Early pregnancy abnormalities

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Goals of the talk:

- Differential diagnosis/work up for first trimester bleeding
- Different types of first trimester pregnancy loss
- Ectopic pregnancies: diagnosis and management
- Miscellaneous other oddities of the first trimester
First trimester bleeding

- Occurs in 20-40% women
- Etiology often unknown, goal = exclusion
- Prognosis: association b/w FTB and adverse outcome (SAB, PTD, PPROM, IUGR)
  - Worse prognosis with heavier bleeding or extending into second trimester
  - PTD frequency with no, light, or heavy FTB was 6, 9.1, and 13.8% respectively
  - Spontaneous loss frequency prior to 24 WG was 0.4, 1.0, and 2.0 % respectively
  - Vaginal bleeding in >1 trimester associated with 7 fold increased in PPROM
Evaluation – part I

History •

Extent (amt, associated signs/sx, pain)

Past history (previous ectopic, prior SABs, medical disorders, risk factors)
1st trimester bleeding cont’d

Eval part II – physical

Vital signs

Tissue if available (clot vs POC)

Abdominal exam (+/- dopplers)

Speculum exam (external and internal) – look for lacerations, warts, vaginitis, cervical polyps, fibroids, ectropion, cervicitis, neoplastic process

Bimanual exam – assess adnexal/cervical tenderness, adnexal masses, uterine enlargement
Ultrasound

Cornerstone of evaluation

Most useful with positive preg test where IUP not previously seen

Uses: location of pregnancy (intra- or extrauterine), viability (+/- FCA), other rare findings (GTD, partial loss of multiple gestation)
Laboratory evaluation

HCG levels – useful only with serial measurements

No role in monitoring once viable IUP has been verified by ultrasonography

Less useful: progesterone, estrogen, inhibin A, Papp-A)

Always get type and screen and give rhogam if applicable
Differential diagnosis

Abortion (threatened, inevitable, complete, incomplete, missed)

Ectopic pregnancy

Vanishing twin

Trauma, wounds, vaginitis, vaginal/cervical neoplasia, warts, polyps, fibroids, ectropion

Physiologic/implantation (diagnosis of exclusion)
Miscarriage

SAB = most COMMON complication of early pregnancy

8-20% of clinically recognized pregnancies under 20 wks undergo SAB, 80% of these will be <12 wks

Low risk of loss after 15 wks (0.6%) if fetus chromosomally normal

Loss of unrecognized/subclinical pregnancies occurs in 13-26% of all pregss

Unlikely to be recognized without daily UPTs
Early loss – the data

With daily hCG assays, total rate of pregnancy loss after implantation was 31% (70% of these prior to detection of pregnancy)

Daily hCG assays on 518 nulliparous women ages 20-34 trying to conceive w/o hx of infertility:

- 26% loss of preclinical pregnancy
- 8% loss of clinically recognized pregnancy
- 64% live birth
- 2% EAB, ectopic, molar, stillbirth
Types of miscarriage

Threatened: closed cervix, uterus appropriately sized, FCA present if gestational age sufficiently advanced

Inevitable: cervix dilated, increased bleeding with cramps/ctx, POC can be at os

Complete/incomplete

Complete (1/3): small contracted uterus, open cervix, scant bleeding/cramping

Incomplete: (2/3): placental tissue remaining, cervix open, POC can be at os, uterus smaller than expected for gestational but not well contracted, variable bleeding/cramping
Types of miscarriage cont’d

Missed: in utero death of embryo prior to 20th wk with retention of pregnancy for prolonged period of time. Cervix closed, +/- bleeding

Septic abortion: rare with SABs, foreign bodies ie IUDs, invasive procedures, legal EABs; common complication of illegal EABs.

Sx: fever, chills, malaise, tachycardia - abdominal pain, vaginal bleeding, sanguinopurulent discharge. Cervix usually dilated, uterus boggy and tender.

