Recurrent Pregnancy Loss

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Discloses no relevant financial relationships with commercial interests.
Objectives

Following this lecture, the learner should be able to

- Define early pregnancy loss and recurrent pregnancy loss
- Identify ultrasound features of early pregnancy loss
- Discuss the evaluation and management options for recurrent pregnancy loss.

Nonviable intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without FHR activity in first 12 6/7 weeks of gestation.

- 10% of all clinically recognized pregnancies
- 80% of all pregnancy losses occur in the first trimester.
- 50% of EPL due to chromosomal abnormalities
- Most common risk factors: Maternal age & prior EPL

ACOG PB 200; Nov, 2018
Maternal Age (years) | Clinically Recognized EPL Rate
--- | ---
20-30 | 9-17%
35 | 20%
40 | 40%
45 | 80%

ASRM. Fertil Steril, 2012

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Table 1. Guidelines for Transvaginal Ultrasonographic Diagnosis of Pregnancy Failure in a Woman With an Intrauterine Pregnancy of Uncertain Viability

<table>
<thead>
<tr>
<th>Findings Diagnostic of Pregnancy Failure</th>
<th>Findings Suspicous for, but Not Diagnostic of, Pregnancy Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crown-rump length of 7 mm or greater and no heartbeat</td>
<td>Crown-rump length of less than 7 mm and no heartbeat</td>
</tr>
<tr>
<td>Mean sac diameter of 25 mm or greater and no embryo</td>
<td>Mean sac diameter of 16-24 mm and no embryo</td>
</tr>
<tr>
<td>Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac</td>
<td>Absence of embryo with heartbeat 7-13 days after a scan that showed a gestational sac without a yolk sac</td>
</tr>
<tr>
<td>Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac</td>
<td>Absence of embryo 4 weeks or longer after last menstrual period</td>
</tr>
<tr>
<td>Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)</td>
<td>Enlarged yolk sac (greater than 7 mm)</td>
</tr>
<tr>
<td>Small gestational sac in relation to the size of the embryo (less than 5 mm difference between mean sac diameter and crown-rump length)</td>
<td></td>
</tr>
</tbody>
</table>
Findings Diagnostic of Pregnancy Failure

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Recurrent Pregnancy Loss (RPL)

Definition

- First literature -1930’s
- Existing guidelines (ASRM, RCOG and ESHRE)
- Occurs in 2-4% of couples (Stephenson, 2007)
- Definition:
  - Loss until 15 weeks (some use 20-24 weeks)
  - Recurrent, not sporadic
  - Typically defined as two or three consecutive losses
  - Controversies
1. What to include as a loss?
   - US, pathology confirmed, US & path, or home +UPT?
   - 71% of self reported preg verified in hospital records
   - For purposes of determining if RPL evaluation is appropriate, US or path documentation required (ASRM)

2. RPL defined as 2 or 3 loss?
   - Risk of SAB after 2 losses similar to 3 losses
   - Two losses (24-29%) vs three losses (31-33%)
   - Thus, starting evaluation after 2 losses reasonable or if AMA or if difficulty conceiving is reasonable

Recurrent Pregnancy Loss (RPL)
Risk of recurrent RPL

- The likelihood of miscarriage increases with increasing numbers of prior miscarriages.

<table>
<thead>
<tr>
<th>Miscarriage number</th>
<th>Likelihood for recurrent losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>5</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>53%</td>
</tr>
</tbody>
</table>
Causes often discussed for RPL

- APS
- Uterine anatomic
- Metabolic / Hormonal
- Genetic
- Environmental
- Psychological
- Infectious
- Genetic Thrombophilias
- Alloimmune

ASRM. Fertil Steril, 2012

Antiphospholipid Syndrome (5-20% of RPL patients)

- Diagnosis: International consensus criteria
  - Lab criteria: Test for lupus anticoagulant, anticardiolipin IgG/IgM, beta-2 glycoprotein IgG/IgM. Repeat in 12 weeks. Medium to high positive values only
  - Clinical criteria: DVT/PE, prior SAB x3 <10wks, prior loss over 10 weeks, prior <34 weeks preeclampsia or IUGR

- Treatment:
  - Heparin 40 bid + ASA 81 mg daily once viable IUP is diagnosed
  - Low molecular weight heparin comparable efficacy has not been confirmed

Antiphospholipid Syndrome (5-20%)

- With the exception of anticardiolipin, lupus anticoagulant, and anti-β2-glycoprotein I, clinical assays for other antiphospholipid antibodies are not standardized and the level of evidence does not warrant routine screening.

