PRE-Congress Course 3

Risk factors for recurrent pregnancy loss – more pieces of the puzzle.

Special Interest Group Early Pregnancy
London - UK, 7 July 2013
Risk factors for recurrent pregnancy loss – more pieces of the puzzle

London, United Kingdom
7 July 2013

Organised by
The ESHRE Special Interest Group Early Pregnancy
Contents

Course coordinators, course description and target audience  Page 5

Programme  Page 7

Speakers’ contributions

Diagnosis solutions for pregnancy of unknown location (PUL) - The role of ultrasound - **Emma Kirk - United Kingdom**  Page 9

Diagnosis solutions for pregnancy of unknown location (PUL) - The role of hCG measurements - **Kurt Barnhart - U.S.A.**  Page 24

How PULs affect future pregnancy outcomes: new ESHRE guidelines - **Astrid Marie Kolte - Denmark**  Page 36

When to screen for thyroid function abnormalities? - **Rosa Vissenberg - The Netherlands**  Page 45

Thyroid antibodies and miscarriage: clinical trial - **Arri Coomarasamy - United Kingdom**  Page 60

Life style factors increase the risk of recurrent miscarriage - **William H. Kutteh - U.S.A.**  Page 66

The impact of genetic testing for couples with recurrent miscarriage - **Fleur Vansenne - The Netherlands**  Page 84

The influence of advanced maternal age: major cause of recurrent pregnancy loss - **Mary Stephenson - U.S.A.**  Page 95

NK cells - **Siobhan Quenby - United Kingdom**  Page 103

NICE guidelines 2012 – dissemination and implementation - **Caroline Overton - United Kingdom**  Page 118

Upcoming ESHRE Campus Courses  Page 131

Notes  Page 132
Course coordinators

Mariëtte Goddijn (The Netherlands)

Course description

This pre-congress course will address the risk factors involved in recurrent pregnancy loss and focuses on potential therapeutic consequences.

Target audience

Reproductive gynaecologists and physicians
Scientific programme

Pregnancies of unknown location (PUL)
Chairman: Siobhan Quenby - United Kingdom

09:00 - 09:20 Diagnosis solutions for pregnancy of unknown location (PUL) - The role of ultrasound
Emma Kirk - United Kingdom

09:20 - 09:40 Diagnosis solutions for pregnancy of unknown location (PUL) - The role of hCG measurements
Kurt Barnhart - U.S.A.

09:40 - 10:00 How PULs affect future pregnancy outcomes: new ESHRE guidelines
Astrid Marie Kolte - Denmark

10:00 - 10:30 Interactive discussion with the speakers and audience: which diagnostic tests to use; how to inform patients about their prognosis

10:30 - 11:00 Coffee break

Thyroid abnormalities and early pregnancy
Chairman: Mariette Goddijn - The Netherlands

11:00 - 11:30 When to screen for thyroid function abnormalities?
Rosa Vissenberg - The Netherlands

11:30 - 12:00 Thyroid antibodies and miscarriage: clinical trial
Arri Coomarasamy - United Kingdom

12:00 - 12:30 Discussion with the speakers and audience: diagnostic tests in setting of scientific studies; RCT design

12:30 - 13:30 Lunch

Societal and life style factors
Chairman: to be announced

13:30 - 13:50 Life style factors increase the risk of recurrent miscarriage
William H. Kutteh - U.S.A.

13:50 - 14:10 The impact of genetic testing for couples with recurrent miscarriage
Fleur Vansenne - The Netherlands

14:10 - 14:30 The influence of advanced maternal age: major cause of recurrent pregnancy loss
Mary Stephenson - U.S.A.

14:30 - 15:00 Discussion with speakers and audience: how to fight bad habits

15:00 - 15:30 Coffee break

New thoughts
Chairman: Mariette Goddijn - The Netherlands

15:30 - 16:00 NK cells
Siobhan Quenby - United Kingdom

16:00 - 16:30 NICE guidelines 2012 – dissemination and implementation
Caroline Overton - United Kingdom

16:30 - 17:00 Discussion with speakers and audience: early pregnancy research networks – bridging the 'pond'
Mariette Goddijn - The Netherlands

16:30 - 17:00  Discussion with speakers and audience: early pregnancy research networks – bridging the 'pond'

Mary Stephenson - U.S.A.
Diagnostic Solutions for Pregnancy of Unknown Location – The Role of Ultrasound

Emma Kirk
MRCPG MD
Whittington Hospital, London

Objectives

1. Define Pregnancy of Unknown Location and subsequent pregnancy outcomes
2. Appreciate the use of ultrasound in diagnosis and management of PULs

Diagram:

Positive Pregnancy Test

- 70-90% Diagnostic
- 10-30% Non-diagnostic

TVS

- Intra-Uterine Pregnancy (IUP)
- Ectopic Pregnancy (EP)
- Pregnancy of Unknown Location

- Failing PUL
- Persistent PUL
Pregnancy of Unknown Location (PUL)

- Positive pregnancy test
- No evidence of an intra-uterine or extra-uterine pregnancy on TVS

Pregnancy of Unknown Location

- 5-42% of women attending for USS in Early Pregnancy
- 8-10% in specialized Early Pregnancy Units
- Rates should be < 15%

Diagnosis

- PUL not a diagnostic term
- Classification term only
- All women need to be followed up in order to determine final clinical outcome
Diagnosis

A woman had an ultrasound examination in very early pregnancy where a diagnosis of 'pregnancy of unknown location' was made, after which serial hCG measurements were arranged. A few weeks later she was admitted to another hospital because of diarrhoea, dizziness, abdominal pain and vaginal bleeding. Repeat ultrasound examination a few hours later queried the presence of a small (9mm) intrauterine sac and a haemoperitoneum. It was decided to perform a uterine evacuation and consider laparoscopy if products of conception were not obtained. An evacuation procedure alone was performed by a junior doctor unfamiliar with the woman, who was then returned to the postoperative ward where she collapsed and died several hours later. Autopsy revealed massive intraperitoneal haemorrhage and a ruptured tubal pregnancy.

The Role of Ultrasound

1. Initial classification

1. Follow-up

1. Classification as a PUL

- Absence of an intra-uterine pregnancy or an ectopic pregnancy
- Clear criteria for diagnosing intra-uterine pregnancies and ectopic pregnancies.
1. Classification as a PUL

- PUL or early IUP?

![Image of 5/40 PV spotting](Image1)

![Image of 7/40 PV spotting](Image2)

1. Classification as a PUL

- PUL or early IUP?

![Image of 5/40 PV spotting](Image1)

![Image of 7/40 PV spotting](Image2)

1. Classification as a PUL

- PUL or miscarriage?

![Image of 9/40 Heavy bleeding with clots](Image1)

![Image of 7/40 PV spotting](Image2)

6% incidence of ectopic pregnancy
Condous et al., 2005
1. Classification as a PUL

- PUL or miscarriage?

- LMP Pain, light bleeding

![Ultrasound image]

1. Classification as a PUL

- PUL or ectopic pregnancy?

- 7/40 PV spotting

![Ultrasound image]

What is a PUL?

<table>
<thead>
<tr>
<th>Empty uterus, no signs of an IUP or EP</th>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early intra-uterine gestational sac</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extra-uterine inhomogeneous mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>? Small amount or retained products of conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>? Yes ? Yes</td>
</tr>
</tbody>
</table>
What is a PUL?

<table>
<thead>
<tr>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty uterus, no signs of an IUP or EP</td>
<td>Yes</td>
</tr>
<tr>
<td>Early intra-uterine gestational sac</td>
<td>No</td>
</tr>
<tr>
<td>Extra-uterine inhomogeneous mass</td>
<td>No</td>
</tr>
<tr>
<td>? Small amount or retained products of conception</td>
<td>? Yes</td>
</tr>
</tbody>
</table>
### What is a PUL?

<table>
<thead>
<tr>
<th>Description</th>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty uterus, no signs of an IUP or EP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Early intra-uterine gestational sac</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Extra-uterine inhomogeneous mass</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>? Small amount or retained products of conception</td>
<td>? Yes</td>
<td>? Yes</td>
</tr>
</tbody>
</table>

### 1. Classification as a PUL

- **Definite EP (Extra-uterine gestational sac with yolk sac and/or embryo (± cardiac activity))**
- **Probable EP (Inhomogeneous adnexal mass or extra-uterine sac-like structure)**
- **PUL (No signs of an IUP or EP on TVS)**
- **Probable IUP (Intrauterine echogenic sac-like structure)**
- **Definite IUP (Intrauterine gestational sac with yolk sac and/or embryo (± cardiac activity))**

### 2. Follow-up

- **Final clinical outcomes**
- **Management**
PUL Outcome

PUL

- Intra-uterine Pregnancy
  - Gestational sac only
  - Sac with yolk sac
  - Sac with CRL
  - Empty sac (anembryonic)
  - Delayed miscarriage
  - Incomplete miscarriage

- Ectopic Pregnancy
  - 7-20%

- Failing PUL or Spontaneous Miscarriage
  - 50-70%

Intra-uterine Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational sac only</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sac with yolk sac</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sac with CRL</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Empty sac (anembryonic)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Delayed miscarriage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Incomplete miscarriage</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>UK</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Sac with a yolk sac /CRL</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Empty gestational sac</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Inhomogeneous mass</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>No chorionic villi on uterine curettage and rising hCG level</td>
<td>Persisting PUL</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UK</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sac with a yolk sac /CRL</td>
<td>Yes</td>
</tr>
<tr>
<td>Empty gestational sac</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhomogeneous mass</td>
<td>Yes</td>
</tr>
<tr>
<td>No chorionic villi on uterine curettage and rising hCG level</td>
<td>Persisting PUL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure</th>
<th>Spontaneous miscarriage</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>USA</td>
</tr>
<tr>
<td>Spontaneous decrease in hCG</td>
<td>Spontaneous decrease in hCG</td>
</tr>
<tr>
<td>Non-viable pregnancy on TVS</td>
<td>Non-viable pregnancy on TVS</td>
</tr>
<tr>
<td>Histological diagnosis of chorionic villi</td>
<td>Histological diagnosis of chorionic villi</td>
</tr>
<tr>
<td>No chorionic villi and spontaneous decrease in hCG</td>
<td>No chorionic villi and spontaneous decrease in hCG</td>
</tr>
</tbody>
</table>
1. Clinical Assessment

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

PUL

Haemodynamically stable
Pain free

Expectant management
Serum hCG & progesterone / hCG 0 & 48 hours

Haemodynamically stable
Pain

? Serum hCG
Consider laparoscopy

Haemodynamically unstable
Pain

Consider laparoscopy/laparotomy

2. Follow-up

1. Clinical assessment
2. Expectant management
3. Prediction of outcome
4. Confirmation of outcome
5. Surgical intervention
2. Expectant Management

- Majority of women will be relatively asymptomatic and haemodynamically stable
- Expectant management has been shown to be safe
- All women should be counseled about the possible outcomes and ideally given written information
2. Expectant Management

- Majority resolve without intervention
- No consensus on intervention rates
- Reported surgical intervention rates 0.5-11%

3. Prediction of outcome

PUL

IUP  Ectopic Pregnancy  Failing PUL

3. Prediction of outcome

PUL

Serum Biochemistry

Serial hCG
hCG at 0 and 48 hours

hCG and progesterone
hCG and progesterone at 0 hours

4. Confirmation of outcome

- TVS
- Serum hCG levels
- Urinary pregnancy test
- Histology
Summary
PULs – Role of Ultrasound

