Pregnancy of Unknown Location: The New Rules

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Disclosures: None

Learning Objectives

• Nomenclature regarding pregnancy of unknown location (PUL)
• Alternative approaches the diagnostic dilemma of evaluating a patient with a possible ectopic pregnancy.
• Understand the value of various diagnostic tests.
• Gain insight into the ultrasound findings in patients with an ectopic pregnancy
Consensus Nomenclature

1. Definite ectopic pregnancy (EP)
2. Probable EP
3. PUL
4. Probable intrauterine pregnancy
5. Definite IUP


Consensus Nomenclature

• Definite ectopic pregnancy (EP)
  – Extraterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)
• Probable EP
  – Inhomogeneous adnexal mass or extrauterine sac-like structure


Consensus Nomenclature

• Probable intrauterine pregnancy
  – Intrauterine echogenic sac-like structure
• Definite IUP
  – Intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)

Consensus Nomenclature

• PUL
  – no signs of either EP or IUP


Pregnancy of Unknown Location


Case Presentation

• 28 y.o. G1P0 presents with pelvic pain and scant vaginal spotting.
• LMP ~ 4-5 weeks ago
• + UPT at home
• Exam: VSS
  Uterus AV, NT, TNS
  Adnexa: NT, without masses
• hCG = 874 IU/L
Increase in hCG in early pregnancy

<table>
<thead>
<tr>
<th>Sampling Interval (days)</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>114</td>
</tr>
<tr>
<td>4</td>
<td>175</td>
</tr>
<tr>
<td>5</td>
<td>255</td>
</tr>
</tbody>
</table>

Kadar et. al. Obstet Gynecol 1981; 58: 162 (Yale)

Doubling time = 2.98 days
15% of normal pregnancies had abnormal ß-hCG increases

Kadar et. al. Obstet Gynecol 1981; 58: 162 (Yale)

Increase in hCG in early pregnancy

<table>
<thead>
<tr>
<th>Days</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.24 – 1.81</td>
<td>1.50</td>
</tr>
<tr>
<td>2</td>
<td>1.53 – 3.28</td>
<td>2.24</td>
</tr>
<tr>
<td>3</td>
<td>1.88 – 5.94</td>
<td>3.35</td>
</tr>
<tr>
<td>4</td>
<td>2.33 – 10.76</td>
<td>5.00</td>
</tr>
<tr>
<td>7</td>
<td>4.38 – 63.88</td>
<td>16.73</td>
</tr>
</tbody>
</table>

Case Presentation

Day 1  hCG = 874 IU/ml
Day 3  hCG = 1,056 IU/ml
Day 5  hCG = 1,110 IU/ml

Threshold vs. Discriminatory Levels

Threshold level
- Lowest β-hCG level at which a normal intrauterine pregnancy can be detected

Discriminatory level
- The level of β-hCG above which all normal intrauterine pregnancies should be seen

Threshold vs. Discriminatory Levels

Threshold level
- β-hCG = 400-500 mIU/mL (1st IRP)

Discriminatory level
- β-hCG = 1000-1500 mIU/mL (1st IRP)

Dependencies
- Transducer frequency, uterine position, body habitus, operator experience/ability
Evidence Against the hCG Discriminatory Level

- January 1, 2000 - December 31, 2010
- TVS and β-hCG on same day
- No intrauterine fluid collection
- Subsequent embryonic or fetal cardiac activity

Doubilet and Benson, J Ultrasound Med 2011; 30:1637-1642

<table>
<thead>
<tr>
<th>hCG (3-4th IS)</th>
<th># (202)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>162</td>
<td>80.2</td>
</tr>
<tr>
<td>1000-1499</td>
<td>19</td>
<td>9.4</td>
</tr>
<tr>
<td>1500-1999</td>
<td>12</td>
<td>5.9</td>
</tr>
<tr>
<td>2000</td>
<td>9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Doubilet and Benson, J Ultrasound Med 2011; 30:1637-1642