- If screening for these additional aPLs is pursued, the statistical probability of finding a positive test will increase and will likely not reflect a true cause for RPL.

ASRM, 2012
Uterine Anatomic Abnormalities
(2-38% of RPL patients)

- Diagnosis: sonohysterography, hysterosalpingogram, 3D ultrasound or MRI
- Treatment: Septum resection conventionally thought to improve outcomes (77-90%), but limited evidence.

Metabolic disorders
(5-9% of RPL patients)

- Diabetes - uncontrolled only
  - check HgA1C (≥ 6.5%) or Fasting BS
- Thyroid - poorly controlled hypo or hyperthyroidism
  - check TSH (< 0.45 or > 4.0 μIU/mL)
- Prolactin
  - check prolactin (>23.3 ng/ml)
Genetic abnormalities (2-5% of RPL patients)

- Very high frequency of sporadic karyotypic abnormalities in POC while the incidence of karyotypic abnormalities in parents is low.

- POC testing: ~60% of SAB POCs will have sporadic chromosomal anomalies

<table>
<thead>
<tr>
<th>Type</th>
<th>Approximate Proportion of Abnormal Karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy</td>
<td></td>
</tr>
<tr>
<td>Autosomal trisomy</td>
<td>52%*</td>
</tr>
<tr>
<td>Autosomal monosomy</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>45, X</td>
<td>19%</td>
</tr>
<tr>
<td>Triploidy</td>
<td>16%</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

* Primarily trisomies that are age-related.

Genetic abnormalities (2-5% of RPL)

- Parental karyotype abnormalities in 2-5% of RPL
  - Testing for balanced reciprocal translocations and Robertsonian translocation

- Treatment:
  - Genetic counseling
  - IVF & Preimplantation genetic testing
  - Amniocentesis / CVS
In losses with a normal karyotype...

- Gross morphological fetal abnormalities described in 18% of patients
- 1st trimester early anatomy US

Environmental

- BMI
- Tobacco
- Alcohol
- Drug use
- Caffeine (over 3 cups coffee/day)
### Summary of recommended management (ASRM, 2012)

**Test / Assess:**

- APLS ➔ 5-20 %
- Uterine cavity ➔ 2-38 %
- TSH, PL, FBS or HgA1C ➔ 5-9 %
- POC and/or parental karyotype ➔ 2-5 %
- Screen for environmental factors ➔ ?
- 1st trimester psychological support ➔ ?

*Diagnosis made and treated in 50% of pts with RPL*

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Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients

F. Popescu¹, C. R. Jaslow¹, and W. H. Kuttel²,³,⁴,⁵

- ASRM Workup and CMA on the POC
- Assessed efficiency and cost savings
- Supporting a new algorithm

New Algorithm: Use of CMA on Products of Conception (increased detection to 95% result)

• 100 patients with ≥ 2 RPL who had both the ASRM RPL work-up and POC CMA

Controversies in evaluation/management of RPL

- PCOS- has not been convincingly tied to RPL
- Infectious causes- ureaplasma, mycoplasma, not associated with loss nor are antibiotics associated with improved outcome
- Thrombophilias (genetic)- not associated with RPL based on prospective cohort studies
- Alloimmune disorders-HLA typing, neither the cause nor proposed treatment (IVIG) are based on evidence
- Male factors- DNA fragmentation or spermploidy- not recommended for testing
- Luteal phase deficiency…

Luteal phase defect

- Concept:

  Progesterone is critical to maintaining a healthy pregnancy and is secreted by the corpus luteum in the second ½ of the menstrual cycle. If the luteal phase is abnormal, the lining of the uterus may not grow properly.