1. Classification as a PUL based on initial USS findings

2. USS used to confirm final clinical outcome:
   - Intrauterine pregnancies – viable and non-viable
   - Ectopic pregnancies
Diagnosis solutions for pregnancy of unknown location (PUL) - The role of hCG measurements

- Kurt Barnhart, M.D., M.S.C.E.
  - William Shippen, Jr., Professor of Obstetrics and Gynecology
  - Penn Fertility Care
  - Perlman School of Medicine at the University of Pennsylvania

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Discuss potential pitfalls in the diagnosis of women with a pregnancy of unknown location.
- Integrate new nomenclature for the definitive ultimate diagnosis of women with a pregnancy of unknown location.
- Understand the role of hCG in the evaluation of a woman with a PUL

DISCLOSURE

- Nothing to disclose
Algorithm for the diagnosis of ectopic pregnancy in a hemodynamically stable patient

Modern Management

- Ultrasound needs clinical context
- hCG surveillance can result in error
- The Discriminatory Zone is too low
- Premature surveillance can lead to error
- Pregnancy of unknown location (PUL)
  - In particular the management of a persistent PUL is a clinical conundrum

Utility of Ultrasound Above and Below the Discriminatory Zone

<table>
<thead>
<tr>
<th></th>
<th>Intratertine pregnancy</th>
<th>Miscarriage</th>
<th>Ectopic pregnancy</th>
<th>Non-diagnostic</th>
<th>Lost to follow-up</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis at presentation</td>
<td>198 (59.0%)</td>
<td>57 (17.0%)</td>
<td>19 (6.0%)</td>
<td>59 (18.0%)</td>
<td>______</td>
<td>______</td>
<td>333 (100%)</td>
</tr>
<tr>
<td>hCG follow-up</td>
<td>200 (60.0%)</td>
<td>82 (24.6%)</td>
<td>27 (8.0%)</td>
<td>______</td>
<td>22 (6.8%)</td>
<td>2 (0.6%)</td>
<td>333 (100%)</td>
</tr>
</tbody>
</table>

### Utility of Ultrasound Above and Below the Discriminatory Zone

<table>
<thead>
<tr>
<th>Ultrasound Diagnosis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine pregnancy</td>
<td>98%*</td>
<td>90%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>73%*</td>
<td>93%</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>80%*</td>
<td>99%</td>
<td>86%</td>
<td>99%</td>
</tr>
</tbody>
</table>


### Utility of Ultrasound Above and Below the Discriminatory Zone (DZ)

<table>
<thead>
<tr>
<th>Ultrasound Diagnosis</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine pregnancy</td>
<td>33%*</td>
<td>98%</td>
<td>80%</td>
<td>86%</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>28%*</td>
<td>100%</td>
<td>100%</td>
<td>47%</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>25%*</td>
<td>96%</td>
<td>60%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Discriminatory Zone

• What has changed?
  – IRP has changed so now 1500 first IU is about 1900 4th IU
  – Most women get US in first trimester (even without symptoms)
  – Ruptured EP uncommon, clinician very aware of risk
    • Effort has shifted to avoid interruption of a desired IUP
    • Methotrexate is common and easy to administer
    • More scans = more false positives (false negatives)

What is the Discriminatory Zone?

• Surrogate for gestation age
  – Level at which normal milestones should be identified (gestational sac): the level does not discriminate location
  – The best DZ is gestational age
    • ≤ 5 5/7 weeks (40 days) regardless of number of gestations
  – Very wide variation in hCG in first trimester
• Not all women know their LMP
  – Maybe off by days, or at times off by 4 weeks
• DZ may need to be 3000 or higher*

*Dockikian T, Benson C. J Ultrasound Med 2011;30:1637-1642
*Metha et al, Radiology 1997;205:569-573

Case Presentation

• Your beeper goes off Friday afternoon, before your planned trip to ASRM.
• Your nurse calls you: Ms. Smith called your nurse.
  – Ms. Smith has a home pregnancy test is positive, and she THINKS she is about 2 weeks late for her period.
  – She has moderate pain in her left side and has been spotting for 4 days.
  – She is a G4 P0, with three miscarriages in the first trimester.
Case Presentation

- Ms. Smith’s hCG level is 1000 mIU/mL.
- She is clinically stable.
- This is a desired pregnancy.

Normal Rise in hCG

- Fit the curve of women who presented to ED at risk for EP who were definitively diagnosed with a viable IUP
- 293 subjects, 873 observations
  - Average age 24 years
  - Average G 2.4; P 0.8
  - Average hCG value 1000 mIU/mL
- Fit a number of models:
  - Linear, spline, exponential
Increase in hCG value at different days (as a percent of initial value)

<table>
<thead>
<tr>
<th>quartile</th>
<th>slope 1 day</th>
<th>2 day</th>
<th>3 days</th>
<th>4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>1.23</td>
<td>1.23</td>
<td>1.53</td>
<td>1.84</td>
</tr>
<tr>
<td>95</td>
<td>1.30</td>
<td>1.30</td>
<td>1.69</td>
<td>2.19</td>
</tr>
<tr>
<td>85</td>
<td>1.37</td>
<td>1.36</td>
<td>1.87</td>
<td>2.55</td>
</tr>
<tr>
<td>50</td>
<td>1.50</td>
<td>1.50</td>
<td>2.22</td>
<td>3.31</td>
</tr>
<tr>
<td>10</td>
<td>1.66</td>
<td>1.66</td>
<td>2.76</td>
<td>4.58</td>
</tr>
<tr>
<td>1</td>
<td>1.81</td>
<td>1.81</td>
<td>3.29</td>
<td>5.96</td>
</tr>
</tbody>
</table>

Normal Fall in hCG

- Fit the curve of women who presented to ED at risk for EP who were definitively diagnosed with a complete SAB
- 719 subjects, 2914 observations
  - Serum hCG confirmed to be > 5
- Fit a number of models:
  - Linear, quadratic, cuboidal, change point with random intercept and random effect
- Final model was random linear effect dependent on initial hCG value

Curve of Complete Miscarriage

Normal Fall of hCG for Complete SAB

<table>
<thead>
<tr>
<th>Initial hCG value (mIU/mL)</th>
<th>hCG value at 2 days (mIU/mL)</th>
<th>hCG value at 7 days (mIU/mL)</th>
<th>hCG value at 21 days (mIU/mL)</th>
<th>Days to negative hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>256</td>
<td>48</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>447 (21%)</td>
<td>337 (60%)</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>513</td>
<td>96</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>894</td>
<td>675</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>1027</td>
<td>193</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>1788</td>
<td>1351</td>
<td>616</td>
<td></td>
</tr>
<tr>
<td>5000</td>
<td>2567</td>
<td>484</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>4470 (35%)</td>
<td>3378 (84%)</td>
<td>1541</td>
<td></td>
</tr>
</tbody>
</table>

### Performance in Validation Cohort versus Original Cohort

<table>
<thead>
<tr>
<th>Expected Two-Day Rise for an IUP</th>
<th>Sensitivity for EP (%)</th>
<th>Sensitivity for IUP (%)</th>
<th>Mean number of days saved (range)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>Original²</td>
<td>Validation</td>
<td>Original²</td>
</tr>
<tr>
<td>35% Rise in hCG (0-35)</td>
<td>93 92</td>
<td>95</td>
<td>(0-35)</td>
</tr>
<tr>
<td></td>
<td>2.87</td>
<td>2.64</td>
<td></td>
</tr>
<tr>
<td>53% Rise in hCG (0-34)</td>
<td>91 88</td>
<td>93 90</td>
<td>(0-34)</td>
</tr>
<tr>
<td></td>
<td>3.27</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>71% Rise in hCG (0-37)</td>
<td>92 91</td>
<td>73 78</td>
<td>(0-37)</td>
</tr>
<tr>
<td></td>
<td>3.44</td>
<td>2.94</td>
<td></td>
</tr>
</tbody>
</table>


### Performance in Validation Cohort versus Original Cohort

<table>
<thead>
<tr>
<th>Expected Two-Day Rise for an IUP</th>
<th>Number of misclassified IUPs (%)</th>
<th>Number of misclassified EPs (%)</th>
<th>Number of miscarriages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>Validation Original</td>
<td>Validation Original</td>
<td>Validation Original</td>
</tr>
<tr>
<td>35% Rise in hCG (0-35)</td>
<td>30 (16.8)</td>
<td>34 (17.3)</td>
<td>20 (12.6)</td>
</tr>
<tr>
<td>53% Rise in hCG (0-34)</td>
<td>16 (8.9)</td>
<td>24 (12.2)</td>
<td>45 (17.4)</td>
</tr>
<tr>
<td>71% Rise in hCG (0-37)</td>
<td>14 (7.4)</td>
<td>18 (9.2)</td>
<td>71 (27.4)</td>
</tr>
</tbody>
</table>


### How does Misclassification Occur?

- Of 30 (17%) patients with “missed” EP (classified as IUP or SAB): 24 has “NL rise” and 6 had “NL fall”
  - 6 were diagnosed due to pain (3 ruptured)
  - Rupture was 0.03% of cohort or 1.7% of EP
- Of 22 (8%) patients with “missed” IUP (classified as EP or SAB):
  - 18 had rise less than 35%
  - 2 had change in direction

How does Misclassification Occur?

How did hCG mislead us into an error?

Such that we “missed” the IUP?

- 13/20 has findings on US suggesting an IUP
- Many of “abnormal” hCG values were the first 2 values and where below 500
- If one considered a third hCG; 6 were reclassified (correctly) as an IUP
  - BUT 9 EP and 2 SAB were reclassified (incorrectly) as an IUP

Practice Patterns Across the Pond

- USA: more aggressive strategies in the diagnosis of women at risk for ectopic pregnancy
  - Determine viability by serial hCG and then distinguish spontaneous abortion from that of EP
  - Use of uterine evacuation
  - Little presumptive diagnosis

- UK: more conservative approach
  - More liberal use of ultrasound in diagnosis
  - Identify Pregnancy of Unknown location
  - Use first 2 hCG values to predict outcome
  - Little use of surgical intervention, more expectant management

Prediction of ectopic pregnancy in women with a pregnancy of unknown location –M4 Model


Validation of M4 with USA data

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK (M4)</td>
<td>68.0</td>
<td>69.6</td>
<td>0.900 (0.812, 0.988)</td>
</tr>
<tr>
<td>US</td>
<td>45.3</td>
<td>67.7</td>
<td>0.620 (0.578, 0.672)</td>
</tr>
<tr>
<td>Adjusted US</td>
<td>54.0</td>
<td>87.4</td>
<td>0.821 (0.778, 0.865)</td>
</tr>
<tr>
<td>IUP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK (M4)</td>
<td>85.9</td>
<td>96.3</td>
<td>0.974 (0.954, 0.994)</td>
</tr>
<tr>
<td>US</td>
<td>64.1</td>
<td>92.8</td>
<td>0.861 (0.841, 0.880)</td>
</tr>
<tr>
<td>Adjusted US</td>
<td>51.9</td>
<td>83.1</td>
<td>0.903 (0.930, 0.977)</td>
</tr>
</tbody>
</table>

Failing PUL, (UK) / SAB (US)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (M4)</td>
<td>87.2</td>
<td>97.5</td>
<td>0.978 (0.954, 1.000)</td>
</tr>
<tr>
<td>US</td>
<td>61.4</td>
<td>83.0</td>
<td>0.933 (0.913, 0.953)</td>
</tr>
<tr>
<td>Adjusted US</td>
<td>83.1</td>
<td>83.1</td>
<td>0.929 (0.907, 0.952)</td>
</tr>
</tbody>
</table>

Two hCG values may not be enough

<table>
<thead>
<tr>
<th></th>
<th>Day 2 vs Day 4</th>
<th>Day 2 vs Day 7</th>
<th>Day 4 vs Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.3* 4.4 4.9*</td>
<td>-1.7 8.3 0.5*</td>
<td>-4.3 6.9 2.8*</td>
</tr>
</tbody>
</table>

Net Reclassification Index (NRI) is the total net reclassification improvement in EP prediction, calculated as the sum of NRIE, the net reclassification improvement in EP prediction among those with an ultimate EP diagnosis, and NRIN, the net reclassification improvement in EP prediction among those with an ultimate IUP or SAB diagnosis.