Reevaluation of Discriminatory and Threshold Levels

- 651 patients
- TVS and β-hCG within 6 hours of each other
- Known intrauterine pregnancies
- Findings visualized 99% of the time
- 1st, 3rd, or 4th International Standard
  - 2nd I.S. ~ ½ that of others

### Table 2: Discriminatory and Threshold Values, Serum hCG Human Chorionic Gonadotropin Levels

<table>
<thead>
<tr>
<th>Discriminatory Values</th>
<th>Gestational Sac</th>
<th>Yolk Sac</th>
<th>Embryo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold level</td>
<td>390</td>
<td>1094</td>
<td>1394</td>
</tr>
<tr>
<td>Discriminatory level</td>
<td>3510</td>
<td>17,716</td>
<td>47,685</td>
</tr>
</tbody>
</table>

Case Presentation

• TVs
  – Uterus
    • No evidence of IUP
  – Ovaries
    • Corpus luteum - left
  – Adnexa
    • No definite adnexal pathology
• Current terminology PUL
• Treatment MTX 50 mg/m²

Case Presentation

• 24 y.o. G2P0010 presents with scant vaginal spotting and pain
• LMP ~ 5 weeks ago
• Exam: VSS
  Uterus NSSC, NT; Adnexa: NT
• Initial: hCG = 710 IU/L
• Repeat in 2 days: hCG = 980 IU/L
Endometrial Thickness in Ectopic Pregnancy when hCG < Discriminatory Zone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean (mm)</th>
<th>Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine pregnancy</td>
<td>13.42</td>
<td>± 0.68</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>9.28</td>
<td>± 0.88</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>5.95</td>
<td>± 0.35</td>
</tr>
<tr>
<td>Abnormal pregnancy (97%)</td>
<td>≤ 8</td>
<td></td>
</tr>
</tbody>
</table>

Case Presentation - #3

- 28 y.o. G1P0 presents with pelvic pain and scant vaginal spotting.
- LMP ~ 7 weeks ago
- Exam: VSS
  - Uterus TNS;
  - Mild adnexal discomfort
- hCG = 4,634 IU/L
Intrauterine Fluid with Ectopic Pregnancy

229 patients with ectopic
• No intrauterine fluid 191 83.4
• Intrauterine fluid 38 16.6
  – Adnexal mass 33 86.8


Intrauterine Fluid with Ectopic Pregnancy

38 patients
• Type A 31 81.6
  – Pointy edged 30 78.9
  – Echoes 28 73.7
  – Located with the cavity 21 55.3
• Type B 7 18.4
  – Smooth walled
  – Located in decidua or uncertain

**Pointed edge Echoes or debris**

**Type A**
- Within the uterine cavity

**Type B**
- Ectopic Pregnancy
- Intrauterine Pregnancy

**Conclusions**
- **Findings**
  - A smooth-walled anechoic intrauterine cystic structure
  - No adnexal mass
- **Probability**
  - Intrauterine pregnancy: 99.8%
  - Ectopic pregnancy: 0.02%
### Adnexal Mass with Ectopic Pregnancy

<table>
<thead>
<tr>
<th>229 pts (38 ectopies)</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adnexal mass</td>
<td>33</td>
<td>86.8</td>
</tr>
<tr>
<td>No adnexal mass</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>- Type A</td>
<td>3</td>
<td>60.0</td>
</tr>
<tr>
<td>- Type B</td>
<td>2</td>
<td>40.0</td>
</tr>
</tbody>
</table>

TVS for Diagnosing Ectopies

Reviewed 10 studies

- 2216 patients
- Ectopic = 565 25.5%
- No ectopic = 1651 74.5%

**TVS for Diagnosing Ectopics**

**Inclusion criteria**
- Clinical suspicion of ectopic pregnancy
- All patients underwent TVS
- All cases of EP were surgically confirmed
- No adnexal masses were excluded, except simple cysts


