Early Pregnancies of Unknown Location or Unknown Viability

**Terminology & Definitions**
- Intrauterine Pregnancy of Unknown Viability (IPUV)
  - Ultrasound findings: Intrauterine gestational sac with no embryonic heartbeat
- Pregnancy of Unknown Location (PUL)
  - hCG & Ultrasound findings: No intrauterine gestational sac or adnexal mass
- Early pregnancy failure
  - Not: Miscarriage, spontaneous abortion...

**Early First Trimester Ultrasound**
- Is the pregnancy intrauterine? OR
- Is the pregnancy ectopic?
- Is the pregnancy viable*? OR
- Is the pregnancy a miscarriage
  - *Has potential to result in live born infant

**Intrauterine Sac-Like Structure 1st Sign of Pregnancy**
- Usually seen Transvaginally by 5.0 weeks
- Usually seen Transabdominally by 5.5 weeks
- Usually when hCG > 1000 mIU/ml (1st or 3rd IRP)

**Published Ultrasound Signs of Early Pregnancy**
- Double sac sign* (reported 1982)
- Intradecidual sign* (reported 1984)
  - *If present, diagnosis = IUP
  - *If absent, does not mean no IUP

IUP = intrauterine pregnancy
Ultrasound Signs of Early Pregnancy

Double Sac Sign

Intradecidual Sign

Intradecidual sign

Double sac sign

Ultrasound of Early Pregnancy

Often the only finding is . . .
Nonspecific fluid collection in central echogenic portion of uterus (decidua)

Early Pregnancy

5.0 weeks

18.0 weeks

Early Pregnancies
**Problem**

If nonspecific fluid collection in central echogenic portion of uterus reported as *no intrauterine pregnancy* or the possibility of a *“pseudogestational sac”*

Clinician concludes ectopic pregnancy

Patient treated with Methotrexate or dilatation & curettage (D&C)

**Problem**

When early intrauterine pregnancy is exposed to Methotrexate (MTX)

Follow up: intrauterine pregnancy with heartbeat

Miscarriage or fetal malformations

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**Study of Ultrasound Signs of Early Pregnancy**

Two readers assessed

199 proven intrauterine gestations

- fluid in uterus, no YS or embryo
- embryonic heartbeat on follow up

First trimester outcome

148 (74.4%) live
51 (25.6%) miscarriage

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**Study of Ultrasound Signs of Early Pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS present*</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>IDS present**</td>
<td>23%</td>
<td>39%</td>
</tr>
<tr>
<td>Neither sign</td>
<td>57%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Kappa = *0.24 & **0.23 (poor inter-observer agreement)

No relationship between outcome and presence/absence of DSS & IDS

($p > 0.10$, Fisher exact test)

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**Early Intrauterine Gestation**

- Early intrauterine gestations often have a nonspecific appearance (>50% in our study)
- Even in the absence of an intradecidual sign or a double sac sign, it’s most likely an early intrauterine gestation
Early Intrauterine Gestation

How should one report an Intrauterine fluid collection with no yolk sac or embryo and normal adnexa?

“Intrauterine sac-like structure that is almost certainly an intrauterine gestational sac”

OR

“Probable early intrauterine gestation. Follow up ultrasound suggested for definitive confirmation”

“Intrauterine sac-like structure that is almost certainly an intrauterine gestational sac”

“Probable early intrauterine gestation. Follow up ultrasound suggested for definitive confirmation”

“Pseudogestational Sac”

Definition:

Fluid in the uterine cavity mimicking a gestational sac with ectopic pregnancy

Misuse of Term Pseudogestational Sac

Definition: fluid in uterine cavity with ectopic pregnancy

Frequency with ectopic pregnancy

1979 report: 20%

1990 reports: 10%

Intrauterine Fluid in Ectopic Pregnancy: A Reappraisal

All proven ectopic pregnancies July 2008 to August 2011 = 229 cases

Fluid, when present, characterized by

Shape:

