MANAGEMENT OF ECTOPIC PREGNANCY

Col. Lance T. Frye, MD, FACOG
Emergency Management Updates
June 2013
DISCLOSURES

- No financial of industry conflicts
- No recommended off use of medications
LEARNING OBJECTIVES

- Identify those individuals with ectopic pregnancy
- Identify those candidates for conservative treatment
- Understand methods for treatment of ectopic pregnancy
SO LET’S DISCUSS ECTOPIC PREGNANCY
Differentiating ectopic pregnancy

From early normal or abnormal intrauterine pregnancy
A 23-year-old presents to emergency department complaining of vaginal spotting and abdominal pain X 1 week

- Pain became acutely worse today
- Positive home urine pregnancy test
- Vital signs are stable

Exam
- RLQ tenderness, no rebound, mild guarding and CMT

Laboratory data
- Hgb 11.0
- hCG is 850 IU/L
CASE #1

- Transvaginal ultrasound (TVUS):
  - Retroverted uterus
  - No IUP
  - Right ovary 2.5cm cystic structure with internal echoes
  - Small amount of free fluid in pelvis
PREGNANCY OF UNKNOWN LOCATION (PUL)

- Pregnancy test is positive
- TVUS does not show evidence of either an intrauterine or an ectopic pregnancy
  - Urine tests will detect pregnancies well before they are visible on TVUS
- Frequent diagnosis
- PUL can represent
  - Non-visualized ectopic pregnancy
  - Abnormal IUP
  - Early normal IUP
- Distinguishing among these is a clinical challenge
DEFINITION / INCIDENCE

- Gestational implantation outside the uterine cavity - Greek - *ektopos* - “Out of Place”
  - Fallopian tube
  - Ommentum
  - Intra-abdominal
- Occurs in 16.8 pregnancies/1000 - (1-2/100)
2% of all first-trimester pregnancies and 6% of all pregnancy-related deaths

Leading cause of maternal death in the first trimester

Risk for ectopic pregnancy increases with age
- Women 35 to 44 years of age - 3-4 X more likely than women ages 15 to 25 years of age

Incidence has increased but mortality has decreased

Prevalence among women presenting to emergency department with first-trimester vaginal bleeding, abdominal pain, or both
- Reported as high as 18%
A 2006 WHO analysis
- pooled data from multiple geographic areas - the rate of death from ectopic pregnancy was 4.9%

Michigan study - 268 pregnancy-related deaths
- 6% Were caused by complications of ectopic pregnancy
- Age at death was 27 (+/- 6) years
- 13 Deaths were to African-American women
- 3 were to caucasion women (P < .01)
- African-American women had an ectopic mortality ratio 18 times higher than white women

CAUSES OF ECTOPIC

- Chronic salpingitis and PID
- Tubal surgery
- Infertility treatments
- IUD contraception
- Previous ectopic pregnancies
Differential Diagnosis

- Missed abortion, inevitable abortion, septic abortion, implantation bleeding
- Ruptured corpus luteum cyst
- Endometriosis
- Appendicitis
- Pelvic inflammatory disease (PID)
- Ovarian cyst ± torsion
- Degenerating fibroid
- Gestational Trophoblastic Disease
- Bleeding disorder
- Bleeding from other gyn/non-gyn sites, trauma, foreign bodies
Prior PID - six-fold increase after one episode
Reconstructive tubal surgery and assisted reproductive technologies - 4x
Tubal sterilization - 9x
IUD use, maybe 2° to increase salpingitis - 4X
Prior ectopic - to 13x increased risk
DES exposure
Other risk factors - age, smoking, race (African American or Hispanic)
Implantation Locations

- **Ampulla (80%)**
- **Isthmus (15%)**
- **Cornual/interstitial (2%)**
- **Extra tubal sites**
  - Ovary
  - Cervix
  - Abdomen (1/100 ectopics)
  - Increased maternal mortality
  - Perinatal survival 5-25%
ECTOPIC INSERTION

95% Insert in Fallopian Tube
SYMPTOMS OF ECTOPIC

Most Common symptoms (Classic Triad)
- Abdominal / Pelvic pain 90-100%
- Absent menses 75-85%
- Vaginal bleeding 50-85%