J. Zee, KT Barnhart et al. 2012 ARSM

Summary

- Most women with an abnormal early gestation are diagnosed with ultrasound
- A single hCG can not help with viability or location
- Serial hCG values can assist in identification of viability
- Case with slow increase or clearance are at risk for EP (but may need more than 2 values)
- hCG values are NOT diagnostic

Take Home Message

A single value of hCG cannot determine location or viability of gestation

A single hCG, regardless of its level, does not justify presumptive treatment for ectopic pregnancy using methotrexate or other medical/surgical means
How pregnancies of unknown location (PULs) affect future pregnancy outcome

- new ESHRE guidelines

Astrid Marie Kolte, MD, PhD fellow
Recurrent Miscarriage Unit, Fertility Clinic 4071
University Hospital Copenhagen, Rigshospitalet
Denmark

Conflict of interest

I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content.

Learning objectives

• To give an overview of definitions of early pregnancy events

• To present current knowledge of PULs and their impact on prognosis for recurrent miscarriage

• To discuss guideline recommendations concerning PULs.
Clinical problem

- Patient 1, 33 years
  - Dec. 2005: Miscarriage 6 wks
  - May 2006: Miscarriage 9 wks
  - Nov. 2006: Miscarriage 8 wks
  - Jan. 2007: Referred to a Recurrent Miscarriage Unit

- Patient 2, 32 years
  - May 2004: PUL 5 wks
  - Oct. 2004: Miscarriage 6 wks
  - March 2005: PUL 5 wks
  - April 2006: Referred to a Recurrent Miscarriage Unit

Early pregnancy loss – definitions (I)

1. Miscarriage
2. Ectopic pregnancy

Ultrasound or histology confirms a non-viable pregnancy
- No ultrasound = biochemical pregnancy
- Inconclusive ultrasound = pregnancy of unknown location (PUL)

Farquharson et al, Hum Reprod 2005
Barnhart et al, Fertil Steril 2011

What is recurrent miscarriage? Definitions (II)

"Recurrent pregnancy loss is (...) defined by two or more failed pregnancies" ASRM Practice committee 2013

"Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies" RCOG 2011

"Recurrent miscarriage is defined as three or more consecutive miscarriages before 22+0 weeks gestation" DBOG 2009

"We refer to recurrent miscarriage (...) if a woman has had two or more objected miscarriages" NVOG 2007

"Recurrent miscarriage (RM) is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks post-menstrual" ESHRE 2006
PULs and recurrent miscarriage – definitions (III)

“Pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination” ASRM Practice committee 2013

“Miscarriage is defined as the spontaneous loss of a pregnancy before the fetus reaches viability” RCOG 2011

“The miscarriages should be confirmed by a positive hCG and at least one by ultrasound and/or histology” DSOG 2009

“These miscarriages (...) do not include (...) biochemical pregnancies” NVOG 2007

PULs: aetiology

• Intrauterine miscarriage
• Spontaneously resorbed ectopic pregnancy

Subclinical pregnancy
Hypothesis

If PULs have a negative impact on the chance of subsequent live birth, then PULs should be part of the definition of recurrent miscarriage.
Assessed for eligibility (n=918):

- Excluded (n=331):
  - At least one pregnancy after IVF/ICSI or donor insemination (n=193)
  - Less than three consecutive miscarriages or PULs (n=30)
  - Age ≥40 at referral (n=25)
  - Positive for lupus anticoagulant (n=8)
  - Parental chromosomal abnormalities (n=15)
  - Uterine abnormalities (n=5)
  - Irregular menstrual cycle with cycle length <23 days or >35 days (n=55)

Included in analysis of pregnancy losses prior to referral (n=587):

- Lost to follow-up (n=40)
- Did not become pregnant after referral (n=48)

Included in analysis of outcome (n=499)

Pregnancy history

Pregnancy losses prior to referral (n=587):

- Early miscarriage: 64
  - 4-6 weeks gestation: 532 (59%)
  - 7-12 weeks: 374 (41%)
- Late miscarriage: 41
- Ectopic pregnancies: 41

Astrid Marie Kolte, University Hospital Copenhagen, Denmark
Ectopic pregnancies prior to referral (n=587)

![Graph showing the distribution of primary and secondary recurrent miscarriages among those referred with only PULs and EPs.

Characteristics for PULs

<table>
<thead>
<tr>
<th>4-6 weeks gestation (n=77)</th>
<th>7-12 weeks gestation (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TVS</td>
<td>14</td>
</tr>
<tr>
<td>TVS</td>
<td>3</td>
</tr>
<tr>
<td>u-hCG, home</td>
<td>10</td>
</tr>
<tr>
<td>u-hCG, GP</td>
<td>9</td>
</tr>
<tr>
<td>s-hCG, home</td>
<td>13</td>
</tr>
<tr>
<td>s-hCG, s-hCG</td>
<td>8</td>
</tr>
<tr>
<td>s-hCG</td>
<td>3</td>
</tr>
</tbody>
</table>

No TVS: Urinary hCG measurement, GP: General practitioner, s-hCG: Serum hCG measurement, TVS: Transvaginal sonography

Chance of live birth
Chance of live birth

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=499)</td>
<td></td>
</tr>
<tr>
<td>Age at index pregnancy*</td>
<td>0.98 (0.96;0.99)</td>
</tr>
<tr>
<td>Miscarriage*</td>
<td>0.88 (0.81;0.95)</td>
</tr>
<tr>
<td>PUL*</td>
<td>0.91 (0.84;0.98)</td>
</tr>
<tr>
<td>BMI (n=312)</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;20</td>
<td>1.12 (0.89;1.40)</td>
</tr>
<tr>
<td>BMI 20-24</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>BMI &gt;24</td>
<td>1.02 (0.77;1.34)</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>1.03 (0.80;1.33)</td>
</tr>
</tbody>
</table>

*Index pregnancy: The first pregnancy after referral. Miscarriage: Histologically or ultrasonically confirmed intrauterine pregnancy loss before 12 weeks gestation. PUL: Positive hCG without definitive diagnosis on location.

Conclusions & guideline recommendations

PULs constitute 37% of all pregnancies reported by RM patients at first consultation.
• Women with no confirmed intrauterine miscarriages have a higher frequency of EPs.

• IVF as treatment? RCT?

• PULs and miscarriages have the same prognostic impact on live birth (RR 0.90)

• Increasing age is a negative prognostic factor for live birth (2% p.a.)

PULs have the same impact on the chance of live birth as miscarriages and should therefore be included in the definition of recurrent miscarriage.
References


When to screen for thyroid function abnormalities?

Rosa Vissenberg
PhD student

Conflict of interest
No commercial or financial interests pertaining to the subject of this presentation or its content.
Implantation

Placentation

Subfertility

Recurrent Miscarriage/ RIF

Pregnancy Complications

Guidelines

Hyperthyroidism

Propylthiouracil (PTU) or

Methimazole (MMI)

Hypothyroidism

Levothyroxine (T4)

What if symptoms are missing?
Debate screening

YES NO

Debate screening

Subfertility
Recurrent Miscarriage
Pregnancy

YES NO

Guidelines – Subfertility

No routine measurement

No routine measurement

No routine measurement
Guidelines – Recurrent Miscarriage

- Not mentioned
- Withdrawn
- Not mentioned

Guidelines - Pregnancy

First trimester screening of risk patients

1. Previous thyroid dysfunction
2. Irradiation of the neck or goiter
3. Family history of thyroid disease
4. TPO-Ab
5. Dysthyroid symptoms
6. DM type 1 or other immune diseases
7. Unexplained subfertility
8. Miscarriage or preterm birth

WHO Screening Criteria
1. The condition should be an important health problem

<table>
<thead>
<tr>
<th>The condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>0.1-0.4%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.6%</td>
</tr>
<tr>
<td>Subclinical hypothyroidism (SCH)</td>
<td>2.0-3.0%</td>
</tr>
<tr>
<td>Thyroid autoimmunity → TPO</td>
<td>8.0-14.0%</td>
</tr>
</tbody>
</table>

1. The condition should be an important health problem

Subclinical hypothyroidism

- **Pregnancy complications**
  - Pre-eclampsia
    - OR 1.68 (95% CI 1.09-2.6)
  - Perinatal mortality
    - OR 2.73 (95% CI 1.59-4.7)
  - ↓ intelligence scores

Abalovich et al. Gynecol Endocrinol 2007

1. The condition should be an important health problem

Subclinical hypothyroidism

Possible association with:

- Subfertility (OR 4.0, 95% CI 1.7–9.8)

van den Boogaard et al. Hum Reprod Update 2011
1. The condition should be an important health problem

**Thyroid autoimmunity**

**Unexplained subfertility**

Thyroid autoimmunity is associated with several pregnancy complications:

- **Recurrent miscarriage**
  - Incidence: 8-36%

- **Miscarriage**
  - OR 3.7 (95% CI 1.8-7.6)

- **Preterm birth**
  - OR 1.9 (95% CI 1.1-3.5)

- **Postpartum thyroid disease**
  - OR 12 (95% CI 5.6-24)

van den Boogaard et al. Hum Reprod Update 2011
WHO Criteria

1. The condition should be an important health problem

2. There should be an accepted treatment for patients with recognized disease

Subclinical hypothyroidism

- Recurrent miscarriage
- Pregnant population

No evidence effective treatment

Vissenberg et al. Human Reprod Update 2012
Lazarus et al. NEJM 2012

---

Subclinical Hypothyroidism

Subfertile population

- Delivery rate
- Fertilized oocytes
- Implantation rate
- Miscarriage rate
  Clinical pregnancy rate – ns

Limitation: no live birth rate as outcome

Velkeniers et al. Human Reprod Update 2013
2. There should be an accepted treatment for patients with recognized disease.

