Pregnancies of Unknown Location

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Whittington Hospital, London
Pregnancy of Unknown Location (PUL)

- Positive pregnancy test
- No pregnancy visualised on scan
- Not interchangeable with ‘ectopic pregnancy’
X Pregnancies of Unknown Location
9/40 Heavy bleeding with clots
5/40  Light PV bleeding
?/40 Lower abdominal discomfort
7/40 Moderate vaginal bleeding
Ectopic Pregnancy

Intra-Uterine Pregnancy (IUP)

Ectopic Pregnancy (EP)

Pregnancy of Unknown Location

Positive Pregnancy Test

TVS

70-90%

Diagnostic

Non-diagnostic

Failing PUL

IUP

EP

Persistent PUL

50-70%

7-20%
Practical Advice - PULs

1. Assess clinical situation

- 5/40 Light PV spotting
- 7/40 Severe lower abdominal pain
PUL

- Haemodynamically stable
  - Pain free
    - Expectant management
      - Serum hCG levels at 0 and 48 hrs +/- progesterone
  - Pain
    - ? Serum hCG
      - Consider laparoscopy

- Haemodynamically unstable
  - Pain
    - Consider laparoscopy/laparotomy
Haemodynamically stable
Pain free
Expectant management
Serum hCG levels at 0 and 48 hrs +/- progesterone

Haemodynamically stable
Pain
? Serum hCG
Consider laparoscopy

Haemodynamically unstable
Pain
Consider laparoscopy/laparotomy
Haemodynamically stable
Pain free

Expectant management
Serum hCG levels at 0 and 48 hrs +/- progesterone

Haemodynamically stable
Pain

? Serum hCG
Consider laparoscopy

Haemodynamically unstable
Pain

Consider laparoscopy/laparotomy
2. Expectant Management

- Safe for the majority of asymptomatic haemodynamically stable women with PULs

- No consensus on appropriate intervention rates

- Surgical intervention rates quoted as 0.3-11%
The combination of a positive pregnancy test and the absence of an IUP on TVS is an accepted indication for laparoscopy.

Serial measurements of hCG and progesterone, TVS and uterine curettage have been combined into various diagnostic algorithms when a pregnancy cannot be seen on TVS.
3. Predicting outcome

- **Hormones**
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
    - CA 125
    - Activin A
    - Inhibin A

- **Mathematical Models**
PUL

Haemodynamically stable
Pain free
Expectant management

Haemodynamically stable
Pain

Haemodynamically unstable
Pain
Consider laparoscopy/laparotomy

Serum hCG levels at 0 and 48 hrs +/- progesterone

? Intra-uterine Pregnancy

? Serum hCG
Consider laparoscopy

? Ectopic Pregnancy

? Failing PUL
3. Predicting outcome

- **Hormones**
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  - Progesterone
  - Other:
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    - Activin A
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- **Mathematical Models**
Serum hCG Levels

Single Levels

Serial Levels
Serum hCG Levels

- Single Levels
- Discriminatory Zone
- Serial Levels
Serum hCG Levels

- Single Levels
- Serial Levels
- Discriminatory Zone

- Developed with respect to transabdominal USS
- Lower levels of hCG used with TVS
- Using a single value of hCG in a PUL population is of limited value:
  - Many ectopic pregnancies have a low hCG
  - Clinicians may be falsely reassured
Intrauterine Pregnancies (IUPs)

- Kadar et al. (1981) first to describe the minimal rate of rise for an IUP to be 66% over 48hrs
- More recently minimal rise reported to be 53% (Barnhart et al. 2004)
- In clinical practice a more conservative cut-off of 35% has been suggested
Serum hCG Levels

Failing PULs
- A decline of 21-35% at 48 hours depending on initial hCG level (↑ levels at presentation –↑ rate of decrease)  
  (Barnhart et al. 2004)
- An hCG decrease of >13% (hCG ratio < 0.87) has been shown to have a sensitivity of 92.7% and a specificity of 96.7% for the prediction of a failing PUL
  (Condous et al., 2006)
Ectopic Pregnancies (EPs)
- ‘No single way to characterize the pattern of serum hCG behaviour’ (Silva et al., 2006)
- hCG profile mimicked IUP in 21% and a spontaneous miscarriage in 8% (Silva et al., 2006)
- Sensitivity of 83% for EP when IUP excluded by hCG rise < 35% and failing PUL excluded by hCG decrease > 21-35% (Seeber et al., 2006)
Evidence based management of PULs

Predicting outcome

- **Hormones**
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
    - CA 125
    - Activin A
    - Inhibin A

- **Mathematical Models**
Serum Progesterone Levels

Serum Progesterone

< 20 nmol/L

PPV > 95% to predict pregnancy failure
(Banerjee et al., 2001)

