Recurrent Pregnancy Loss

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Definitions

- First literature on this was in 1930s
- Existing guidelines (ASRM, RCOG, and ESHRE)
- Occurs in 2-4% of couples
- Loss until 15 weeks (some use 20-24 weeks)
- Recurrent, not sporadic
- Typically defined as two or three consecutive losses

Miscarriage number Likelihood for recurrent losses
3 20%
4 27%
5 40%
6 53%

- Risk of abortion after two losses (30%) is similar to three losses (33%)
- Controversy exists about which to include (only ultrasound or pathology confirmed or home + UPT)


Causes often discussed for RPL

- Autoimmune
- Uterine anatomic
- Metabolic
- Genetic
- Environmental
- Infections
- Thrombophilia
- Allergies
Antiphospholipid Syndrome (5-20%)

- **Diagnosis:** International consensus criteria
  - Lab criteria: Test for lupus anticoagulant, antiphospholipid IgG/IgM, beta2glycoprotein IgG/IgM. Repeat in 12 weeks. Medium to high positive values only.
  - Clinical criteria: DVT/PE, prior salpingectomy, prior loss over 10 weeks, prior <34 week pregnancy or IUGR.

- **Treatment:**
  - Heparin 40 bid/ASA 81 mg qd once viable IUP is diagnosed.
  - Low molecular weight heparin: Comparable efficacy has not been confirmed.

Uterine anatomic abnormalities (2-38%)

- **Diagnosis:** sonohysterogram, hysterosalpingogram, 3D ultrasound or MRI

- **Treatment:**
  - Septum resection: Conventionally thought to improve outcomes (77-90%) but limited evidence.
  - Ongoing trial of septum resection for reproductive outcomes Rikeen 2018.

Metabolic disorders

- **Diabetes:** uncontrolled only - check HgA1C or fasting glucose
- **Thyroid:** poorly controlled hypo or hyperthyroidism – check TSH
- **Prolactin:** prolactin level
Genetic abnormalities (2-5%)

**Diagnosis:**
- Can do POC testing (40% of miscarriages will have sporadic chromosomal anomalies)
- Maternal and paternal balanced translocation testing

**Treatment:**
- Genetic counseling
- Prenatalcff: Amniocentesis

(IVF with PGD has not been found to improve live birth rates)
- Amniocentesis/CVS

Diagram from the Infertile Farmer

Use of CMA on Products of Conception (99% result)

Most common abnormalities

- Four percent of pregnancies had parental karyotype abnormalities

<table>
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<th>Chromosomal abnormality</th>
<th>Cases</th>
<th>Prevalence</th>
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<tr>
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<tr>
<td>Total</td>
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Environmental

- BMI
- Tobacco
- Alcohol
- Drug use
- Caffeine (over 3 cups coffee/day)

Summary of recommended management

- Test for APLS
- Uterine cavity assessment
- TSH, Prolactin, fasting glucose (or HgA1C)
- Consider POC testing and/or parental kary
- Screen for environmental factors
- First trimester psychological support

Controversies in evaluation/management of RPL

- PCOS- has not been convincing tied to RPL
- Infectious causes- ureaplasma, mycoplasma, not associated with loss nor are antibiotics associated with improved outcome
- Thrombophilia- not associated 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 (see next slide)
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: Live birth 65.8% in progesterone, 65.3% in placebo, RR 1.04 (0.94-1.15) p 0.45.

Unexplained RPL

- Up to 50%
- Live birth rates are 35-85% in this group

What’s new in RPL?

- Early data on use of hydroxychloroquine for prevention of RPL results 2023
- Pharmacologic properties: antithrombotic, vascular protective, immunomodulatory, lipid lowering, anti-inflammatory
- Randomizing 300 women
- Starting treatment preconception through the 10th week
- Luteal phase defect treatment periconceptionally
  - 2018 randomized, the RCT of 400 mg progesterone or placebo bid
  - Started in luteal phase until 20 weeks
  - No women needed
  - Livebirth rate 95% versus 77% (p<0.05)

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

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