**Thyroid autoimmunity**

Subfertility

Recurrent miscarriage

Pregnancy

No evidence effective treatment

**WHO Criteria**

1. The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage.
5. There should be a suitable test.
6. The test should be acceptable to the population.
7. The natural history of the condition should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The costs should be balanced against the benefits.
10. The risks, both physical and psychological, should be less than the benefits.
4. There should be a detectable early stage

↑ Level of TSH

TPO-Ab – annual risk 2.1%

Whickham Survey

WHO Criteria

1. The condition should be an important health problem
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage
5. There should be a suitable test
WHO Criteria

1. The condition should be an important health problem
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage
5. There should be a suitable test
6. The test should be acceptable to the population
7. The natural history of the condition should be adequately understood
8. There should be an agreed policy on whom to treat as patients

TSH > 2.5mU/L: treatment T4 (evidence poor)
8. There should be an agreed policy on whom to treat as patients

TSH > 2.5 mU/L: treatment T4 (evidence poor)

TSH > 2.5 mU/L and TPO-Ab: T4

TSH > 4.0 mU/L: treatment T4

TSH > 4.0 mU/L: treatment T4

Population specific reference intervals

WHO Criteria

The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage.
5. There should be a suitable test.
6. The test should be acceptable to the population.
7. The natural history of the condition should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The costs should be balanced against the benefits

- State transition Markov model
- 15-45 jaar
- TSH >5 mE/L

Limitations
- Endpoints
- Only treatment abnormal TSH
- Assumed beneficial treatment effect SCH

Screening cost-effective in case of effective treatment intervention SCH or TAI
WHO Criteria

1. The condition should be an important health problem
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage
5. There should be a suitable test
6. The test should be acceptable to the population
7. The natural history of the condition should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The costs should be balanced against the benefits
10. The risks, both physical and psychological, should be less than the benefits

Conclusion

Subfertility
Recurrent Miscarriage
Pregnancy

NO
NO
WHO Criteria
The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a detectable early stage
5. There should be a suitable test
6. The test should be acceptable to the population
7. The natural history of the condition should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The costs should be balanced against the benefits
10. The risks, both physical and psychological, should be less than the benefits

Evidence & Gaps
Treatment effects subclinical hypothyroidism pregnancy
CATS trial
IQ level 3 yr
Obstetric outcomes

RCT for treatment of subclinical hypothyroidism in a subfertile population- effect on Live Birth Rate

Evidence & Gaps
Treatment effects thyroid autoimmunity
T4-LIFE trial
http://www.studies-obsgyn.nl/T4-LIFE

Tablet-trial:
live birth rate
Thyroid antibodies and miscarriage: Clinical trial
Arri Coomarasamy
University of Birmingham

Conflict of Interest

- I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content

Agenda

- What is it?
- Why are we doing it?
- How are we doing it?
- Where are we with it?
TABLET Trial: What is it?
Primary objective: To test the hypothesis that

- ...in euthyroid women with thyroid peroxidase antibodies (TPO),
- ...levothyroxine (50mcg, oral, once daily), started pre-conceptually and continued to the end of pregnancy,
- ...compared with placebo,
- ...increases the proportion of women who attain a live birth beyond 34 completed weeks of gestation by at least 10%.
Our own meta-analysis

BMJ 2011

Pre-term birth

BMJ 2011

TSH?

BMJ 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>TSH pos (%)</th>
<th>TSH neg (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagis 2001</td>
<td>52</td>
<td>48</td>
<td>1.86</td>
<td>0.82 - 2.30</td>
</tr>
<tr>
<td>Irawani 2008</td>
<td>105</td>
<td>105</td>
<td>2.1</td>
<td>1.37 - 3.42</td>
</tr>
<tr>
<td>Mecacci 2000</td>
<td>25</td>
<td>25</td>
<td>3.62</td>
<td>2.01 - 6.50</td>
</tr>
<tr>
<td>Muller 1999</td>
<td>175</td>
<td>175</td>
<td>3.8</td>
<td>2.42 - 5.96</td>
</tr>
<tr>
<td>Nance 1994</td>
<td>68</td>
<td>68</td>
<td>3.7</td>
<td>1.44 - 9.56</td>
</tr>
<tr>
<td>Total</td>
<td>577</td>
<td>577</td>
<td></td>
<td>2.97 - 4.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>TSH pos (%)</th>
<th>TSH neg (%)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller 2002</td>
<td>25</td>
<td>25</td>
<td>1.7</td>
<td>1.37 - 2.05</td>
</tr>
<tr>
<td>Negro 2005</td>
<td>36</td>
<td>36</td>
<td>1.6</td>
<td>1.16 - 2.25</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>155</td>
<td>155</td>
<td></td>
<td>1.33 - 1.87</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 23.85$, df = 5 (P = 0.0002); $I^2 = 79\%$

Test for overall effect: $Z = 3.59$ (P = 0.0003)

Weight 

23.1% 23.6% 4.5% 12.0%

IV, Random, 95% CI

0.66 [0.45, 0.86] 0.22 [0.04, 0.40] 1.03 [-0.31, 2.38] 0.84 [0.18, 1.51]

TAI pos  TAI neg  Std. Mean Difference

IV, Random, 95% CI

1.13 [0.69, 1.57] 0.16 [-0.18, 0.50] 0.58 [0.26, 0.89] 1.13 [0.68, 1.67]

Favours experimental  Favours control
Thyroid replacement: Study 1
Negro, HR, 2005
• Population: 86 women TPO +ve undergoing ART (TPO +ve rate was 15%)
• Intervention: levothyroxine
• Comparison: placebo
• Outcome: pregnancy, miscarriage rate
• Design: RCT
• Findings
  • Pregnancy rate: 56% vs 49% NS
  • Miscarriage rate: 33% vs 52% NS – Type II error?

Thyroid replacement: Study 2
Negro 2006
• Population: 115 Euthyroid women TPO +ve (screened from unselected population) (TPO +ve rate was 11.7%)
• Intervention: levothyroxine
• Comparison: untreated
• Outcome: miscarriage rate, obstetric outcome
• Design: RCT
• Findings
  • Miscarriage rate: 3.5% vs 13.8% (2.4% in TPO –ve group [n=869]!!!)
  • Preterm birth: 7% vs 22.4% (7.1% in TPO –ve group!!!)

Do we need a trial?
• Clinician Survey (to see if there is collective uncertainly – equipoise)
  • Now over 183 responses (1/3 gynaecologists; 1/3 obstetricians; 1/3 endocrinologists)
  • >85% will randomise
• Patient survey – support
• EP-CSG – Support
• MA – support
• BTF - support

TABLET study
TABLET study: HOW?

RCT of Levothyroxine in thyroid antibody positive women.

- EPAU (Early Pregnancy Assessment Unit):
  - TPO Antibody Positive (and TSH & Free T4 within normal range), and
  - Waiting to conceive.
  - Levothyroxine: (Approximately 80% of subjects)
  - TFTs: every trimester

If:
- TSH, Free T4, or both abnormal, refer to thyroid clinic (standard care)
- 6-8w
- 11-13w
- 34-42w

Await up to 1 year for conception; Check TFTs at 2, 6 and 10 months after randomisation.

- Follow-up schedule for Levothyroxine group:
- Blood for cytokine assays (at the time of TFTs)
- Outcome Assessment 1 – ongoing pregnancy
- Outcome Assessment 2 – Neonatal outcome at 36 days

Decidua and placenta at delivery

TFTs – Thyroid Function Tests (TSH and Free T4 levels)

TPO: Thyroid Peroxidase; TSH: Thyroid Stimulating Hormone; Free T4: Free thyroxine level

Mechanistic studies on Birmingham Women’s Hospital women only

TPO prevalence

- Unselected women:
- Miscarriage women:
- Recurrent miscarriage women:
- IVF patients:

TABLET centres
TABLET: Where are we?

- 129 randomised.
- T4Life Trial
LIFE STYLE FACTORS INCREASE THE RISK OF RECURRENT MISCARRIAGE

William H. Kutteh, M.D., Ph.D., H.C.L.D.
Clinical Professor, Vanderbilt University

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:
1. Discuss the lifestyle issues that influence the outcome of pregnancy.
2. Screen all patients for obesity, alcohol use, tobacco use, and caffeine use.
3. Counsel patients about the harmful effects of certain lifestyle factors on successful pregnancy outcome.
4. Understand the effect of maternal age and number of prior losses on predicting future live births

DISCLOSURES

- Research Support - Finox
- Research Support - Merck
- Owner/Director - Reproductive Lab
Spontaneous Pregnancy Loss: Role of Maternal Age

Spontaneous Pregnancy Loss: Role of Maternal Oocyte Aneuploidy

Spectrum of Pregnancy Loss

- Pregnancy of Unknown Location (PUL)
- Early embryonic (< 6 wks)
- Embryonic (> 6 to 9 wks)
- Fetal loss (> 9 to 20 wks)
- Miscarriage (< 20 wks)
- Stillbirth (> 20 wks)

What about Lifestyle Factors?
Effects on the Risk of miscarriage

- Obesity
- Tobacco
- Caffeine
- Ethanol

CONTROVERSIES

- How much alcohol is safe before pregnancy?
  “I will stop drinking when I get pregnant”
- Why pressure me about my weight?
  “My overweight friends had babies”
- How many cigarettes are safe while pregnant?
  “I’ll stop smoking when I get pregnant”

Obesity Trends Among U.S. Adults
Between 1985 and 2010

- Obesity: Body Mass Index (BMI) of 30 or higher.
- Body Mass Index (BMI): A measure of an adult’s weight in relation to his or her height, specifically the adult’s weight in kilograms divided by the square of his or her height in meters.
Pregnancy, Implantation, and Take Home Baby Rates based on BMI

Overweight (BMI >25) and miscarriage

• Retrospective study of 393 women undergoing IVF with single blastocyst transfer
• Cases: 169 women with BMI ≥25 kg/m²
• Controls: 224 women with BMI 18.5-24.9
• More than double the risk of miscarriage in women with BMI >25 kg/m² vs controls (OR=2.4 CI=95%, 1.6-3.8 p=.001)


Euploid miscarriage and Body Mass Index

Retrospective study of 204 miscarriages sent for chromosome testing based on BMI

<table>
<thead>
<tr>
<th>Age</th>
<th>Euploid</th>
<th>Noneuploid</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 yrs</td>
<td>51%</td>
<td>40%</td>
<td>0.009</td>
</tr>
<tr>
<td>≥35 yrs</td>
<td>32%</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt;25</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>≥25</td>
<td>53%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Obesity associated with an increased rate of euploid miscarriage

Spontaneous pregnancy and Obesity

Increased risk of Miscarriage

- Systematic review of published studies
- Six studies with a cohort of 28,538 women
- In women with a BMI of >30kg/m, the probability of spontaneous miscarriage was 27% higher
- In women with recurrent miscarriage who had a BMI of >30kg/m, probability of spontaneous miscarriage was 7% higher


OR of Miscarriage regardless of the Method of Conception


Obesity (BMI >30) and miscarriage

- Obesity has been shown to be a risk factor for miscarriage
- Obesity has been shown to be an independent risk factor for first trimester miscarriage
- Miscarriage association is strongest in women with morbid obesity (BMI > 40 kg/m²)
- Increased risk may be linked to a generalized increase in systemic inflammatory responses

Obesity and Effect on Sperm
Possible role for increased miscarriage

- Cross sectional study of 305 males presenting to a urology clinic
- Cases: 187 overweight males (≥ 25 kg/m² < 30)
- 36 obese males (≥ 30 kg/m²)
- Controls: 82 normal weight males (< 25 kg/m²).
- Performed semen analysis and sperm DNA fragmentation assay
- Percentage of DNA damage higher in obese groups (p = 0.004)
  - 7.7 (4.9-10.5) in BMI ≥ 30 kg/m²
  - 4.7 (4.0-5.3) in BMI ≥ 25 kg/m² < 30
  - 4.4 (3.3-5.5) in BMI < 25 kg/m²