- pointy-edged or smooth *

Location:

- clearly in cavity * or uncertain

Fluid contents:

- echoes & debris or anechoic *

*Features of early intrauterine pregnancy

Intrauterine Fluid in Ectopic Pregnancy: Fluid Characterization

Fluid inconsistent with gestational sac

- pointy-edged

- clearly within uterine cavity (not the decidua)

- containing echoes or debris

Fluid similar to a gestational sac

- smooth margins

- not clearly within uterine cavity

- anechoic

Intrauterine Fluid in Patients With Ectopic Pregnancy

No fluid 83.4%

Fluid 16.6%
Intrauterine Fluid in Ectopic Pregnancy:

- Inconsistent with gestational sac:
  - Pointy-edged internal echoes: 30/38 (79.2%)
  - Internal echoes or debris not decidua: 28/38 (73.7%)
  - Within cavity not decidua: 7/38 (18.4%)

38 ectopics (16.6%) had fluid in cavity

- Fluid: Inconsistent with gestational sac: 13.5%
- Fluid: Similar to gestational sac: 3.1%
- No fluid: 83.4%

Intrauterine Fluid in Patients With Ectopic Pregnancy

- 7 with fluid similar to a gestational sac
- 5 had adnexal mass of ectopic (2 no mass)

Calculations

- Intrauterine gestations: 98%
- Nonspecific fluid: 50%
- Ectopic pregnancies (per CDC): 2%
- Nonspecific fluid & no mass: 1%

For nonspecific fluid collection in cavity & no adnexal mass

Do the math:

99.9% likelihood of intrauterine pregnancy (>1000 to 1)
Pseudogestational Sac
- Little or no value, avoid the term
- If definite ectopic pregnancy term has no value
- Otherwise, odds are strongly in favor of intrauterine gestation (99.9%)
- Report nonspecific fluid collection in uterus as “almost certainly an intrauterine gestational sac”

Yolk Sac
- Usually seen on transvaginal ultrasound by 5.5 weeks
- Usually seen when mean sac diameter > 10 mm
- Visualization of yolk sac confirms gestational sac is a pregnancy

Fetal Cardiac Activity
- Usually seen on transvaginal ultrasound by 6.0 weeks
- Visualization of embryonic heartbeat confirms viability

Embryonic heartbeat
GA = 6.0 weeks

Pregnancy Failure
Most frequent early in pregnancy:
- 6 - 8 weeks with heartbeat 10 - 17% will be lost
- After 8 weeks with heartbeat < 4% will be lost
**Pregnancy Failure**

**Increased loss rates**

**Existing conditions**
- Prior miscarriages
- Uterine duplication anomalies
- Fibroids
- Advanced maternal age

**Pregnancy Failure**

**Increased loss rates**

**Once pregnant**
- Bleeding
- Slow fetal heart rate
- Subchorionic hematoma

**Pregnancy Failure**

**Definitive diagnosis**
- Embryo ≥ 7 mm* with no heartbeat
- Mean sac diameter ≥ 25 mm* with no heartbeat
- No heartbeat & gestational age 2 wks after gestational sac seen* (GA >7 wks by prior ultrasound)
- Sliding sac

*SRU Consensus Panel on Dx of Early Pregnancy Failure 2012

**Pregnancy Failure**

**Findings on follow up ultrasound**

<table>
<thead>
<tr>
<th>Current U/S Finding</th>
<th>Definite failed pregnancy if:</th>
<th>Suspicious for failed pregnancy if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational sac with no embryo</td>
<td>≥2 wks since GS without YS</td>
<td>7-13 days since GS without YS</td>
</tr>
<tr>
<td>Gestational sac with no embryo</td>
<td>≥11 days since GS with YS</td>
<td>7-10 days since GS with YS</td>
</tr>
</tbody>
</table>