Bugs: Usually S. aureus, GNRs.
Varieties of spontaneous abortion, A. Threatened, B. Inevitable, C. Incomplete, D. Missed.
Ultrasound and SABs

Definitive diagnosis of SAB when:

- Absence of FCA with CRL >5mm
- Absence of fetal pole when mean sac diameter >25 mm (TAUS) or >18 mm (TVUS)
- Absence of yolk sac 32 days post IVF

Promising findings for lack of SAB

- Yolk sac b/w 22-32 days from IVF associated with +FCA in 94% pregs
- Positive FCA.... But age matters!
- Women <36 +FCA associated with SAB in only 4.5% pregs. 36-39 y/o SAB rate 10%, women >40 y/o SAB rate 29%.
You might worry when...

- YS abnormal (irregular, LGA, free floating)
- Slow fetal heart rate (ie HR <85 bmp at 6-8 wks associated with 0% survival)
- Small sac (MSS-CRL <5 mm)
- Subchorionic hematoma (ie double SAB rate with women with large >25% of gest sac volume -- subchorionic hematomas in study of first trimester bleeders)

Management? Repeat US in one week
Management

Threatened: expectant

Complete: ideally nothing, but difficult to distinguish clinically/radiologically so consider D&C

Septic: stabilize pt, obtain blood and endometrial cultures, broad spectrum Abx (gent + clinda +/- amp), D&C
Management cont’d

3 options for incomplete, inevitable, and missed ABs

Surgical: D&C – use this if bleeding heavy, suction curettage is best. Data on Abx (doxycycline) post SABs limited. Has shown 42% decrease in infection with EABs

Medical: Miso (some studies show expulsion in 71% by day 3, 84% by day 8)

Expectant: use if stable vital signs, no evidence of infection. Can be used for up to one month
Ectopic pregnancy

3 classic symptoms: abdominal pain (99%), amenorrhea (74%), vaginal bleeding (56%)

Occur with both ruptured and unruptured cases

Clinical manifestations often appear 6-8 wks after LMP but can appear later

Often see above symptoms with breast tenderness, frequency urination, and nausea

Shoulder pain (blood irritating diaphragm), urge to defecate (blood pooling in cul-de-sac) can also be seen with ruptured ectopic pregnancies

50% women asymptomatic before rupture with no identifiable risk factors
Differential diagnosis abdominal pain (a very limited list)

- UTIs
- Nephrolithiasis
- Diverticulitis
- Appendicitis
- Ovarian neoplasms
- Endometriosis
- Endometritis
- PID
- IBS
- Fibroids
- Gastroenteritis
- Interstitial cystitis
- Pregnancy
- Miscellaneous!
Risk factors - high

Previous ectopic (post methotrexate, salpingectomy, linear salpingostomy) – 8, 9.8, and 15.4% respectively

Tubal pathology/sterilization (1/3 of pregnancies after BTL, total 0.1-0.8%, are ectopic)

In-utero DES exposure (abnormal morphology, impaired fimbriae)

IUD – worse with Mirena than Paraguard
Risk factors – moderate

- Previous genital infection (salpingitis, GC, CT)
- Infertility
- Multiple sexual partners (secondary to increased risk PID)
- Smoking (risk is dose dependent) – possible impaired tubal motility, possible impaired immunity and predisposition to PID
Risk factors - low

- IVF – overall rate 2.1%
- Vaginal douching – increased rate of PID
- Age: <18 y/o at first sexual encounter, new data suggest increase in older age groups (possibility of cumulative risk factors over time)
Initial evaluation

Pregnancy test on all reproductive aged women with abdominal pain

Ultrasound diagnostic when extrauterine gestational sac is seen (but often is not)

Suggestive with complex adnexal mass with +UPT and empty uterus (84% sensitive, 99% specific), fluid filled adnexal mass surrounded by echogenic ring (bagel sign), free fluid in peritoneal cavity/cul-de-sac
Ectopic preg: ultrasound pics

Red: uterine outline
Green: uterine lining
Yellow: ectopic pregnancy
Blue: pseudosac
hCG rising in curvilinear fashion until 41 days gestation, then rises more slowly to 10 wks and declines until plateaus in 2nd-3rd trimesters.

Mean doubling time: 1.4-2.1 days.

Should rise by 66% every 48 hours (will do so in 85% viable pregs).

Trivia: slowed recorded 48-hr rise with viable IUP was 53%.