BMI and Uterine Receptivity in Oocyte Recipients
Potential role in Miscarriage

- 122 patients in 30+ group
- P=0.017


Obesity and Oocyte and Embryo quality

- Prospective, multi-center study of women undergoing IVF
- 487 patients and 1417 cycles
- Correlations with increased BMI were:
  - Increased cancelled cycles
  - Fewer oocytes retrieved
  - Fewer embryos available
  - Lower odds of clinical pregnancy
  - Decreased live birth rate

Metformin and Miscarriage

- 197 obese PCOS women in Pakistan
- Cases conceived on metformin and continued throughout pregnancy
- Controls conceived without metformin or stopped metformin in early pregnancy
- Miscarriage rate 8.8% on metformin vs 29.9% in controls (p<0.001)

Nawaz FH. Gynecol Obstet Invest 69: 184-9, 2010

Metformin and Miscarriage

- Prospective, single center study
- Cases: 98 pregnant, hyperinsulinemic PCOS treated with metformin > 1700 mg/day to 37 weeks
- Controls: 110 normal pregnant women
- Comparable Apgars, birth weight and birth length
- Miscarriage rate 9.1% on metformin vs 20 % in controls
- Less gestational HTN and DM compared to controls

Smoking in the US

- 30% reproductive aged women smoke
- 35% of reproductive aged men smoke
- Only 22% of female reproductive health care providers were aware of the deleterious effect on fertility


Smoking and Fertility

- 60% more likely to be infertile (CI=1.34-1.91)
- Require nearly twice the number of IVF attempts to conceive
- Menopause occurs 1 to 4 years earlier
- Basal FSH significantly higher
- Increased miscarriage (natural & IVF)


Time to conception Based on Smoking

[Graph showing comparison in time for conception between smokers and non-smokers]

JAMA (1985) 253:
Smoking and Miscarriage

Light smoker < 10 per day. Heavy smoker more than 10 per day.

Risk for smokers divided by risk for non-smokers


Smoking and Miscarriage

- Smoking increased miscarriage in natural and IVF conceptions
- Accounted for 16% of miscarriages of inner-city women age 14 to 39
- Vasoconstrictive and antimetabolic effects may lead to placental insufficiency, embryonic and fetal growth restriction and demise
- Proportion of diploid oocytes in the ovary increases with the number of cigarettes smoked per day


Smoking Increases IVF Miscarriages

- Retrospective study 8323 women undergoing IVF
  Smokers=3617, Non Smokers= 4706
- Smoking was associated with a significantly lower delivery rate
  OR= .72, (95% CI 0.61-0.84)
- Smoking was associated with a higher miscarriage rate compared 21.4% vs 16.4% (p=0.01)
- Adjusted effect of smoking on live birth was stronger than an increase in female age with >10years from 20-30
  OR= .78 (95%CI 0.63-.96)

Smoking and Miscarriage

Odds ratio of miscarriage per pregnancy.

- Meta-analysis of 7 studies of women undergoing IVF
- 211 smokers and 1688 non-smokers
- Miscarriage defined as any loss before 20 weeks
- Smokers defined as any amount of active smoking
- Smoking patients demonstrated significantly lower odds of live birth per cycle
  \( OR \) 0.54, 95% CI 0.30 to 0.99
- Smokers had a significantly higher odds of spontaneous miscarriage
  \( OR \) 2.65, 95% CI 1.33 to 5.30


Cigarette smoking and uterine receptivity

Possibly due to implantation failure

- Retrospective study of reproductive aged women
- Cases: 44 heavy smokers (>10/day)
- Controls: 741 non heavy smokers (0-10/day)
- Pregnancy rates significantly lower in heavy smokers vs non heavy smokers (34.1% vs 52.2%)

Proposed FDA Warning

Smoking during pregnancy can increase the risk of miscarriage, stillborn or premature infants, infants with low birth weight and an increased risk for sudden infant death syndrome (SIDS).

Caffeine May Double Miscarriage Risk: Study

Jan 21, 2008 9:28 AM CST

Amounts of Caffeine in Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee (8 oz)</td>
<td>66-80</td>
</tr>
<tr>
<td>Tea (8 oz)</td>
<td>100-150</td>
</tr>
<tr>
<td>Regular coffee</td>
<td>85-115</td>
</tr>
<tr>
<td>Diet coffee</td>
<td>0</td>
</tr>
<tr>
<td>Regular soda</td>
<td>35-45</td>
</tr>
<tr>
<td>Diet soda</td>
<td>0</td>
</tr>
<tr>
<td>Cola (12 oz)</td>
<td>31</td>
</tr>
<tr>
<td>Hot cocoa (8 oz)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Amounts of caffeine will vary depending on brand and results.
Maternal caffeine consumption during pregnancy and risk of miscarriage

- Prospective Cohort Study
- Cases: 635 pregnant women with caffeine consumption of ≤200 mg/d and 164 pregnant women with consumption of >200 mg/d
- Controls: 264 pregnant women, no caffeine
- Risk of miscarriage compared with no caffeine
  - OR = 1.42 (95% CI 0.93-2.15) if ≤200 mg/d
  - OR = 2.23 (95% CI 1.34-3.69) if >200 mg/d


Caffeine intake and Miscarriage

- Nested case control study
- Case: Women drink ≥75 mg/d of caffeine
- Controls: 206 Women drink <75 mg/d
- Increased spontaneous abortion with adjusted OR of 1.26, 1.45, 1.44, 1.72 for prepregnancy intake of 75-300, 301-500, 501-900 and >900 mg of caffeine compared to controls.

### Caffeine intake and Miscarriage

- >200-300 mg/day (2-3 cups/day) may increase the risk of miscarriage
- >500 mg/day (>5 cups) decreases fertility
- "Overall, moderate caffeine consumption (2 cups of coffee/day or its equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes"

ASRM Committee Opinion. Fertil Steril. 2013

### Alcohol Use and Pregnancy

Among women in the US seeking pregnancy:
- 54.9% reported alcohol use
- 12.4% reported binge drinking
- 12.5% continue to drink during pregnancy

ACOG Committee Opinion #422. December 2008

### Alcohol Use in US Women

**Ages 18 to 44, 1991 to 2005**

Binge drinking is >5 drinks in one day in the past 30 days.

Behavioral Risk Factor Surveillance System, US. 2009
Miscarriage Risk with Alcohol and Tobacco Use in Women

<table>
<thead>
<tr>
<th>DRINKS /WEEK</th>
<th>% IN THIS GROUP</th>
<th>LOSS &lt; 13 WEEKS</th>
<th>LOSS 13-16 WEDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>55%</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2 to 3.5</td>
<td>43%</td>
<td>1.66 (1.43-1.92)</td>
<td>1.57 (1.5-1.6)</td>
</tr>
<tr>
<td>More than 4</td>
<td>2%</td>
<td>4.25 (2.77-6.45)</td>
<td>1.73 (1.24-2.41)</td>
</tr>
</tbody>
</table>


Alcohol use and Miscarriage

• Associated with an increased risk of miscarriage
• A few as five (5) alcoholic drinks per week significantly increase the risk for first trimester miscarriage
• When combined with cigarette smoking, alcohol use may increase the risk of miscarriage 4-fold


Two drinks/week Increase the Risk of Miscarriage

• 92,719 women in Danish National Birth Cohort
• Determined risk of first trimester miscarriage (<13 weeks) and fetal death (13 to 16 weeks)

Summary: Effects of Smoking, Alcohol, Caffeine, and Stress on Miscarriage

Summary: Future Prognosis of Live Birth Based on Age and Miscarriage History

Summary of Prognostic Factors

<table>
<thead>
<tr>
<th>FACTOR EVALUATED</th>
<th>INCREASE in INFERTILITY</th>
<th>STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (BMI &gt; 35)</td>
<td>2-fold</td>
<td>Hassan &amp; Killick, 2004</td>
</tr>
<tr>
<td>Smoking</td>
<td>60%</td>
<td>Clark et al, 1996</td>
</tr>
<tr>
<td>Alcohol (&gt; 2 drinks/day)</td>
<td>60%</td>
<td>Eggert et al., 2004</td>
</tr>
<tr>
<td>Caffeine (&gt;250mg/day)</td>
<td>45%</td>
<td>Wilcox et al., 1986</td>
</tr>
</tbody>
</table>

ASRM Committee Opinion. Fertil Steril epub 2013
Summary of Lifestyle Factors
Risks of miscarriage increase 1.5 - 2 fold

- Tobacco (>10/day)
- Ethanol (> 2/week)
- Obesity (BMI > 30)
- Caffeine (> 2-3 cups/day)
The impact of genetic testing for couples with recurrent miscarriage

Fleur Vansanne, MD, PhD
Department of Clinical Genetics
Academic Medical Center, Amsterdam

ESHRE-meeting
London 2013

Conflict of interest

• I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content

Learning objectives

• Overview of karyotyping in recurrent miscarriage
• Efficacy from doctors’ perspective
• Efficacy from patients’ perspective
• Impact of genetic testing for patients in terms of anxiety, depression and distress
Genetic testing in recurrent miscarriage

- Chromosome abnormality risk factor for recurrent miscarriage (RM)
- 2-5% of couples with RM carry a chromosomal abnormality
  - Balanced reciprocal translocation
  - Robertsonian translocation
- Risk for unbalanced offspring
  - Miscarriage
  - Stillborn
  - Live born with congenital malformations
- Offered invasive prenatal diagnosis in subsequent pregnancies

Genetic testing in recurrent miscarriage

- Karyotyping advised after two or more, not necessarily consecutive miscarriages
- Adopted by guidelines (until 2010):

Efficacy of parental karyotyping?

Doctor/health-care centered
- Frequency of identification of carrier couples
- Risk factors for carrier status
- Subsequent pregnancies
- Obstetric outcome
- Risk of unbalanced offspring
Identification of carrier couples*

- Karyotyping in the Netherlands
- 1992-2001: 11971 couples karyotyped
- 382 carriers identified → 3.1%

Identification of risk factors for carrier status?

- Higher number of miscarriages
- Younger age at second miscarriage
- Recurrent miscarriage in parents
- Recurrent miscarriage in siblings

*Franssen et al. BMJ 2005

Subsequent pregnancies*

- Follow-up at least 24 months after karyotyping

<table>
<thead>
<tr>
<th>Event</th>
<th>Carriers (n=278)</th>
<th>Non-carriers (n=427)</th>
<th>Difference in % (95% CI)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages</td>
<td>4 (1.4)</td>
<td>8 (1.9)</td>
<td>-4.5% (95% CI: -9.4 to 0.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Preterm births</td>
<td>15 (5.4)</td>
<td>31 (7.3)</td>
<td>-1.9% (95% CI: -5.5 to 2.0)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>4 (1.4)</td>
<td>1 (0.2)</td>
<td>1.2% (95% CI: 0.1 to 2.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Invasive prenatal diagnosis</td>
<td>58 (21.0)</td>
<td>138 (32.4)</td>
<td>-11.4% (95% CI: -16.2 to -6.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cytogenetic study</td>
<td>24 (8.7)</td>
<td>26 (6.1)</td>
<td>2.7% (95% CI: -1.4 to 6.8)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Franssen et al. BMJ 2006

Risk unbalanced offspring*

- 278 carrier couples → 550 pregnancies
- 4 unbalanced fetal karyotypes (0.7%)
- 3 detected at invasive prenatal diagnosis (PND) → 2 aborted
- 1 couple refrained from invasive PND
- 2 children with unbalanced karyotype born
- → uptake of invasive PND?