Clinical Manifestation
- No symptoms
- Shock

50% are asymptomatic before rupture
SIGNS OF ECTOPIC

- Adnexal tenderness 80-90%
- Abdominal tenderness (peritoneal signs)
- Abnormal bleeding 50-85%
- Adnexal mass 40% - use caution not to rupture
- Enlarged uterus
- Fever (low-grade)
- Orthostatic changes
- Cervical motion tenderness
High index of suspicion with clinical findings

- **βhCG**
  - Low for dates
  - Doesn’t increase appropriately - doubles every 48 hours

- **Progesterone**
  - < 5 ng/mL - suggestive of ectopic
  - > 25 ng/mL - normal IUP

- **Ultrasound (vaginal probe) (Discriminatory Zone)**
  - Fetal sac ~ 1000-1500 βhCG
  - Should see fetal pole > 4000 βhCG - 6000 if transabdominal
  - Fetal cardiac activity > 13,000 βhCG

- **Culdocentesis**
  - Non-clotted blood - found in 83% but only 50-60% ruptured
  - Hematocrit > 15%

- **Laparoscopy ± curettage**
WORK UP

- Obtain a detailed history
- Complete set of vital signs
- Pregnancy test - Quantitative β-HCG
- Pelvic examination
- Ultrasound - “ring of fire”
- Serum progesterone level - some benefit in
  - Progesterone levels less than 5ng/ml indicate no viability
Serum hCG level
Diagnostic for pregnancy as early as 10 days following ovulation
Useful in identifying abnormal pregnancy
Less than a 66% ↑ hCG levels during 48hr
5% of normal pregnancies would fall in the ectopic category, and 13% of the ectopic pregnancies would be missed
Monitoring resolution of hCG levels
The usefulness is limited because

- significant number of tests fall in the intermediate range 5-25 ng/ml
- Less than 5 ng/ml considered nonviable
- Reported cases of viable pregnancies with progesterone <5 ng/mL and ectopic pregnancies with normal progesterone levels
- Progesterone <5 ng/mL likely to indicate an abnormal pregnancy (but not location)
- Availability of the assay is not immediate
  - limited clinical use
TVUS - combine hCG level has improved the diagnostic accuracy
At an hCG of 1500 IU/L - IUP should be seen
Heterotrophic pregnancy is more common with the increased use ARTs
- up to 1% of IVF versus 1:3,800 naturally conceived pregnancies
Ring of Fire Appearance
Uterus Left
Ovary Right
Ectopic in Center
CONSERVATIVE MANAGEMENT WITH HCG LESS THAN 1500 IU/ML

- Repeat 48h later if stable
- Rise by less than 66% probable abnormal gestation
- Condition worsens - move to laparoscopy
- 66% Rise or more may allow:
  - Repeat scan in 1 wk
  - Unless condition changes
CONSERVATIVE MANAGEMENT

- Distinguishing patients who are experiencing spontaneous resolution of their ectopic from those who have proliferating ectopic pregnancies and require active intervention can be difficult

- Expectant management - reasonable with adequate consents

- Many ectopic pregnancies will resolve spontaneously

- The range of success in observational studies is 44%-69%

- Maintain Beta Board

DIAGNOSIS WITH TVUS

- Suspected ectopic - urine hCG positive
- Clinical assessment
- Stable
- TVUS performed at appropriate levels
- Empty Uterus
- Adnexal mass or free fluid
CLINICAL MANAGEMENT

- Medical Management
- Surgical Management
Expectant Management

- The success depends on the US appearance and the level of hCG level
- Adnexal mass ≤ 4 cm
- Absence of a intrauterine gestational sac
- Free fluid <100ml - 300ml
- hCG < 10,000 IU/L and a fall at least 15% in first 24hr = most predictive factor (5000 IU/L)
- No cut-off value has been found below which expectant management is uniformly safe
- hCG < 1000 IU/L failure rate 1.5%, 5-10,000 failure rate 14.3%
Expectant Management

- Need serial hCG measurements twice a week and weekly TVS to ensure resolution
  - hCG should progressively decrease to nonpregnant level
  - 15% decrease between day 4 and 7
- Weekly hCG and TVS should be carried out until serum levels are less than 5 IU
EXPECTANT MANAGEMENT

- Should be counseled about the importance of compliance with follow-up
- Should have easy access to hospital
- However, tubal patency rates have been reported to be the same with either expectant or salpingostomy
Medical Management