Ectopics: only 21% follow minimal doubling time.
Discriminatory zone (a.k.a., “why the beta book exists”)

DZ = serum hCG above which gest sac should be seen by TVUS if +IUP
1500-2000 with TVUS (6500 TAUS)

Above DZ – no gest sac – ectopic/nonviable IUP

Below DZ – no gest sac – early viable IUP, nonviable IUP, ectopic. Anywhere from 8-40% ultimately diagnosed as ectopic pregns

DZ dependent on ultrasonographer, US equipment, physical factors (fibroids, multiple gestation)
Management – above the DZ

If adnexal mass seen on TVUS, manage as ectopic

If no adnexal mass seen, repeat TVUS and hCG in two days. If still no IUP seen and no adnexal mass, manage as ectopic

Why? US skills, multiple gestation
Management: below DZ

Repeat hCG in 48-72 hours and repeat TVUS when hCG >DZ

If hCG does not double:
- Adnexal mass present – tx as ectopic
- No adnexal mass seen: methotrexate vs D&C to exclude/characterize nonviable pregnancy
Positively, the worst case of 'ectopic pregnancy' I've seen.
Uncommon ectopic cases

Hetertopic – both intrauterine and extrauterine; 1/30,000 normal population, as much as 1% with ART
  Cervical: 1/2,500-1/18,000 (1%)
  Ovarian: 1/ 2,100-1/60,000 (1-3%)

Interstitial (1-3%) - swelling adjacent to round ligament. Often misdiagnosed as early, oddly placed IUP leading to delay of diagnosis. Associated with uterine rupture

Abdominal (1.4%) – can go undetected longer resulting in severe hemorrhage, maternal mortality as high as 20%

Intramural: Rare. Occurs within uterine myometrium (<50 cases in literature)
Sites of ectopic pregnancy

- >95% ectopic pregns in fallopian tubes
- 70% ampulla
- 12% isthmic
- 11.1% fimbrial
- 3.2% ovarian
- 2.4% interstitial
- 1.3% abdominal
Cervical pregnancy

Sx: profuse, painless vaginal bleeding
Lower abdominal pain/cramping occur in <1/3 cases

Physical exam: disproportionately enlarged cervix ("hour-glass" shaped uterus)

Differential: IUP in process of aborting (will not see trophoblastic tissue invading cervical stroma, no FCA, probable movement down endocervical canal)

Tx: methotrexate, KCL, D&C with hysterectomy if uncontrollable hemorrhage, consider UAE first
Natural history

Rupture: associated with profound hemorrhage, major cause of preg-related maternal mortality in first trimester, most occur prior to hospitalization/evaluation in ER

Abortion: expulsion through fimbria f/b resorption, reimplantation

Resolution: consider expectant management with hemodynamically stable with initial hCG <2000 and declining
Management

Indications for surgery:

- Ruptured (esp when hemodynamically unstable)
- Inability to comply with medical therapy or contraindications
- Lack of access to medical facility in event of rupture
- Failed medical therapy
Management cont’ed

Consider medical therapy when:

- Unruptured
- Compliant patients
- hCG <5000
- Small tubal diameter
- Gest sac <3.5 cm
- No FCA

Usually given as 1-2 injections of 50 mg/m2 IM
Gestational trophoblastic disease

Made up of interrelated lesions from trophoblastic epithelium of placenta

- Hydatiform mole (complete or partial) – make up 80% of GTD
- GTN
- Choriocarcinoma
- Placental site trophoblastic tumors
Epidemiology

Incidence: b/w 23-1,299 per 1,000 preg

Risk factors:

- Extremes of maternal age (>35 yrs, slightly increased if <20)
- Previous GTD – 1% chance of recurrence, 16-28% after 2 prior
- Misc: smoking >15 cigs/day, blood type A,B, or AB, hx of infertility, nulliparity, use of OCPs
Clinical manifestations

- Vaginal bleeding
- Enlarged uterus
- Pelvic pressure/pain
- Theca lutein cysts
- Anemia
- Hyperemesis gravidarum
- Hyperthyroidism
- Preeclampsia prior to 20 wks gestation
- Vaginal passage of hydropic vesicles
Complete moles

No fetus present, results from aberrant fertilization followed by trophoblastic proliferation

Excessive uterine size, excessively elevated hCG (40% >100,000)