Efficacy of parental karyotyping?

Patient centered
• Knowledge about genetic test
• Perceived risks for adverse outcomes
• Psychological impact of karyotyping for couples (anxiety, depression, distress)
• Consequences in terms of reproductive options

Uptake invasive PND*

*Vansasse et al. Fertil Steril 2010
Patients’ perspective
CONGENO-study
• CONsequences of GENOtyping in reproductive medicine
• Multicenter
• 7 Academic medical centers in the Netherlands
• 01/2006 - 07-2009
• Prospective, longitudinal, index-control study
• 3 Questionnaires
• Both RM and subfertile couples (poor semen quality)

Inclusion criteria
• Recurrent miscarriage
  • ≥ 2 miscarriages, not necessarily consecutive
• Poor semen quality
  • < 1.10^6 sperm cells per ejaculate
• Both groups
  • Sufficient knowledge of Dutch language
  • Unaware of genetic test result at inclusion

Selection of participants
• Identification of carrier couple in the lab → index couple
• Selection of first two couples karyotyped after index → control couples
• Referring gynaecologist or urologist contacted
• Couples contacted for participation
Methods

- Questionnaire study
  - T0: before disclosure (baseline)
  - T1: 3 months after disclosure
  - T2: 12 months after disclosure
- Both partners invited

Questionnaire T0

- Anxiety (STAI)
  - 20 questions on Likert scale 1-4 → sumscore 20-80
- Depression (BDI-II-NL)
  - 21 questions on Likert scale 0-3 → sumscore 0-63
- Knowledge and awareness genetic test
- Perceived risks potential outcomes (VAS-scale)
- Comparison to Dutch reference population* 

Inclusion
Baseline characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n)</th>
<th>Rate per 100</th>
<th>Cases (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>241 (75%)</td>
<td>203 (68%)</td>
<td>241 (75%)</td>
<td>203 (68%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>126 (40%)</td>
<td>102 (34%)</td>
<td>126 (40%)</td>
<td>102 (34%)</td>
</tr>
<tr>
<td>Female</td>
<td>115 (35%)</td>
<td>91 (30%)</td>
<td>115 (35%)</td>
<td>91 (30%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>172 (53%)</td>
<td>142 (47%)</td>
<td>172 (53%)</td>
<td>142 (47%)</td>
</tr>
<tr>
<td>Single</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
</tr>
<tr>
<td>Secondary school or more</td>
<td>126 (39%)</td>
<td>102 (34%)</td>
<td>126 (39%)</td>
<td>102 (34%)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Students</td>
<td>17 (5%)</td>
<td>14 (5%)</td>
<td>17 (5%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Employees</td>
<td>111 (34%)</td>
<td>91 (30%)</td>
<td>111 (34%)</td>
<td>91 (30%)</td>
</tr>
<tr>
<td>Others</td>
<td>153 (46%)</td>
<td>123 (41%)</td>
<td>153 (46%)</td>
<td>123 (41%)</td>
</tr>
<tr>
<td>Living situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single person</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
<td>101 (31%)</td>
<td>79 (27%)</td>
</tr>
<tr>
<td>Couple</td>
<td>142 (42%)</td>
<td>112 (38%)</td>
<td>142 (42%)</td>
<td>112 (38%)</td>
</tr>
<tr>
<td>Others</td>
<td>88 (26%)</td>
<td>68 (22%)</td>
<td>88 (26%)</td>
<td>68 (22%)</td>
</tr>
<tr>
<td>Income level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500€</td>
<td>79 (27%)</td>
<td>63 (21%)</td>
<td>79 (27%)</td>
<td>63 (21%)</td>
</tr>
<tr>
<td>1500€ - 2499€</td>
<td>102 (34%)</td>
<td>83 (27%)</td>
<td>102 (34%)</td>
<td>83 (27%)</td>
</tr>
<tr>
<td>≥2500€</td>
<td>83 (25%)</td>
<td>68 (22%)</td>
<td>83 (25%)</td>
<td>68 (22%)</td>
</tr>
</tbody>
</table>
| Knowledge about the genetic test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
</table>
| Anxiety and depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
</table>
| Knowledge about the genetic test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
</table>
| Anxiety and depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
</table>
| Knowledge about the genetic test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (n)</th>
<th>Rate per 100</th>
</tr>
</thead>
</table>
Perceived Risks RM group

Risk scenario
- desire to postpone treatment
- limited support from family
- uncertain disease outcome
- characteristics of tumor
- loss of normal body image

Perceived risk vs. actual risk* (median and IQR)

* Brigham 1999, Franssen 2006

Questionnaires T1 and T2

- Anxiety (STAI)
  - 40 questions on Likert scale 1-4 \( \rightarrow \) sum score 40-160
- Depression (BDI-II-NL)
  - 21 questions on Likert scale 0-3 \( \rightarrow \) sum score 0-63
- Distress (IES-R)
  - 22 items on Likert scale 0,1,3,5 \( \rightarrow \) sum score 0-110
- Comparison to Dutch reference population*

* De Weerd 2001, Van der Does 2002

Inclusion

[Graph with data points and annotations]
Anxiety men
Mean score STAI (range 40-160) comparable to reference population Non-significant

Anxiety women
Mean score STAI (range 40-160) comparable to reference population Non-significant

Distress
Scores on RS-R at three and 12 months (range 0-110, cut-off 39)
*p<0.01
Conclusions

1. Unaware of genetic test performed
2. Overestimation of potential risks
3. Disclosure genetic test result does not lead to more anxiety or depressive feelings
4. Increase in distress, persists for longer time
5. Balanced against potential benefits, before offering genetic testing

Karyotyping in RM 2013

1. Guideline 2011 → karyotyping no longer advised after RM
2. Guideline withdrawn

Acknowledgements

- Study group
  - Center for Reproductive Medicine, M. Goddijn, F. van der Veen, J. Langerak
  - dept. of Clinical Genetics, M.C. van Maarle, B. Redeker, S. Snijder
  - dept. Clinical Epidemiology, C. de Borgie, P.M. Bossuyt
- Participating centers
  - University Medical Center Utrecht
  - University Medical Center Leiden
  - Vrije Universitair Medical Center
  - Erasmus Medical Center Rotterdam
  - University Medical Center Groningen
  - University Medical Center Nijmegen
- And of course all participants!
References


The Influence of Advanced Maternal Age: Major Cause of Recurrent Pregnancy Loss

Mary D. Stephenson, MD, MSc, ELAM*
Professor and Head

Disclosure

- I have no conflict of interest

Objectives

For RPL and advanced maternal age (AMA):
- Compare the frequency and type of chromosome errors with AMA
- Present an AMA-dependent cost-saving algorithm to determine when a RPL evaluation is warranted
- Discuss the impact of AMA on the frequency of RPL/Translocation carriers
What is Recurrent Pregnancy Loss?

- ASRM Practice Committee Opinion (2012):
  RPL: ≥2 more failed clinical pregnancies, documented by ultrasound or histopathology

Chance of Live Birth Based on Number of Prior Miscarriages

Lund et al, Obstet Gynecol 2012

Chance of Live Birth based on Maternal Age

Lund et al, Obstet Gynecol 2012
General Reproductive Population: All ages

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Risk of Pregnancy Loss</th>
<th>Chromosome errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical (&lt; 6 wks)</td>
<td>30-50%1,2</td>
<td>70%5</td>
</tr>
<tr>
<td>Clinical (6 to &lt;10 wks)</td>
<td>15%3</td>
<td>50%3</td>
</tr>
<tr>
<td>Fetal (≥ 10 wks)</td>
<td>2-3%4</td>
<td>5%4</td>
</tr>
</tbody>
</table>


Types of Miscarriage Chromosome Errors

- 50% trisomy
- 20% polyploidy
- 18% monosomy X
- 4% structural rearrangement: balanced or unbalanced
- 2% other

Jacobs et al, Human Genetics 1987

Clinical Miscarriage and Advancing Maternal Age

Hassold and Chiu, Hum Genet 1985

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Risk of Clinical Miscarriage (≥6 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>40%</td>
</tr>
<tr>
<td>20-24</td>
<td>30%</td>
</tr>
<tr>
<td>25-29</td>
<td>20%</td>
</tr>
<tr>
<td>30-34</td>
<td>10%</td>
</tr>
<tr>
<td>35-39</td>
<td>5%</td>
</tr>
<tr>
<td>40+</td>
<td>0%</td>
</tr>
</tbody>
</table>
Recurrent Miscarriage: Chromosome Testing

<table>
<thead>
<tr>
<th></th>
<th>Number of miscarriages</th>
<th>Chromosome errors</th>
<th>46,XX/46,XY miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al. 1996</td>
<td>94</td>
<td>57%</td>
<td>?</td>
</tr>
<tr>
<td>Ogasawara et al. 2000</td>
<td>114</td>
<td>49%</td>
<td>?</td>
</tr>
<tr>
<td>Carp et al. 2001</td>
<td>125</td>
<td>29%</td>
<td>?</td>
</tr>
<tr>
<td>Stephenson et al. 2002</td>
<td>420</td>
<td>46%</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Cytogenetic Analysis of Miscarriages From Couples With Recurrent Miscarriage

Comparison of Trisomies

- General reproductive population
  Trisomy 16, 22, 21, 15, 13
  Jacobs et al, Human Genetics 1987

- Recurrent miscarriage cohort
  Trisomy 15, 16, 22, 21, 14, 13
  Stephenson et al, Human Reprod 2002

Adjusted for AMA, frequency of trisomies was identical
--- No evidence of recurrent trisomy

Hassold et al, Hum Genet 1985 vs
Stephenson et al, 2002
Cytogenetic Analysis of Miscarriages From Couples With Recurrent Miscarriage

General population (Control) vs recurrent miscarriage

Hassold and Chiu, Hum Genet 1985 vs Stephenson et al, Hum Reprod 2002

With Accurate Chromosome Testing...

- 98% yield of results

1st Miscarriage <10 wks
Try again

2nd Miscarriage <10 wks
Chromosome Testing

- Aneuploid or Polyploid
  Try again
- Unbalanced translocation
  Cytogenetics of both partners
- Euploid Miscarriage
  RPL Evaluation

Stephenson, ESHRE 2009

Is Miscarriage Chromosome Testing Cost Saving, Especially with Advancing Maternal Age?

- National sources for costs
- RPL evaluation: ACOG and RCOG guidelines

- Selective
  If 2nd miscarriage has normal chromosomes
  \( \downarrow \)
  RPL evaluation

- Universal
  Following 2nd miscarriage
  \( \downarrow \)
  RPL evaluation

Bernardi, Stephenson et al, Fertil Steril 2012
## Decision Analytic Model

Bernardi, Stephenson et al, Fertil Steril 2012

---

## Is Miscarriage Chromosome Testing Cost Saving?

Bernardi, Stephenson et al, Fertil Steril 2012

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Estimated cost</th>
<th>Cost savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal RPL evaluation</td>
<td>$4,507</td>
<td></td>
</tr>
<tr>
<td>Selective RPL evaluation when 2nd miscarriage euploid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All maternal ages</td>
<td>$3,352</td>
<td>$1,155</td>
</tr>
<tr>
<td>18-35 years</td>
<td>$3,766</td>
<td>$794</td>
</tr>
<tr>
<td>36-39 years</td>
<td>$2,973</td>
<td>$1,534</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>$2,598</td>
<td>$1,909</td>
</tr>
</tbody>
</table>

Yes! Especially with advancing maternal age

---

## RPL/Translocation Carriers: 3-5% of RPL Couples

Stephenson and Sierra, Hum Reprod 2006

Prospective study of 40 translocation carriers with a history of RPL

- 40% had concomitant RPL factors

Management: IVF/PGD or treat concomitant factors?

