Management of Ectopic, Heterotopic, and Interstitial Pregnancy

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I. Ectopic Pregnancy

i. Incidence - 2% of all pregnancies, 18% of all women presenting to the ER with vaginal bleeding, abdominal pain, or both have an ectopic pregnancy. The risk of rupture was 18%.

ii. Etiology - 98% present in the fallopian tube (70% ampullary), 3.2% in the ovary (usually have a history of infertility and recurrent ectopics).

- Tubal surgery (i.e. sterilization procedures), STI's leading to PID (particularly chlamydia), previous ectopic, in utero exposure to DES, Infertility (although likely reflects tubal abnormalities), Clomid doubles risk (5-6%), IVF, previous pelvic or abdominal surgery, smoking (decreased immunity and impaired tubal motility), vaginal douching (increased risk of PID), those who conceive with IUD (50% of pregnancies with levonorgestrol IUD are ectopic, 1 in 16 with copper IUD).

iii. Diagnosis - 50% have no identifiable risk factors and initial physical findings.

- Most common clinical presentation is 1st trimester vaginal bleeding (most commonly intermittent) and/or abdominal pain which is generally not crampy.

- Normal pregnancy symptoms may be less reported and typically appear 6-8 weeks after LMP.

- Severe abdominal pain, loss of consciousness and dizziness are more specific findings for rupture.

- "Discriminatory zone" of beta hcg is 1,500-2,000 mIU/ml: Beta at which an IUP should be seen (consider a 2,000 cut off with IVF pregnancies, as multiples gestations may not appear until then).

- In early pregnancy, the beta should rise by at least 53% in 48 hours. If there is abnormal rise, the patient is stable, but not above the discriminatory zone, the beta should be repeated.

- If their is inappropriate rise and the beta is above the discriminatory zone without an IUP, the patient should be treated for an ectopic (15-26% of women with ectopic pregnancy will have an initial ultrasound with no findings).

- A presumptive diagnosis of ectopic pregnancy can be made when the beta does not rise appropriately across 3 measurements 48-72 hours apart, in the absence of an IUP.

- IUP must have a gestational sac with a yolk sac or embryo.

Sonographic findings - Confirmation is made when an extrauterine sac with a yolk sac and/or embryo is visualized. An absence of color flow Doppler and presence of "ring of fire" does
not differentiate a tubal pregnancy from a corpus luteum so results should be correlated with the beta hcg and symptoms (89-100% of ectopics have an extraovarian adnexal mass, the "ring of fire" tends to be more echogenic than a corpus luteum, and cysts tend to change in appearance), a pseudosac is present in 20% of ectopics (usually centrally located in endometrial cavity, do not have an echogenic rim, can change shaped during the scan, and may appear complex since it contains blood), echogenic peritoneal free fluid is associated with ectopic pregnancy (almost always hemoperitoneum and can indicate rupture vs tubal abortion), if fluid is anechoic and isolated to the cul-de-sac, usually physiologic.

- Initial suspicion should prompt a type and screen, CBC, CMP, and Beta.

- Predictors of hemoperitoneum ≥ 300 mL include: moderate to severe pelvic pain, fluid above the fundus or around the ovary, and serum hemoglobin < 10 g/dL. 2 or more of these criteria was 92% diagnostic.

iv. **Treatment** - high beta levels are the most important factor associated with treatment failure.

a. **Methotrexate** - antimetabolite which binds to dihydrofolate reductase, interrupting synthesis of purines and amino acids, thus inhibiting DNA synthesis and cell replication. Particularly active on proliferating tissues such as bone marrow, intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue.

- 71.2 - 94.2% overall treatment success rate.
- Single dose treatment has a 3.7% failure rate, 30% have side effects, 15-20% will need a second dose, <1% need more than two.
- 13% failure rate with two-dose regimen, 40% have side effects.
- **Contraindications** - Breastfeeding, immunodeficiency, liver disease, blood dyscrasias, sensitivity to methotrexate, active pulmonary disease, peptic ulcer disease, hemodynamic instability, anyone who cannot committ to the protocol, heterotopic pregnancy, and the presence of free peritoneal fluid. Relative include sac >3.5 cm and cardiac motion.
- Typically, CBC and CMP are repeated 1 week after MTX administration.
- Beta levels should be followed after MTX until non-pregnant levels to allow diagnosis of treatment failure.
- Beta levels commonly rise initially from continued syncyiotrophiclastic activity.
- **Side Effects** - most common are stomatitis, nausea and vomiting, and conjunctivitis (avoid NSAIDS and alcohol to avoid liver and gastric toxicity), alopecia is rare.
- Abdominal pain is common 2-7 days after treatment due to tubal abortion (can monitor with sonogram and hemoglobin level).
- Other than ectopic precautions, give fever and respiratory precautions as pneumonitis has been reported.

- Elevated LFTs and cytopenias are usually seen with multidose treatment and resolve by discontinuing MTX and giving leucovorin.

- **More counseling** - discontinue prenatales/folic acid, avoid foods with folic acid, avoid sunlight, refrain from intercourse or vigorous physical activity, avoid conception for 3 months after treatment, hcg usually declines to nonpregnant levels by 35 days, but may take as long as 109 days, **recurrence rate for ectopic is 15%**.