US shows central heterogeneous mass with numerous anechoic spaces (swelling of hydropic chorionic villi); “snowstorm pattern”
Partial moles

- Associated with fetus and amniotic fluid
- Possible FCA present
- Usually triploid
- Less associated with signs/sx of excessive hCG
- US shows possible fetus, often growth restricted, reduced amniotic fluid, “Swiss cheese pattern” of chorionic villi
Management

Evacuation with D&E first

Serial hCG monitoring (average time to normalization 99 and 59 days respectively)

Worry when: hCG concentration plateaus for 3 weeks, hCG concentration rises, hCG present for more than 6 months post molar evacuation

75% of these cases represent invasive mole, 25% are choriocarcinomas, PSTTs rare
Fetal membranes rupture or not?

True labor or not?
Fern test •
Nitrazin test •
Amonosure
Prom test
Nitrazine (pH)

**Technique:**
Amniotic fluid is alkaline and, as such, turns Nitrazine pH indicator blue.

**Performance Metrics:**
- False positive results are up to 17.4%.
- False negative results are 12.9%.
- Sensitivity 90.7%.
- Specificity 77.2%.

**Drawbacks:**
Speculum exam. False-positive results with other fluids, infections.

*Friedman, ML. Diagnosis of ruptured membranes. AJOG. 1969; 104:544-550.*
Ferning

Technique:
Arborization pattern (crystallization) of dry amniotic fluid as seen through a microscope

Performance Metrics:

- False positive results are 5-30%
- False negative results are 12.9%
- Sensitivity 51.4% (no labor)
- Specificity 70.8% (no labor)

Drawbacks:

Speculum exam, microscope. Contamination.
Amnio-dye Infusion

**Technique:**
Instillation of dilute indigo carmine into the amniotic cavity and confirmation of rupture of membranes by documenting leakage of dye into the vagina (staining of tampon)

**Accuracy:**
“Gold Standard” for diagnosis of rupture of membranes

**Drawbacks:**
Accurate, but highly invasive (requires amniocentesis). Expensive.
# Prom test

**IGFBP-1**

<table>
<thead>
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<th>Sample</th>
<th>Values</th>
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<tr>
<td>Normal adult serum</td>
<td>0.5-30</td>
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<tr>
<td>Serum (pregnancy)</td>
<td>58-600</td>
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<tr>
<td>Urine</td>
<td>undetectable</td>
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<tr>
<td>Semen</td>
<td>undetectable</td>
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<tr>
<td>Amniotic fluid</td>
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Comparison of methods to detect PROM

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<td>specificity</td>
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AmniSure® TEST

- FDA approved use of the test by nurses and nurse-midwives as well as physicians
- Clinical multi-site peer-reviewed study conducted on patients 15-42 weeks of gestation
- Cousins et al, Am J Perinat, 2005

**Study results:**

- Sensitivity: ~ 99%
- Specificity: 100%
- PPV: 100%
- NPV: ~ 99%
Placental Alpha Microglobulin-1 (PAMG-1) is a protein expressed by the cells of the decidual part of placenta. Discovered in 1970s in the Soviet Union and remained relatively unknown until much later.

PAMG-1 was selected as a marker of fetal membrane rupture due to its unique characteristic: Extremely low background level measured in cervico-vaginal secretions when the fetal membranes are intact.

During pregnancy, PAMG-1 is secreted into the amniotic fluid in great quantities.

AmniSure® TEST

- AMNISURE® is a one-step immunochromatographic assay
- Several monoclonal antibodies are used in the test to detect the PAMG-1 protein marker of amniotic fluid
- AMNISURE® works within a wide range of PAMG-1 concentrations in vaginal secretions (from 5 ng/ml to 100 µg/ml)
Administering AmniSure Test

Negative Result
PARTUS TEST

To detect cervix maturity and preterm delivery

Ph LGFBP-1
### cervical level of phLGFBP-1 maturity of cervix

<table>
<thead>
<tr>
<th>cervical status</th>
<th>Median phLGFBP-1</th>
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<tr>
<td>Ripe cervix</td>
<td>27</td>
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<tr>
<td>6h after pGE2 application</td>
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</table>
The best work available on earth... will anyone pay me for this !!!