*SRU Consensus Panel on Dx of Early Pregnancy Failure 2012

**GS = gestational sac; YS = yolk sac**

**Pregnancy Failure by Crown-Rump Length (CRL)**

**Rationale for ≥ 7 mm cutoff**
- Set value to virtually eliminate any false positive diagnoses (100% specificity)
- Prior criteria not stringent enough based on small numbers of cases
- Need to account for interobserver variability (± 15%)
One week later (7 weeks)

7.5 mm embryo

Rationale for ≥ 25 mm cutoff
- Set value to virtually eliminate any false positive diagnoses (100% specificity)
- Prior criteria not stringent enough
  Based on small numbers of cases
- Need to account for interobserver variability (± 19%)

Pregnancy Failure by Mean Sac Diameter (MSD)

Failed pregnancy

Mean sac diameter (MSD)

(35 + 20 + 28) ÷ 3 = 28 mm

Sliding Intrauterine Gestational Sac

- Gestational sac within uterine cavity, not embedded in decidua
- Shifts position within uterine cavity on realtime scanning

Failed pregnancy – Sliding sac
**Pregnancy Failure**

Suspicious but not definitive
- Embryo < 7 mm with no heartbeat
  - larger the embryo, higher the risk
- Mean sac diameter 16 - 24 mm
  - with no heartbeat
- > 6 weeks gestation by LMP with gestational sac, but no embryo

---

Suspicious for Failed pregnancy
Enlarged empty gestational sac (MSD = 19.3 mm)

---

**Pregnancy Failure**

High likelihood of subsequent pregnancy failure
- Small sac size (MSD – CRL < 5 mm)
  - even with heartbeat
- Embryonic bradycardia
  - (the slower the rate, the greater the risk)
- Large subchorionic hematoma
  - size > 50% gestational sac size

---

Suspicious for Failing Pregnancy
Small sac size
- MSD = 10.1
- CRL = 11.2
- Δ = – 1.1 mm

---

Suspicious for Failing Pregnancy
Small sac size
Demise 10 days later
**Slow Fetal Heart Rate**

Associated with first trimester pregnancy loss

Especially for FHR < 90 bpm

---

**Subchorionic Hematoma & Live Embryo**

Prognosis (risk of failed pregnancy)*

- Hematoma size
- Gestational age at diagnosis
- Maternal age

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>6.0-7.0</th>
<th>7.1-8.0</th>
<th>8.1-11.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demise %</td>
<td>19.6%</td>
<td>14.6%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal Age (Years)</th>
<th>&lt;35</th>
<th>≥35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demise %</td>
<td>9.6%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

*n=434; demise by end of 1st trimester

---

Subchorionic hematoma – 5.5 weeks

- Subjective size: Moderate
- Hematoma size >50% size of gestational sac
- Surrounds 25-50% of gestational sac
- Measured 19 x 16 x 10 mm

**Subchorionic Hematoma & Live Embryo**

Which method is best for assessing hematoma size?

- Subjective: small, moderate, large?
- Size compared to gestational sac? (%): ≤10; 10-25; 25-50; >50
- Fraction of gestational sac surrounded by hematoma? (%): ≤10; 10-25; 25-50; >50
- 3 orthogonal measurements to calculate “volume”?

---

**Subchorionic Hematoma & Live Embryo**

434 pregnancies 6-11 weeks

- Size compared to gestational sac (%): ≤10; 10-25; 25-50; >50
  
  Correlated best with outcome (p<0.001)
  
  X Subjective: small, moderate, large (p=0.142)
  
  X Fraction of gestational sac surrounded (%): ≤10; 10-25; 25-50; >50 (p=0.085)
  
  X 3 orthogonal measurements calculate “volume” (poor correlation, spurious results)
434 pregnancies 6-11 weeks*