Viable IUPs reported with levels < 16nmol/L

> 60 nmol/L

‘Strongly’ associated with viable pregnancies

Discriminative capacity insufficient to diagnose ectopic pregnancy with certainty
(Mol et al., 1998)

Good at predicting viability but not location
Practical Advice - PULs

3. Predicting outcome

- **Hormones**
  - Human chorionic gonadotrophin (hCG)
  - Progesterone
  - Other:
    - Creatine kinase
    - CA 125
    - Activin A
    - Inhibin A

- **Mathematical Models**
Mathematical models

- **Prediction of failing PULs**
  - Probability of spontaneous resolution \( \frac{1}{1+e^{-z}} \)
  - Where \( z = -2.20 - 0.15 \times \text{progesterone (nmol/L)} + 3.36 \times \text{bleeding score} - 0.0013 \times \text{serum } \beta-\text{hCG (IU/L)} + 0.45 \times \text{endometrial thickness (mm)} \) (Banerjee et al., 2001)
  - PPV > 95% for the prediction of pregnancy resolution

- **Prediction of failing PULs, IUPs and EPs**
  - Logistic regression models based on the hCG ratio (hCG 48hrs/hCG 0 hrs) (Condous et al., 2004, Condous et al., 2007)
  - Sensitivities >90% for the detection of EP
<table>
<thead>
<tr>
<th>Prior cost to each class</th>
<th>True-pred</th>
<th>Fail</th>
<th>IUP</th>
<th>EP</th>
<th>Tot</th>
<th>Sensitivity</th>
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<th>PPV</th>
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</thead>
<tbody>
<tr>
<td>1: Failing 2: IUP 3: Ectopic</td>
<td>Total</td>
<td>Failing</td>
<td>66</td>
<td>1</td>
<td>26</td>
<td>93</td>
<td>Failing</td>
<td>70.97%</td>
<td>86.21%</td>
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<tr>
<td>Cost(prior)</td>
<td>1.0</td>
<td>1.0</td>
<td>5.00</td>
<td>IUP</td>
<td>0</td>
<td>64</td>
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<td>EP</td>
<td>12</td>
<td>12</td>
<td>77.90%</td>
<td>77.38%</td>
<td>98.48%</td>
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</table>

* $hcgratio = \frac{hcg_{48hr}}{hcg_{0hr}}$

<table>
<thead>
<tr>
<th>ID</th>
<th>hcg_0hr</th>
<th>hcg_48hr</th>
<th>hcgratio*</th>
<th>Posterior Probability</th>
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$hcG$ ratio = $hcG$ 48 hours / $hcG$ 0 hours
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<td>Failing 66 1 26 93</td>
<td>Failing 70.97% 86.21%</td>
<td>65.79%</td>
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<tr>
<td>Accuracy</td>
<td>IUP 0 64 11 75</td>
<td>IUP 85.33% 73.33% 96.97% 67.54%</td>
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<tr>
<td>EP 0 1 11 12</td>
<td>EP 91.67% 77.38% 22.92% 98.48%</td>
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hCG ratio = hCG 48 hours / hCG 0 hours
### Prior cost to each class

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</tr>
<tr>
<td>Tot</td>
<td>66</td>
<td>66</td>
<td>48</td>
<td>180</td>
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1: Failing  2: IUP  3: Ectopic

| Accuracy | IUP 0 | 64  | 11 | 75  | IUP 85.33% | 73.33% | 96.97% | 67.54% |
|----------|--------|-----|----|-----|            |        |        |        |
| EP       | 0      | 11  | 12 |     | EP 91.67%  | 77.38% | 22.92% | 98.48% |

\* hcgratio = hCG 48 hours / hCG 0 hours

### Real vs. Predicted Probabilities

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hCG ratio = hCG 48 hours / hCG 0 hours
Practical Advice - PULs

4. Follow-up

- Methods?
- Timing of visits
PUL

Haemodynamically stable
  Pain free
    Expectant management
      Serum hCG levels at 0 and 48 hrs +/- progesterone

Haemodynamically stable
  Pain
    ? Serum hCG
      Consider laparoscopy

Haemodynamically unstable
  Pain
    Consider laparoscopy/laparotomy

? Intra-uterine Pregnancy
? Ectopic Pregnancy
? Failing PUL
**PUL**

- **Haemodynamically stable**
  - **Pain free**
    - Expectant management
    - **Serum hCG levels at 0 and 48 hrs +/- progesterone**
      - ? Intra-uterine Pregnancy
      - Rescan in 1 week to confirm pregnancy location

- **Haemodynamically stable**
  - **Pain**
    - ? Serum hCG
    - Consider laparoscopy
      - ? Ectopic Pregnancy

- **Haemodynamically unstable**
  - **Pain**
    - Consider laparoscopy/laparotomy
    - ? Failing PUL
      - Repeat serum hCG in 1 week to confirm failing pregnancy
PUL