- Considered in selected cases
- Factors to be considered in selecting patients:
  - Size of the ectopic pregnancy
  - Compliancy of the patient
  - Signs of rupture
  - Hemodynamic stability
  - Size less than 4 cm (Gest Sac no larger than 3.5cm)
  - Quant less than 10,000 IU/ml
  - No cardiac activity
  - Platelets < 100,000
  - HIV, WBC < 3000
- Progesterone less than 5ng/ml
- Uterus empty on transvaginal ultrasound
  - Quant hCG needs > 1500 IU/ml
- Ectopic mass less than 4-5cm as determined by transvaginal ultrasound
Methotrexate

- Folic antagonist
- Used for over 20 years
- Aimed at patients before ectopic ruptures
- Need to be hemodynamically stable
- Dosing 50 mg/m²
Methotrexate can be successful at small GS < 4cm
- Lower serum hCG < 3000 IU/L
- Absence of blood in the peritoneal cavity
- Absent fetal heart activity
- High failure rate if progesterone > 10ng/mL
- High failure rate if hCG > 5000 IU/L or presence cardiac activity or yolk sac are seen
RR 5.5
Abdominal pain is common - 75% (2-3 days after MTX)
Some need to be admitted if rupture is suspected
Should be advised to avoid folate intake
Fluid intake during treatment
Understand treatment and potential problem
Conception avoided until 3 months after MTX has been given
METHOTREXATE CAUTIONS

- Should not be given to women with:
  - blood dyscrasias or active gastrointestinal and respiratory disease
  - Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion
  - Should not be used in women with liver or kidney disease.
CONTRAINDICATIONS TO MEDICAL MANAGEMENT

- Absolute Contraindications
  - Hemodynamically unstable
  - Breastfeeding
  - Overt laboratory evidence of immunodeficiency
  - Alcoholism, alcoholic liver disease, chronic liver disease
  - Preexisting blood dyscrasias
  - Known sensitivity to methotrexate
  - Active pulmonary disease
  - Peptic ulcer disease
  - Hepatic, renal or hematologic dysfunction
CONTRAINDICATIONS TO MEDICAL MANAGEMENT

- Relative Contraindications
  - Gestational sac larger than 3.5 cm
  - Embryonic cardiac motion
Prior to therapy labs should include
- CBC, LFT, BUN/Cr and coagulation

Side effects of MTX are rare and usually mild
- Include nausea
- Vomiting
- Diarrhea
- Stomatitis
- Reversible alopecia
- Neutropenia
- And pneumonitis

**FDA has not approved use of methotrexate for the treatment of ectopic pregnancy, studies support its safety and efficacy for this purpose**
MEDICAL MANAGEMENT PATIENT INSTRUCTIONS

- No intercourse until hCG titer is negative
- No alcohol until hCG titer negative
- Do not take vitamins with folic acid.
- Do not take aspirin or non-steroidal anti-inflammatory drugs.
- Decrease sun exposure while taking Methotrexate
- Contact your physician with these symptoms:
  - Increased vaginal bleeding
  - Abdominal pain
  - Feeling light-headed or experiencing fainting spells
# Methotrexate Therapy Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Single dose</th>
<th>Multiple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>50 mg per square meter of body surface methotrexate IM</td>
<td>Alternate every other day: 1 mg per kg methotrexate IM and 0.1 mg per kg leucovorin*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>LFTs, CBC, and renal function at baseline</th>
<th>LFTs, CBC, and renal function at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta-hCG at baseline, day 4, and day 7</td>
<td>Beta-hCG at baseline, day 1, day 3, day 5, and day 7 until levels decrease</td>
</tr>
</tbody>
</table>

| Repeat medication | Repeat regimen if beta-hCG level does not decrease by 15 percent between day 4 and day 7 | Repeat regimen (for up to four doses of each medication) if beta-hCG level does not decrease by 15 percent with each measurement |

| Follow-up         | Beta-hCG level weekly, and continue regimen until no longer detected | Beta-hCG level weekly, and continue regimen until no longer detected |
single 50 mg/m² dose regimen is the simplest
ds. shown by some to be as effective as the fixed
dmultidose regimen
deliminates need for folinic acid rescue to
minimize side effects
Recent meta-analysis has shown fixed
multidose regimen to be more effective
especially in treating more advanced
gestations and those with embryonic cardiac
activity
**PERSISTANT TROPHOBLASTIC DISEASE**