**Hematoma Size as Fraction of Gestational Sac Size (p<0.001)**

<table>
<thead>
<tr>
<th>Hematoma Size as Fraction of Gestational Sac Size</th>
<th>Live</th>
<th>Demise</th>
<th>Demise %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10%</td>
<td>114</td>
<td>7</td>
<td>5.8%</td>
</tr>
<tr>
<td>10-25%</td>
<td>112</td>
<td>11</td>
<td>8.9%</td>
</tr>
<tr>
<td>25-50%</td>
<td>66</td>
<td>8</td>
<td>10.8%</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>89</td>
<td>27</td>
<td>23.3%</td>
</tr>
</tbody>
</table>

*Live at end of 1st trimester

**Pregnancy Failure**

Recommended follow up of suspicious but not definitive findings (IPUV*)

- Ultrasound, not hCG
- 7-10 days (in most cases)

*Intrauterine pregnancy of unknown viability

**hCG & No Intrauterine Gestational Sac**

Ultrasound diagnosis

- Pregnancy of Unknown Location (PUL)
- hCG & Ultrasound findings:
  - No intrauterine gestational sac or adnexal mass
- Ectopic Pregnancy
  - No intrauterine gestational sac & findings of ectopic pregnancy

**Ectopic Pregnancy**

Transvaginal Ultrasound Findings

**No intrauterine gestation**

- Adnexal mass separate from ovary
- Tubal ring
- Internal yolk sac
- Embryo with heartbeat
- Free fluid

**hCG Discriminatory Level**

Rationale for setting this:

If hCG > discriminatory level and
No intrauterine gestation (IUP) seen
Safe to treat suspected ectopic
Will not damage a normal pregnancy
**hCG Discriminatory Level**

Levels proposed (mIU/ml):
- 6,500 (1981)
- 3,600 (1985)
- 1,000-2,000 (1990 and beyond)

Improved equipment and transvaginal probes

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**Our Study**

Methods:
- Transvaginal sonograms 2000-2010
- Positive pregnancy test and no intrauterine fluid collection
- Subsequent live intrauterine gestation
- hCG at time of no IUP recorded
- Pregnancy outcomes collected

---

**hCG levels**

<table>
<thead>
<tr>
<th>hCG</th>
<th>N</th>
<th>Live at 14w*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1000</td>
<td>162</td>
<td>89.9%</td>
</tr>
<tr>
<td>1000-1499</td>
<td>19</td>
<td>88.6%</td>
</tr>
<tr>
<td>1500-1999</td>
<td>12</td>
<td>86.6%</td>
</tr>
<tr>
<td>≥ 2000</td>
<td>9</td>
<td>80.6%</td>
</tr>
</tbody>
</table>

*No difference in miscarriage rates among hCG groups (p>0.05)

---

**9 Cases with hCG ≥2000**

<table>
<thead>
<tr>
<th>hCG</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2215</td>
<td>Term singleton</td>
</tr>
<tr>
<td>2217</td>
<td>Term twins</td>
</tr>
<tr>
<td>2374</td>
<td>Term singleton</td>
</tr>
<tr>
<td>2530</td>
<td>Live at 21w, loss from chorio</td>
</tr>
<tr>
<td>2539</td>
<td>Term singleton</td>
</tr>
<tr>
<td>2993</td>
<td>Term singleton</td>
</tr>
<tr>
<td>4336</td>
<td>Term singleton</td>
</tr>
<tr>
<td>4476</td>
<td>Live at 7.6w, loss before 14w</td>
</tr>
<tr>
<td>6567</td>
<td>Live at 7.1w, slow FH, 8w demise</td>
</tr>
</tbody>
</table>

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**hCG & Ectopic Pregnancy***

- 6567 = Highest hCG with subsequent live IUP
- 4336 = Highest hCG with subsequent live born