- Traditional teaching: supplement with progesterone through the first trimester

- PROMISE study: NEJM 2015 study Coomarasamy
  - Women with 3+ losses
  - 400 mg vaginal micronized progesterone versus placebo
  - Outcome: LB 65.8% in progesterone, 63.3% in placebo, RR 1.04 (0.94-1.15) p 0.45.

Luteal phase defect

Administration of progesterone to women with sporadic miscarriages is ineffective (Haas; Goldstein).

However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit (Hirahara; Oat-Whitehead; Dara).
What’s new in RPL?

- Trial: on use of hydroxychloroquine (Plaquenil) for prevention of RPL - results 2023
  - Pasquier et al
  - Pharmacologic properties: antithrombotic, vascular protective, immunomodulatory, lipid lowering, anti-infectious)
  - Randomizing 300 women
  - Starting treatment prior to conception through the 10th week

What’s new in RPL?

- Luteal phase defect treatment periconceptionally
  - 2018 Ismail et al. Did RCT of 400 mg progesterone or placebo bid
  - Started in luteal phase until 28 weeks
  - 700 women enrolled
  - Livebirth rate 92% versus 77% (p<0.05)

- Aspirin for prophylaxis in unexplained RPL
  - Blomquist et al 2018
  - RCT of 400 women
  - Live birth rate 83% versus 85.5% (p=0.58) CI 0.89-10.6
References

• ACOG Practice Bulletin: Management of recurrent early pregnancy loss (2001)
• Youssef et al. "Comparison and appraisal of (inter)national recurrent pregnancy loss guidelines." RBMO 2019
• Branch et al. "Practical work-up and management of RPL for the Front-Line clinician." Clinical Ob/Gyn 2016
• Coomarasamy "A randomized trial of progesterone in women with recurrent miscarriages." NEJM 2015.
• Pasquier et al. "hydroxychloroquine for prevention of recurrent miscarriage: study protocol for a multicenter RCT BBQ study. BMJ 2019
• Popescu et al. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue Human Reprod 2018
• Jaslow et al. Diagnostic factors identified in 1020 women with two versus thr more recurrent pregnancy losses. Fertility and Sterility. 2010
• Ismail et al. Matern Fetal Neonatal Med 2018

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• Oates-Whitehead Progestogen for preventing miscarriage. Cochrane Database Syst Rev 2003;4
Recurrent pregnancy loss (RPL): We discussed early pregnancy loss and the definition, diagnosis and management of RPL and her history. The incidence of recurrent pregnancy loss in the general population is about 2-4%. We reviewed that there are numerous causes for RPL that include parental chromosomal abnormalities (2-5%) and other fetal genetic causes, uterine anatomical factors such as Asherman syndrome or anomalies, autoimmune disease, alloimmune factors (APS; 5-20%), endocrinologic disease (i.e. diabetes, hypothyroidism), and environmental causes (e.g. EtOH, Tob, drugs, excess caffeine), and less commonly teratogen and infectious exposure. However, over 50% of all miscarriages have no known etiology. Discussed that management can begin by screening for hypertension, hormone levels (TSH, prolactin), diabetes (FBG, hemoglobin A1C), renal disease (creatinine), and for maternal APS (anticardiolipin antibodies, lupus anticoagulant, beta-2 glycoprotein antibodies). If any of the laboratory tests are positive for antiphospholipid antibody syndrome, repeat testing would need to be performed in 12 weeks to confirm the diagnosis. Screening for genetic thrombophilias is not indicated without a history of thromboembolism, as a definitive causal relationship between thrombophilias and adverse pregnancy outcomes has not been established.(ACOG Practice Bulletin #138, Sept 2013). Discussed uterine cavity assessment and karyotype assessment (POC, parental).

Thank You!
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Baby Loss Awareness Week

Baby Loss Awareness Week is held annually from 9 to 15 October

A collaboration between more than 60 charities across the UK, Baby Loss Awareness Week aims to raise awareness about the key issues affecting those who have experienced pregnancy or baby loss in the UK.