- Reciprocal translocation
- Robertsonian translocation

---
RPL/Translocation Carriers: Frequency of Miscarriages with An Unbalanced Translocation

![Graph showing frequency of miscarriages with unbalanced translocations.](Image)

*Stephenson et al, Hum Reprod 2006 vs 2002*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cumulative live birth rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer et al. 2010</td>
<td>IVF/PGD 31% (60/192)</td>
</tr>
<tr>
<td>Franssen et al. 2006</td>
<td>Tx other factors, close monitoring 83% (205/247)</td>
</tr>
<tr>
<td>Stephenson et al. 2006</td>
<td>Tx other factors, close monitoring 65% (26/40)</td>
</tr>
<tr>
<td>Goddijn et al. 2004</td>
<td>Tx other factors, close monitoring 72% (18/25)</td>
</tr>
<tr>
<td>Higher live birth rate with treating concomitant RPL factors</td>
<td></td>
</tr>
</tbody>
</table>

**Selective Parental Testing For Translocations**

Franssen et al, BMJ 2005

<table>
<thead>
<tr>
<th>Age at 2nd misc</th>
<th>Sibling Hx RPL</th>
<th>+ve Parents RPL Hx</th>
<th>+ve Parents RPL Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 misc</td>
<td>2 misc</td>
<td>3 misc</td>
</tr>
<tr>
<td>&lt;23 yrs</td>
<td>Yes 10%</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td></td>
<td>No 5.5%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>23-24 yrs</td>
<td>Yes 10%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>No 5.5%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>34-37 yrs</td>
<td>Yes 6%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>No 5.5%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>37-39 yrs</td>
<td>Yes 4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>No 2%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>≥39 yrs</td>
<td>Yes 2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>No 1%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Fertility and Sterility

Volume 95, Issue 1, January 2004

A critical tool in the evaluation of couples with a history of recurrent losses

Marie C. Stephenson, MB, BS, FRANZCO

Michael Goode, MB, BS, DGAOG

Page 101 of 139
Summary

For RPL and advanced maternal age:

- Trisomic miscarriages increase exponentially with AMA, in sporadic and recurrent pregnancy loss
- Miscarriage chromosome testing is cost-saving, especially with AMA
- Marked decrease of RPL/Translocation carriers with AMA, especially with no family history of RPL
NK cells

Professor Siobhan Quenby MD FRCOG
Professor of Obstetrics University of Warwick
Honorary Consultant University Hospitals Coventry and Warwickshire NHS Trust
Director of the BRU in Reproductive Health

• I have no conflict of interest to declare

Learning Objectives

• To gain insights into:
  – Biological significance of high uNK cell density
  – Benefits and limitations of testing for high density of uNK cells
  – Possible treatments for women with high uNK cell density
### uNK cells in endometrium

Control patient with normal endometrium in luteal phase

Patient who had spontaneous abortion in luteal phase

Quenby et al., 1999, 2005; Ollford et al., 1999; Tuckerman et al., 2007

### Mechanism of fetal loss when uNK cells density is high

- Direct killing?
- Excessive oxygenation?
- High uNK cell density result of poor decidualisation?

### Maternal uNK interact with fetal trophoblast

- Have correct receptors
- Certain HLA-C/KIR combinations associated with
  - PET, RM, IUGR
  - Hiby et al., 2008
- Lack killing ability

<table>
<thead>
<tr>
<th>Trophoblast Antigen</th>
<th>uNK cells Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-E</td>
<td>CD94, NKG2</td>
</tr>
<tr>
<td>HLA-C</td>
<td>KIRs</td>
</tr>
<tr>
<td>HLA-G</td>
<td>ILT-2, ILT 4KIR2DL4</td>
</tr>
<tr>
<td>7</td>
<td>NKG44</td>
</tr>
</tbody>
</table>
Hanna et al., NATURE MEDICINE 2006

Editorial:
Killer cells become builders during pregnancy

Mechanism of fetal loss when uNK cells density is high
- Direct killing?
- Excessive oxygenation?
- High uNK cell density result of poor decidualisation?

More blood uNK cells more blood flow

Quenby et al., 2009
Increased IL15 = increased uNK=Increased blood flow

Mechanism of fetal loss when uNK cells density is high

- Direct killing?

- Excessive oxygenation?
  - Possible lack of direct evidence

- High uNK cell density result of poor decidualisation?
PRL - A CLASSICAL DECIDUAL MARKER

DEFECTIVE DECIDUALIZATION IN RPL: IN VITRO EVIDENCE

PROK1: A PRO-IMPLANTATION CYTOKINE

Stromal cells are biosensors of embryo quality
(Salker et al., 2010)

Stromal cell supernatant on mouse implantation
(Salker et al., 2012)
uNK cells in vivo correlate with abnormal decidualization in vivo

- Cortisol
  - Acts via GR and MR receptors
  - Kuroda et al., 2012

High uNK density = Low 11βHSD1
  - Cortisol
    - Acts via GR and MR receptors
    - Kuroda et al., 2012

What do GR and MR control?
  - Deacetylation & methyltransferase complexes
  - Lipid droplet formation
  - Vit A pathway

Kuroda et al., 2012
Mechanism of fetal loss when uNK cells density is high

- Direct killing?
- Excessive oxygenation?
  - Possible lack of direct evidence
- High uNK cell density result of poor decidualisation?
  - Yes

Peripheral NK Cells in Infertility

Odds of implantation failure after ART with high pre-pregnancy peripheral NK cell parameters in women with infertility

<table>
<thead>
<tr>
<th>Variable</th>
<th>ART-NK(+)</th>
<th>ART-NK(-)</th>
<th>Implantation Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cell density</td>
<td>0.5</td>
<td>0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>NK cell frequency</td>
<td>0.3</td>
<td>0.2</td>
<td>0.12</td>
</tr>
<tr>
<td>NK cell count</td>
<td>1000</td>
<td>1500</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*ART: Assisted Reproductive Technology*
Peripheral NK Cells in Infertility

- Odds of miscarriage (after implantation success from ART) with high levels of pre-pregnancy peripheral NK cell parameters in women with infertility

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cell count</td>
<td>High</td>
<td>1000</td>
<td>200</td>
<td>900</td>
<td>500</td>
<td>1500</td>
</tr>
<tr>
<td>NK cell ratio</td>
<td>High</td>
<td>0.25</td>
<td>0.05</td>
<td>0.20</td>
<td>0.10</td>
<td>0.30</td>
</tr>
</tbody>
</table>

N = 79

 Peripheral NK Cells in RM

- Odds of miscarriage with high pre-pregnancy peripheral NK cell parameters in women with idiopathic RM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cell count</td>
<td>High</td>
<td>1000</td>
<td>200</td>
<td>900</td>
<td>500</td>
<td>1500</td>
</tr>
<tr>
<td>NK cell ratio</td>
<td>High</td>
<td>0.25</td>
<td>0.05</td>
<td>0.20</td>
<td>0.10</td>
<td>0.30</td>
</tr>
</tbody>
</table>

N = 92

Uterine NK Cells in RM

- Odds of miscarriage with high levels of pre-pregnancy uterine NK cells in women with idiopathic RM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cell count</td>
<td>High</td>
<td>1000</td>
<td>200</td>
<td>900</td>
<td>500</td>
<td>1500</td>
</tr>
<tr>
<td>NK cell ratio</td>
<td>High</td>
<td>0.25</td>
<td>0.05</td>
<td>0.20</td>
<td>0.10</td>
<td>0.30</td>
</tr>
</tbody>
</table>

N = 72
Live birth rate in control groups (Tang et al., 2013)

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Patients</th>
<th>Control</th>
<th>Live birth rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quenby</td>
<td>2013</td>
<td>Raised uNK cell</td>
<td>Placebo</td>
<td>40%</td>
</tr>
<tr>
<td>Visser</td>
<td>2011</td>
<td>Idiopathic aspirin</td>
<td>Placebo</td>
<td>64%</td>
</tr>
<tr>
<td>Stephenson</td>
<td>2010</td>
<td>Secondary placebo</td>
<td>Placebo</td>
<td>63%</td>
</tr>
<tr>
<td>Kaandorp</td>
<td>2010</td>
<td>Idiopathic thrombophilia</td>
<td>Placebo</td>
<td>67%</td>
</tr>
<tr>
<td>Clarke</td>
<td>2010</td>
<td>Idiopathic and thrombophilia</td>
<td>Ultrasound Scans</td>
<td>80%</td>
</tr>
<tr>
<td>Laskin</td>
<td>2009</td>
<td>Thrombophilia</td>
<td>Placebo</td>
<td>69%</td>
</tr>
<tr>
<td>El-Zibdeh</td>
<td>2005</td>
<td>Idiopathic Placebo</td>
<td>Placebo</td>
<td>71%</td>
</tr>
<tr>
<td>Total other</td>
<td>Trials</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment?

- “A specific assay to diagnose immune-mediated early pregnancy loss and a reliable method to determine which women might benefit from manipulation of the maternal immune system are urgently needed”
  – Porter et al, cochrane 2006

Case History

- 17 consecutive miscarriages
- No Cause found
- Most NK cells in study n=40
- Preconceptual prednisolone 5mg
- Two further miscarriages
- Higher dose (prednisolone 20mg)
- Live Birth aged 42
  (IUGR 32/40)
- Alive and well age 4 years
  – Quenby et al., 2004
Effect of Prednisolone on uNK cells

Before Prednisolone After Prednisolone

Prednisolone reduces preconceptual endometrial NK cell density in women with recurrent miscarriage.