**Criteria for ectopic pregnancy**
- **A**: Adnexal embryo with heartbeat
- **B**: Adnexal mass containing yolk sac or embryo
- **C**: Adnexal mass with central anechoic area and hyperechoic rim ("tubal ring")
- **D**: Any adnexal mass other than a simple cyst or an intraovarian lesion


**Adnexal Findings**

**TVS Criteria for Ectopic Pregnancy**

<table>
<thead>
<tr>
<th>TVS Finding</th>
<th>Likelihood of Ectopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrauterine embryo + heartbeat</td>
<td>100%</td>
</tr>
<tr>
<td>Adnexal mass with yolk sac or embryo</td>
<td>100%</td>
</tr>
<tr>
<td>Tubal ring</td>
<td>95%</td>
</tr>
<tr>
<td>Complex or solid adnexal mass</td>
<td>92%</td>
</tr>
</tbody>
</table>

Embryo without cardiac activity

Adnexal mass with yolk sac (100%)
Tubal ring (95%)

OVARY

MASS

Tubal ring (95%)

RIGHT TUBE

RIGHT ADNEKA

95%

92%
Diagnosing Ectopic Pregnancy
Six Strategies

- Ultrasound followed by quantitative hCG
- Quantitative hCG followed by ultrasound
- Progesterone followed by ultrasound and quantitative hCG
- Progesterone followed by quantitative hCG and ultrasound
- Ultrasound followed by repeat ultrasound
- Clinical examination


Ectopic Pregnancy and Serum P

Serum progesterone

- < 5 ng/ml
  - Abnormal pregnancy
  - Ectopic or intrauterine
- 15 ng/ml = Threshold
- > 25 ng/ml
  - Normal pregnancy in 97% of patients

Diagnosing Ectopic Pregnancy
Six Strategies-Outcomes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Days to Dx</th>
<th>Blood draws/10,000</th>
<th>Total Charge/Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>US → hCG</td>
<td>1.46</td>
<td>5,227</td>
<td>$1958</td>
</tr>
<tr>
<td>hCG → US</td>
<td>1.66</td>
<td>14,375</td>
<td>$1842</td>
</tr>
<tr>
<td>P → US → hCG</td>
<td>1.25</td>
<td>12,108</td>
<td>$1692</td>
</tr>
<tr>
<td>P → hCG → US</td>
<td>1.26</td>
<td>15,003</td>
<td>$1569</td>
</tr>
<tr>
<td>US → US</td>
<td>1.21</td>
<td>0</td>
<td>$2486</td>
</tr>
<tr>
<td>Clinical Exam</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70
**Diagnosing Ectopic Pregnancy**
Six Strategies-Outcomes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Missed EP/10,000</th>
<th>Interrupted IUP/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>US → hCG</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>hCG → US</td>
<td>0</td>
<td>122</td>
</tr>
<tr>
<td>P → US → hCG</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>P → hCG → US</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>US → US</td>
<td>0</td>
<td>121</td>
</tr>
<tr>
<td>Clinical Exam</td>
<td>940</td>
<td>0</td>
</tr>
</tbody>
</table>

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70

**Diagnosing Ectopic Pregnancy**
Six Strategies-Recommendations

- Ultrasound followed by hCG
- hCG followed by ultrasound
- Either progesterone protocol
  - More missed ectopic pregnancies
- Ultrasound followed by repeat ultrasound
  - May be applicable in poorly compliant patient
- Clinical exam only – NOT recommended

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70

**Case Presentation**

- 41 G2P0010 with LMP 3 weeks ago
- c/o vaginal bleeding and abdominal pain
- Unprotected intercourse x 10 years
- + UCG
Quantitative hCG = 78

Ectopic Pregnancy

hCG Dynamics with Spontaneous Resolution of Ectopic

Helsinki, Finland

118 patients

Entry criteria

- Decreasing or stable hCG
- No signs of rupture/intraperitoneal hemorrhage
- Adnexal mass < 4 cm
- No cardiac activity