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**US Finding**

<table>
<thead>
<tr>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A single hCG in a woman with an &quot;empty&quot; uterus on U/S: DOES NOT reliably distinguish between ectopic and intrauterine pregnancy</td>
</tr>
<tr>
<td>- DOES NOT definitively exclude a potentially normal IUP (though normal IUP is unlikely if &gt;3000 mIU/ml)</td>
</tr>
<tr>
<td>- DOES NOT exclude an ectopic pregnancy (even if &lt;1000 mIU/ml)</td>
</tr>
<tr>
<td>- DOES NOT justify presumptive treatment for ectopic pregnancy, using methotrexate or other medical/surgical means</td>
</tr>
<tr>
<td>- The concept of a &quot;discriminatory&quot; hCG level – an hCG value for ruling in or ruling out ectopic pregnancy at a single point in time – should not be used to guide management decisions</td>
</tr>
</tbody>
</table>

*SRU Consensus Panel on Dx of Early Pregnancy Failure 2012
**Safe Rule**

- No matter what the hCG, definitive interventions, like D&C or MTX, should be avoided in suspected but unproven ectopic pregnancy
- Unless patient is unstable, get f/u ultrasound and/or hCG before intervention

**Ectopic Pregnancy**

Transvaginal Ultrasound Findings
- No intrauterine gestation
- Adnexal mass separate from ovary
  - Tubal ring
  - Internal yolk sac
  - Embryo with heartbeat
- Free fluid

**231 Ectopic Pregnancies**

Ultrasound findings present in 94.8%
- Adnexal mass 94.4%
- Nonspecific mass 54.1%
- Tubal ring (no YS or heartbeat) 24.7%
- Yolk sac (no heartbeat) 8.3%
- Live embryo 7.4%
- Free fluid: Moderate – large 0.4%
  - (no adnexal mass)

*Frates et al. J Ultrasound Med 2014*

**Ectopic Pregnancy**

Ultrasound findings

<table>
<thead>
<tr>
<th>Ultrasound findings</th>
<th>Likelihood of ectopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine pregnancy (IUP)</td>
<td>~0%</td>
</tr>
<tr>
<td>No IUP, normal pelvis/simple cyst</td>
<td>1%</td>
</tr>
<tr>
<td>No IUP, complex mass</td>
<td>92%</td>
</tr>
<tr>
<td>No IUP, tubal ring</td>
<td>95%</td>
</tr>
<tr>
<td>Live embryo outside uterus</td>
<td>100%</td>
</tr>
</tbody>
</table>
**Doppler for Ectopic Pregnancy**

**Ultrasound findings**
- Adnexal mass

**Color Doppler findings**
- Rim of color around mass

**Spectral Doppler findings**
- Low resistance waveform

**Caution**
- Intraovarian lesion with rim of color is likely corpus luteum

**Doppler for Ectopic Pregnancy**

- Doppler has limited use over and above ultrasound.
- If there is an adnexal mass, Doppler does **not** assist the diagnosis, because the interpretation should already be probable ectopic.

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**Ectopic Pregnancy**

**Unusual Ectopic Pregnancies**

- Abdominal
- Interstitial (Cornual)
- Cervical
- Ovarian
- Heterotopic (IUP & ectopic)
- Cesarean section scar/defect implantation

---

**Interstitial Ectopic Pregnancy**

- Embedded in interstitial portion of tube
- Gestational sac upper outer edge of uterus
- Gestational sac outside uterine cavity
- Thin layer or no myometrium around outer gestational sac
- 3D imaging often helpful
**Heterotopic Pregnancy**

- Intrauterine & ectopic pregnancies coexisting
- **Incidence**
  - ~ 1 / 4,000 - 8,000 (natural)
  - 10x – 20x higher (Rx infertility)
- **Ultrasound findings**
  - Intrauterine gestation
  - Ectopic pregnancy

**Cervical Ectopic Pregnancy**

- Gestational sac implanted in the cervix
- Differential diagnosis includes miscarriage if no embryo with heartbeat
  - May slide within cervical canal
  - May pass on short-term follow up