- This is mostly a problem after salpingostomy.
- Incidence around 8%.
- More likely if the preoperative serum hCG are above 3000 IU/L.
- There are insufficient data to recommended the correct definition and units needs to develop their criteria.
- Patients lost to follow-up increased risk for persistent disease.
Suggested criteria for starting the treatment are if hCG level fail to fall below 65% at 48hr post-op or
- hCG level is greater than 10% at 10 days post-op
- If diagnosed: MTX 50mg/m2 is preferable to repeat surgical procedure
- Removal of entire Fallopian may be necessary
Surgical Options

- Salpingostomy VS salpingectomy
- Laparotomy VS Laparoscopy
- Combined medical-surgical treatment
Surgical Management

- Laparoscopy with salpingostomy or salpingotomy
  - Less intraoperative blood loss occurs
  - Less postoperative anesthesia
  - Shorter hospital stay
  - Cost effective
- Measure hCG levels serially until they decrease to nonpregnant levels
  - If hCG levels plateau, increase, or do not decrease by more than 15% in 48 hours
  - Methotrexate treatment or salpingectomy is required
- Laparotomy with salpingectomy
- Serial measurement of hCG levels is not required after salpingectomy
Laparotomy VS Laparoscopy

In case where is rupture of tube and hemodynamically unstable
- laparotomy is preferred

Laparoscopy decision should be made by clinical state of the patient and skill of the operator
In the surgical management, one must consider the patient’s desire for further childbearing.

The couple is fully informed of the possibility of laparotomy with salpingectomy or more extensive surgery.

Even if neither tube can be saved every effort to preserve the uterus and at least one ovary to keep available use of the IVF.
SO...LET’S LOOK AT SOME CASES
PATIENT #1

- Vaginal spotting and 5-1/7th weeks of amenorrhea
- History of PID
- IVF with the transfer of 2 blastocysts into her uterus 3 weeks ago
- The REI noted what was believed to be an appropriate elevation in her serum hCG level
- Based on dating criteria, she is 5 postmenstrual weeks and 1 day
- The day prior to presentation, hCG was 2,500 IU/L
- TVUS - retroverted uterus, 16mm endometrium, 2 small intramural myomas, but no IUP
  - Both ovaries contain several cystic structures of varying sizes (between 15 mm and 26 mm), some with peripheral flow
  - Some pelvic fluid
CORRECT MANAGEMENT OF THIS PATIENT IS TO:

a. Obtain a serum progesterone level
b. Obtain another serum hCG level and perform a transvaginal ultrasound in 48 hours
c. Perform a laparoscopy to rule out a tubal pregnancy
d. Obtain a TVS in 3 days; if no IUP is observed, administer methotrexate
PATIENT #2

- 8 or 9 days late for her period
- History of prior early pregnancy loss
- Positive home pregnancy test
- Consults with her gynecologist, who orders a TVUS
- The scan reveals a 12-mm endometrium, but no IUP
  - Normal left ovary with a corpus luteum
  - Right ovary with a 2.5-cm heterogeneous cyst
  - No free fluid is seen in the pelvis
THE PATIENT'S DIAGNOSIS IS:

a. Early pregnancy failure
b. Suspected right tubal pregnancy
c. PUL
d. Chemical pregnancy
THE MANAGEMENT YOU SELECT FOR THIS PATIENT IS:

a. Dilation and curettage to verify the presence or absence of villi
b. Laparoscopy to rule out/in an EP
c. Quantitative serum hCG now and again in 48 hours
d. TVS in 1 week
QUESTIONS
REFERENCES

- Lisa Keder M.D., Contemporary Ob/Gyn, March 2013, Extrauterine pregnancy detection and management
- I. Timor-Tritsch, M.D., Contemporary Ob/Gyn, August 2011, Pinpointing Extrauterine Pregnancy
- Obstetrics and Gynecology: Medical management of ectopic pregnancy. ACOG Practice Bulletin No. 94
- Togas Tulandi, MD, et.al., Methotrexate treatment of tubal and interstitial ectopic pregnancy, Up-to-Date, Last Literature Review 18.3, Sept 2010