Korhonen, Stenman, Ylostalo. Fertil Steril 1994; 61: 632-36 (Finland)
hCG Dynamics with Spontaneous Resolution of Ectopic

Helsinki, Finland
- TVS q 1-3 days
- Serial hCG until < 10 IU/L (3rd IS)
- Laparoscopy
  - Increasing hCG levels
  - Increasing abdominal pain
  - Intra-abdominal hemorrhage on TVS


Rate of Spontaneous Resolution

<table>
<thead>
<tr>
<th>hCG</th>
<th>Spontaneous Resolution Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG &lt; 200 IU/L</td>
<td>88%</td>
</tr>
<tr>
<td>hCG &gt; 2000 IU/L</td>
<td>25%</td>
</tr>
</tbody>
</table>


Initial hCG
Case Presentation

• 36 y.o. G3P0020 seen in ER with c/o slight spotting and mild abdominal discomfort
• Uterus: Mid-position, TNS
• Adnexa: No definite masses
• hCG = 357 IU/L
• Hct = 36.4
• D/C home with F/U 2 days in WCC

Case Presentation

• WCC – c/o increasing pain and weakness

hCG = 465 IU/L
Serum hCG and Tubal Rupture

<table>
<thead>
<tr>
<th>β-hCG (IU/L)</th>
<th>Unruptured</th>
<th>Ruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>9.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>100 – 999</td>
<td>47.3%</td>
<td>38.6%</td>
</tr>
<tr>
<td>1000 - 9,999</td>
<td>38.2%</td>
<td>38.6%</td>
</tr>
<tr>
<td>&gt; 10,000</td>
<td>5.3%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

Saxon et al. Obstet Gynecol 1997; 90: 46
(McGill, Cleveland Clinic)

Serum hCG and Tubal Rupture

<table>
<thead>
<tr>
<th>hCG, mIU/mL</th>
<th>Unruptured</th>
<th>Ruptured</th>
<th>Rupture Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1000</td>
<td>53</td>
<td>14 (41.2%)</td>
<td>20.9</td>
</tr>
<tr>
<td>1000-1999</td>
<td>14</td>
<td>6 (17.6%)</td>
<td>30.0</td>
</tr>
<tr>
<td>&gt; 2000</td>
<td>38</td>
<td>14 (41.2%)</td>
<td>26.9</td>
</tr>
</tbody>
</table>

Case Presentation

21 yo G1P0 at 6w3d by LMP
• c/o vaginal bleeding x 1 day
• LLQ pain x 1 day
• + home pregnancy test 3 days ago
• BC: progestin oral contraceptives
• Negative past gyn history
• Quantitative hCG = 25,340
Case Presentation

- Ultrasound
  - Uterus
    - IUP with + yolk sac, CRL c/w 5w6d
    - + cardiac activity
  - Left adnexa
    - Mass = 4 x 3 x 4 cm, with gestational sac
- Diagnosis: heterotopic pregnancy
Heterotopic Pregnancy

• More common with ART
• Incidence
  – Spontaneous 1:30,000
  – ART 1:110-1:667


Case presentation

• 28 y.o. G2P0010
• Presents with pelvic pain and vaginal spotting
• LMP = 7 weeks ago
• hCG: positive
Ultrasound Diagnosis of Interstitial Pregnancy

- Empty uterine cavity
- Chorionic sac > 1 cm from the lateral edge of the uterine cavity (endometrium)
- Thin (<5 mm) layer of myometrium surrounding the chorionic sac

Terminology

- **Interstitial pregnancy**
  - Embryo implants in the interstitial or intramural portion of the Fallopian tube

- **Cornual pregnancy**
  - Pregnancies that occur in a rudimentary horn, unicornuate uterus, cornual region of a septate uterus, a bicornuate uterus, or a uterus didelphys

- **Angular pregnancy**
  - Embryo implants in one of the lateral angles of the uterine cavity, medial to the utero-tubal junction
Terminology

• Interstitial pregnancy
  – Embryo implants in the interstitial or intramural portion of the Fallopian tube.