Quenby et al., 2005;

Prednisolone treatment reduces endometrial angiogenic growth factor expression at LH+7

Lash et al 2012

Prednisolone Trial

Evaluate if prednisolone therapy during the first trimester of pregnancy is able to reduce the risk of miscarriage and improve live birth rates in women with RM and high uterine natural killer (uNK) cells density

Pilot phase: to assess feasibility of recruitment, integrity of trial procedures and preliminary data for accurate power calculations

Tang et al., 2013 in press
Study Population

- Recruitment – August 2008 to August 2010
- Inclusion Criteria
  - ≥3 consecutive miscarriages with no cause found (idiopathic)
  - ≤40 years old
  - ≥5% uNK cells at day LH +6 to +9 (mid-luteal)
- Exclusion Criteria
  - Known cause for recurrent miscarriage
  - Contraindications to steroid therapy: hypertension, diabetes, mental health problems or obesity with BMI >35
  - Decline consent to randomisation

Study Design – Randomisation

- Randomised to either prednisolone (50%) or placebo (50%)
- Confirmed 4-8 weeks pregnant
- Treatment regime
  - 4 tablets for 6 weeks, 2 tablets for 1 week, 1 tablet for 1 week
  - Active tablets has 5mg of prednisolone
- Monitoring in pregnancy (in addition to routine antenatal care)
  - Reviewed and scanned every 2 weeks until 14 weeks gestation
  - Growth scans at 28 weeks and 34 weeks gestation
  - Post-delivery follow-up at 6 weeks

Trial Flow Chart
Baseline characteristics of women randomised

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone (N=20)</th>
<th>Placebo (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean)</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>% uNK cells (Mean (Range))</td>
<td>8.3 (5-22.8)</td>
<td>7.2 (5-18.3)</td>
</tr>
<tr>
<td>BMI (Mean)</td>
<td>26.1</td>
<td>25.6</td>
</tr>
<tr>
<td>Women with previous live birth (No.)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mean number of previous early miscarriages</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Women with previous 2nd trimester miscarriage (No.)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Women with previous ectopics (No.)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Current Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic Acid Intake</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Aspirin Intake</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sac present at randomisation</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>FH present at randomisation</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Side effects of Steroids

<table>
<thead>
<tr>
<th>Side Effects (Count (%))</th>
<th>Prednisolone (N=20)</th>
<th>Placebo (N=20)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>4 (33.3)</td>
<td>2 (25)</td>
<td>1.33 (0.32-5.64)</td>
</tr>
<tr>
<td>Bruising</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Flushing</td>
<td>4 (33.3)</td>
<td>1 (12.5)</td>
<td>2.67 (0.36-19.71)</td>
</tr>
<tr>
<td>GI problems</td>
<td>4 (33.3)</td>
<td>2 (25)</td>
<td>1.33 (0.32-5.64)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (41.7)</td>
<td>1 (12.5)</td>
<td>3.33 (0.47-22.47)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>0</td>
<td>1 (12.5)</td>
<td>0.23 (0.01-5.05)</td>
</tr>
<tr>
<td>Mood changes</td>
<td>3 (25)</td>
<td>2 (25)</td>
<td>1.00 (0.23-4.71)</td>
</tr>
<tr>
<td>Others (headaches, nausea, increased appetite, palpitations)</td>
<td>7 (58.3)</td>
<td>2 (25)</td>
<td>2.33 (0.64-8.49)</td>
</tr>
</tbody>
</table>

Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Prednisolone (N=20)</th>
<th>Placebo (N=20)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirths (%)</td>
<td>12 (60)</td>
<td>8 (40)</td>
<td>1.5 (0.79-2.86)</td>
</tr>
<tr>
<td>Delivery &gt;37 weeks (%)</td>
<td>1 (8.3)</td>
<td>0</td>
<td>3.00 (0.13-69.52)</td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td>3 (25)</td>
<td>4 (50)</td>
<td>0.75 (0.19-2.93)</td>
</tr>
<tr>
<td>Cesarean Section Delivery</td>
<td>9 (75)</td>
<td>4 (50)</td>
<td>2.25 (0.83-6.13)</td>
</tr>
<tr>
<td>Birthweight (mean)</td>
<td>3516g</td>
<td>3547g</td>
<td>-</td>
</tr>
<tr>
<td>Admission to SCBU</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>1.00 (0.07-14.80)</td>
</tr>
</tbody>
</table>
Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Prednisolone (N=20)</th>
<th>Placebo (N=20)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages (%)</td>
<td>8 (40)</td>
<td>12 (60)</td>
<td>0.67 (0.35-1.27)</td>
</tr>
<tr>
<td>Mechanical loss</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Empty gestation Sac.</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Familial loss</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Trisomy 22</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Ectopic (treated methotrexate)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

uNK cells and pregnancy outcomes

Can we test and treat endometrium?

- Close
- Progesterone and prednisolone?
- When?
  - Start of decidualisation 7 days after ovulation?
  - Make endometrium more selective?
Acknowledgements

Jan Brosens
Keiji Kuroda
Madhuri Salker
Andy Blanks
Radha Venkatakrishnan
Sooan James
Sandra Šuurović
Antoly Shymgol

HEFT
Rachel Small
University of Newcastle
Judith Bulmer
Gendie Lash

LWFT
Aie-Wei Tang
Lisa Heathcote
Jo Drury

References -1


References - 2

- Lash GE, Bulmer JN, Innes BI, Drury JA, Robson SC, Quenby S. Prednisolone treatment decreases endometrial spiral artery development in women with recurrent miscarriage. Angiogenesis 2011; 14: 523-532

References - 3

- Quenby S, Nik H, Innes B, et al. Uterine natural killer cells and angiogenesis in recurrent reproductive failure. Hum Reprod 2009; 24: 45-54
References 3


NICE guidelines 2012
Dissemination and implementation
Mrs Caroline Overton

Declaration of Interest
Mrs Caroline Overton
St Michael’s University Hospital Bristol
Chair Association of Early Pregnancy Units (AEPU)
Member of the NICE GDG on miscarriage & ectopic pregnancy
Medical advisor for Endometriosis UK
Consultant for Swiss Precision Diagnostics

www.earlypregnancy.org.uk
Via the website
Email: aepu@rcog.org.uk
RCOG, 27 Sussex Place, Regent’s Park, London NW1 7RG
AEPU: support through the cycle of pregnancy
Diagnosis of miscarriage

Never by one observer

Never on one occasion
2 Guidance

2.3 (a) ultrasound scans should be carried out if any doubts exist. The following features should be noted:

2.3.1 If the gestational sac has a mean diameter greater than 15 mm, with no evidence of an embryo or yolk sac, this is highly suggestive of a missed abortion.

2.3.2 If the embryo has a crown-rump length greater than 5 mm, with no evidence of heart activity, this is highly suggestive of a missed abortion.

2.3.3 When the crown-rump length is less than 32 mm or the crown-rump length is less than 15 mm, a repeat ultrasound should be performed at least one week later to confirm growth of the gestation sac and embryo and to establish whether heart activity exists.

2.3.4 If the gestation sac is smaller than expected for gestational age, the possibility of occult demise should always be considered, especially in the absence of fetal heart beats indicative of a threatened abortion. Under these circumstances, a repeat scan should be arranged after a period of 1 week to be performed by experienced personnel.
New crown-rump length curve based on over 3500 pregnancies


Department of Obstetrics and Gynecology, Ghent University Hospital, University of Ghent, and Department of Obstetrics and Gynecology, University of Ghent, Belgium, and Department of Obstetrics and Gynecology, University of Antwerp, Belgium

Abstract: There is a need for a new and improved reference range for crown-rump length (CRL) in early pregnancy. The purpose of this study was to establish a new CRL reference range based on a large cohort of singleton pregnancies.

Clinical implications of intra- and interobserver reproducibility of transvaginal sonographic measurement of gestational sac and crown-rump length at 6-9 weeks gestation


Department of Obstetrics and Gynecology, Ghent University Hospital, University of Ghent, and Department of Obstetrics and Gynecology, University of Antwerp, Belgium

Abstract: The present study aimed to assess the intra- and interobserver reproducibility of transvaginal sonographic measurement of the gestational sac and crown-rump length (CRL) at 6-9 weeks gestation.

The Management of Early Pregnancy Loss

This is the second edition of this guideline, which was previously published in November 2010 under the same title.

Royal College of Obstetricians and Gynaecologists

Setting standards to improve women’s health
Diagnosis of miscarriage
Never by one observer
Never on one occasion
NICE 2012 Miscarriage

• Key change in guidance
• Expectant management of miscarriage for 7-14 days having considered safety & acceptability
• 50% miscarry spontaneously within 7-14 days of diagnosis
• Anti D is not required for expectant or medical management of miscarriage less than 13 weeks

Severe haemorrhage or pain
Signs of infection: purulent discharge, Pyrexia >37.5°C, tender uterus, white cell count >15
Haemolytic disease or blood dyscrasia
Twins or more
Inability to understand written English and/or difficulty in accessing help
Anaemia
Women in late first trimester (63 days)
Women more than 13 weeks by gestation
No emergency gynaecology provision

All studies compared expectant management with medical and/or surgical management of miscarriage (both of which isolated or in combination were defined as “active” by the GDG), and reported at least one priority outcome. The trials were all conducted in developed countries, and their populations include women with missed miscarriages and/or women with ongoing miscarriages.

Expectant management
- 238/632 (35%) unplanned intervention
- 2% infection
- 13% gastrointestinal side effects
- 1.6% need for a blood transfusion
- 7-14 bleeding days
- 0-5 days in pain
- 49% unplanned admission

Expectant versus active management
No difference in
- Infection rates
- Bleeding time for expectant and medical
- Duration and severity of pain
- Satisfaction
- Anxiety scores
- Fertility or Live birth rate
Expectant versus active management

- More unplanned interventions (165 more to 302 more)
- Greater need for blood transfusion as a result of heavy bleeding (0 more to 42 more)
- Longer time bleeding with expectant compared to surgical treatment
- More unplanned admissions
- Better mental health scores

Condolences

Good verbal and written information on what to expect
Adequate pain relief (codeine 30-60mg)
Emergency telephone number
System for cancelling Antenatal & scan appointments

All studies compared medical and surgical management of miscarriage, and reported at least one priority outcome. The trials were conducted in both developed and developing countries, and their populations include women with missed miscarriages and/or women with ongoing miscarriages.

Medical versus surgical management
No difference in
- Unplanned visits to a medical facility
- Infection
- Need for a blood transfusion
- Satisfaction, social function, mental health, subsequent live birth rate

Medical versus surgical management
- Higher rate of unplanned intervention 36% versus 5%
- Higher rate of gastrointestinal side effects
- Longer duration of bleeding
- Longer duration and more severe pain
- Higher rate of admissions 18% versus 8%
Area with possible intervention:

Plan: There was no uniform bar of intervention, especially anesthetic and a perception of hospitalization and surgery as traumatic events.

Predictability: Women wanted a predictable end, so they could get on with their lives, and they wanted the management and patients to have a predictable course.

Avoid the course interventions: Ensure that the area is known and the patient is informed in terms of treatment and all goals and expected course details in timing, duration and effects of interventions.
Decidual cast

Check pregnancy test after three weeks

Follow-up
- Personalized
- Cancel routine follow-ups especially dating scans and antenatal appointments
Confidential Enquiries

- One death due to anaphylaxis to opioid analgesia administered by a paramedic
- 5 deaths due to infection associated with miscarriage

It’s not a "retained product of conception". For us, as soon as we see those two lines on the pregnancy test, that is OUR baby growing inside of me.

- I had an ERPC last month and have never been able to call it that. I’ve always said ‘surgical management of my miscarriage’
- What’s an ERPC? Is it the same as a D&C?

National survey results 2012
Surgical management of miscarriage (SMM) should replace ERPC
Choice

- It is no longer acceptable to offer only surgical management for women diagnosed with miscarriage.
- Expectant management is at least as effective as medical management for women with incomplete miscarriage.
- Many women would prefer the options of expectant or medical management.

Via the website www.earlypregnancy.org.uk
Email aepu@rcog.org.uk
RCOG, 27 Sussex Place, Regent’s Park, London NW1 7RG

AEPU: support through the cycle of pregnancy
You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis  
  12-13 September 2013 - Prague, Czech Republic

- Female genital tract congenital malformations: new insights in an old problem  
  27-28 September 2013 - Thessaloniki, Greece

- Introducing new techniques into the lab  
  4-5 October 2013 - Barcelona, Spain

- Polycystic ovary syndrome: A new look at an old subject  
  25-26 October 2013 - Rome, Italy

- Infections from conception to birth: role of ART  
  7-8 November 2013 - Berlin, Germany

- Endoscopy in reproductive medicine  
  20-22 November 2013 - Leuven, Belgium

- From early implantation to later in life  
  28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency  
  6-7 December 2013 - Utrecht, The Netherlands

www.eshre.eu
(see “Calendar”)

Contact us at info@eshre.eu