Haemodynamically stable
- Pain free
  - Expectant management
    - Serum hCG levels at 0 and 48 hrs +/- progesterone
      - ? Intra-uterine Pregnancy
      - ? Ectopic Pregnancy
      - Rescan in 1 week to confirm pregnancy location
        - Early IUP
        - Ectopic Pregnancy
        - PUL
  - ? Serum hCG
    - Consider laparoscopy
      - ? Ectopic Pregnancy

Haemodynamically stable
- Pain
  - ? Serum hCG
    - Consider laparoscopy

Haemodynamically unstable
- Pain
  - Consider laparoscopy/laparotomy
  - ? Failing PUL
    - Repeat serum hCG in 1 week to confirm failing pregnancy
PUL

Haemodynamically stable
Pain free

Expectant management
Serum hCG levels at 0 and 48 hrs +/- progesterone

? Intra-uterine Pregnancy

Rescan in 1 week to confirm pregnancy location

Haemodynamically stable
Pain

? Serum hCG
Consider laparoscopy

? Ectopic Pregnancy

Haemodynamically unstable
Pain

Consider laparoscopy/laparotomy

? Failing PUL
Repeat serum hCG in 1 week to confirm failing pregnancy
PUL

Haemodynamically stable
- Pain free
  - Expectant management
    - Serum hCG levels at 0 and 48 hrs +/- progesterone
      - ? Intra-uterine Pregnancy
      - ? Ectopic Pregnancy
        - Rescan in 1 week to confirm pregnancy location
  - ? Serum hCG
    - Consider laparoscopy
    - ? Failing PUL
      - Repeat serum hCG in 1 week to confirm failing pregnancy
        - Consider weekly monitoring until < 15 IU/L

Haemodynamically stable
- Pain
  - ? Serum hCG
  - Consider laparoscopy

Haemodynamically unstable
- Pain
  - Consider laparoscopy/laparotomy
Rationalizing the follow-up of PULs

Hum Reprod 2007; 22:1744-50

0 hrs

TVS

PUL

Serum hCG
0 hrs  48 hrs

TVS  PUL  Repeat hCG  Model Prediction  Failing PUL

Serum hCG
0 hrs 48 hrs

TVS
PUL
Serum hCG
Repeat hCG
Model Prediction
Confirmed Failing PUL if hCG ratio < 0.87*
Failing PUL
IUP
Ectopic

* Condous et al BJOG 2006
0 hrs

TVS

PUL

Repeat hCG

Model Prediction

Confirmed Failing PUL if hCG ratio < 0.87*

Failing PUL

Repeat hCG if initial hCG ratio >0.87

Day 7

IUP

Ectopic

Repeat TVS

Serum hCG

Advised representation before day 7 if any pain, bleeding.
0 hrs

TVS

PUL

Repeat hCG

Model Prediction

IUP

Ectopic

48 hrs

Confirm Failing PUL if hCG ratio < 0.87*

Repeat hCG if initial hCG ratio > 0.87

Failing PUL

Repeat TVS

Confirmed IUP

Confirmed EP

Day 7

7 days – 3 visits

Confirmed IUP

7 days – 3 visits

Confirmed EP

Failing PULs – 2 blood tests and 1 USS / 48 hrs - 2 visits

IUP – 2 blood tests and 2 USS / 7 days – 3 visits

EP – 2 blood tests and 2 USS / 7 days – 3 visits
Rationalizing follow-up of PULs

- **0 hrs**
  - TVS
  - Serum hCG

- **48 hrs**
  - Repeat hCG
  - Model Prediction
  - Failing PUL
  - Repeat hCG if initial hCG ratio >0.87

- **Day 7**
  - Repeat TVS
  - Confirmed IUP
  - Confirmed EP

- **231 PULs** (64%)
- **363 PULs** (100%)
- **132 PULs** (36%)
- **108 PULs** (36%)
- **14 PULs** (3%)
- **10 PULs** (3%)
PUL

Haemodynamically stable
- Pain free
  - Expectant management
    - Serum hCG levels at 0 and 48 hrs +/- progesterone
      - ? Intra-uterine Pregnancy
      - ? Ectopic Pregnancy
        - Rescan in 1 week to confirm pregnancy location
          - Early IUP
          - Ectopic Pregnancy
          - PUL

Haemodynamically stable
- Pain
  - ? Serum hCG
    - Consider laparoscopy

Haemodynamically unstable
- Pain
  - Consider laparoscopy/laparotomy
  - Repeat serum hCG in 1 week to confirm failing pregnancy

- Failing PUL
Summary

1. Expectant management suitable for majority of women
2. No consensus on appropriate intervention rates but no routine role for curettage
3. Serum hCG and progesterone levels useful, but no role for single hCG measurement
4. Mathematical models may be useful
5. Follow-up visits may be rationalised using management algorithms