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  – Pregnancies that occur in a rudimentary horn, unicornuate uterus, cornual region of a septate uterus, a bicornuate uterus, or a uterus didelphys.

• Angular pregnancy
  – Embryo implants in one of the lateral angles of the uterine cavity at the utero-tubal junction.
Terminology

- **Interstitial pregnancy**
  - Embryo implants in the interstitial or intramural portion of the Fallopian tube

- **Cornual pregnancy**
  - Pregnancies that occur in a rudimentary horn, unicornuate uterus, cornual region of a septate uterus, a bicornuate uterus, or a uterus didelphys

- **Angular pregnancy**
  - Embryo implants in one of the lateral angles of the uterine cavity, medial to the utero-tubal junction
Case Presentation

• 29 y.o. G3P1011 presents to ED with c/o vaginal bleeding with clots. No tissue passed.
• hCG = 50,637 one week prior
• hCG = 71,460
• Hct = 40.9
Case Presentation

- Cervical pregnancy
- hCG = 25,9789
- Under transvaginal ultrasound, transcervical injection of MTX into the placenta and intracardiac KCl
- Ultrasound direction in the OR
- Admitted for observation

Cervical Ectopic
MTX + KCl

<table>
<thead>
<tr>
<th>Weeks from treatment</th>
<th>hCG levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>71,460</td>
</tr>
<tr>
<td>2</td>
<td>62,011</td>
</tr>
<tr>
<td>4</td>
<td>50,637</td>
</tr>
<tr>
<td>6</td>
<td>2,564</td>
</tr>
<tr>
<td>8</td>
<td>11,222</td>
</tr>
</tbody>
</table>

hCG levels vs weeks from treatment graph
Case Presentation

- 24 y.o. G2P1001 presents with pelvic pain and scant spotting
- LMP ~ 5 weeks ago
- Exam: VSS
  Uterus: TNS, moderate tenderness
  Adnexa: Slight fullness,
  ? Left mass
- Initial: hCG = 1,340 IU/L
Cesarean Scar Pregnancy

Treatment C-Section Scar Ectopic
Case Presentation

- 23 y.o. G2P1001
- Enters c/o slight spotting and cramping
- LMP = Unknown
- UCG = positive
- hCG = 2,392

12/30/10
hCG = 2392

ET = 17.84 mm
Consensus Nomenclature

- Pregnancy of unknown location (PUL)
  - Possible IUP
    - Increased endometrial thickness


Quantitative hCG

<table>
<thead>
<tr>
<th>Date</th>
<th>hCG Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/30/10</td>
<td>2392</td>
</tr>
<tr>
<td>1/01/11</td>
<td>7721</td>
</tr>
</tbody>
</table>
hCG = 7721
Ectopic Pregnancy-Summary

- Ultrasound can be justified prior to obtaining a quantitative hCG
  - ~50% of ruptured ectopics had hCG levels below the discriminatory zone (<1000 IU)
- Endometrial thickness when hCG < discriminatory level
  - An endometrial thickness < 8 mm is associated with an abnormal pregnancy 97% of the time
Ectopic Pregnancy-Summary

- The discriminatory level has changed
  - It may be as high as 2500-3500 IU/L
- A cystic structure within the endometrium, in the absence of an adnexal mass
  - Is associated with an IUP in > 99% of patients

Ectopic Pregnancy-Summary

- Finding an IUP r/o ectopic pregnancy
  - Exception: heterotopic pregnancy
    - (1:667-1:30,000)
- Finding of embryo + heart beat or yolk sac in adnexa
  - Diagnostic of ectopic pregnancy
- No IUP. Complex/solid mass, sep from ovary
  - 92% likelihood of ectopic

Thank You