  increase = IUP or 15% chance of ectopic → sonogram when above discriminatory zone
    - iv)  $\leq 66\%$  increase = ectopic pregnancy, abortion, or normal IUP (15% of them) → laparoscopy or progesterone level
  - b) Serum progesterone level to further stratify
    - i)  $> 25$  ng/ml → probable IUP
    - ii)  $< 5$  ng/ml → probable ectopic or nonviable pregnancy → D&C
  - c) Laparoscopy
  - d) Culdocentesis
- 4) If D&C, the OB-GYN evaluates for presence of villi
  - a) No villi = ectopic pregnancy
  - b) Villi = nonviable IUP → observation



### **Important facts to remember**

- There is no combination of historical and/or physical findings that will confirm or exclude the diagnosis of ectopic pregnancy with a high degree of certainty.
- A single quantitative serum  $\beta$ hCG level is not sufficient to rule in or rule out ectopic pregnancy as ruptured and unruptured ectopics are seen at  $\beta$ hCG levels  $< 100$  and  $> 50,000$  mIU/ml
- In one series, 7% of all ectopic ruptures occurred at  $\beta$ hCG  $< 100$  mIU/ml
- For progesterone, a single level of  $\geq 25$  ng/ml excludes ectopic pregnancy with 97.5% sensitivity
- For progesterone, a single level of  $\leq 5$  ng/ml identifies a nonviable pregnancy with 100% sensitivity
- The diagnosis of ectopic pregnancy is made based on a serum  $\beta$ hCG level of  $\geq 1,500$  mIU/ml and an *empty uterus* on sonography
- 13% of abnormal IUPs and 39% of ectopic pregnancies with  $\beta$ hCG values less than 1,000 mIU/ml can be identified at ultrasonography, thus clinicians should not defer the ultrasound based upon the quantitative level
- 20% of confirmed ectopics will have normal pelvic sonograms

### **References**

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