- Women who conceive before 3 months should take the recommended preconception dose of folic acid.

- 38-89% will achieve a subsequent IUP.

- Serial sonograms are not helpful unless women have severe abdominal pain. Ectopics may increase in size and persist on sonogram for weeks. Usually represents a hematoma and not persistent trophoblastic tissue.

b. **Conservative therapy** - 88% resolve spontaneously if beta is less than 200.

c. **Surgery** - indications include hemodynamic instability, severe abdominal pain or evidence of intraperitoneal bleeding suggestive of rupture, contraindications to MTX, failed medical therapy, and perhaps those who desire surgical sterilization.

- Laparoscopic Salpingectomy for tube compromise, uncontrolled bleeding, or gestation cannot be safely removed. Can be considered for women desiring sterilization (reducing risk of ovarian cancer) or those who are planning IVF.

- Laparoscopic Salpingostomy is preferred if there are no contraindications for women desiring ongoing fertility. Especially in those with an absent or damaged contralateral tube. Follow up beta hcg is recommended.

- 2 randomized studies (although small) found similar fertility outcomes and risk of recurrent ectopic. Observational studies show a higher IUP rate with salpingostomy but also higher rate of recurrent ectopic and persistent ectopic (4-15%).

- Women can conceive following their next menses.

- Surgical treatment has similar recurrence rates to MTX and ongoing fertility.

v. **Screening asymptomatic women** - routine screening with beta hcg should be considered in those women with IVF pregnancies, pregnancy after sterilization, or women with a prior history of ectopic pregnancy.
II. **Heterotopic Pregnancy**

i. **Incidence** - 1% of all IVF pregnancies (combined IUP and EUP). 1 in 3900 spontaneous pregnancies. High incidence of rupture, given the high potential for misdiagnosis. 1 in 3 coexistent IUP’s will spontaneously abort.

ii. **Etiology** - 90% present in the fallopian tube, interstitial 4%, less common in ovary, cervix and abdomen. 50% are asymptomatic.

- Risk factors include history of ectopic, history of abortion, ovarian hyperstimulation syndrome, and those undergoing IVF.
- Suspect in patients who have undergone IVF and present with abdominal pain, vaginal bleeding, and an enlarged uterus OR rising beta hcg after treatment of ectopic.

iii. **Diagnosis** -

- Beta hcg levels are not helpful. Sonogram usually visualizes both an ectopic and IUP OR an IUP is visualized with echogenic fluid in the posterior cul-de-sac.
- Weekly sonograms are suggested in patients with an IUP and continued abdominal pain or vaginal bleeding until the possibility of an ectopic can be eliminated.

iv. **Treatment** -

a. **Conservative treatment** - weekly sonograms, usually considered when the sac is small, without cardiac activity, and patient is stable (rarely considered). 20% **rupture rate** with 5% **abortion rate**.

b. **Surgery** - laparoscopic salpingectomy for hemodynamic instability or other signs of rupture. 15% **abortion rate**.

c. **Ultrasound guided injection of ectopic** - KCL or hyperosmolar glucose injection, followed by weekly sonograms. If enlargement is seen, another injection can be given. 0% **abortion rate**.

d. **Total abortion rate in the literature is 26-31%**.

III. **Interstitial (cornual) Pregnancy**

i. **Incidence** - 2.4% of all ectopics, and implants in the proximal tubal segment embodied within the muscular wall of the uterus. **20-50% rupture rate** (increased risk after 9 weeks). **2-2.5% mortality rate** (vascular area) especially if occurring after 12 weeks.

ii. **Etiology** - More likely in IVF pregnancies and patients with a history of ipsilateral salpingectomy.
iii. **Diagnosis** - sonogram findings usually are:

- Eccentric (high in uterine fundus) location of the gestational sac proximal to the uterine cornua.
- Surrounded by thin (<5 mm) myometrium and close to the uterine serosa.
- "Interstitial line" - echogenic line that extends from the most superior and lateral aspect of the endometrium to the midportion of the interstitial mass or sac.
- Can be misinterpreted (IUP in a bicornuate or septate uterus).

iv. **Treatment** -

a. **Multi-dose MTX** - 1 mg/kg per day IM on Days 1,3,5, and 7 with leucovorin (0.1 mg/kg orally) on Days 2,4,6, and 8. A second course can be given 7 days after the last dose. **Success rate 66-100%.** Serial sonograms after treatment should be performed to look for a residual mass (can even present when there is complete hcg resolution).

b. **Surgery** - For treatment failures, high beta hcg (>3,000-5,000) (since MTX failure is dependent upon beta hcg levels), and larger gestations (>3.5-4 cm). Includes cornual resection, local injection of MTX, selective arterial embolization, hysteroscopic removal, and worse case hysterectomy.

c. After treatment there is an unknown risk of uterine rupture in a future pregnancy, so patients should be counseled on mode of delivery. Decreased fertility rates have also been reported, and an unknown risk of recurrence may also be present if there is tubal pathology, a history of medical treatment for an interstitial pregnancy, current pregnancy was conceived via IVF, and the patient has uterine fibroids.

REFERENCES:


