Recurrent Pregnancy Loss: 
The myths, the controversies and 
the evidence
Mamie McLean, MD
Assistant Professor
Reproductive Endocrinology and Infertility
University of Alabama at Birmingham

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Objectives
Define recurrent pregnancy loss (RPL)
Etiology of RPL
Evidence based evaluation and treatment
Common myths and controversies
Case #1

• 28 yo G2P0020 trying to conceive for 1.5 years
• G1 = 6 week loss
• G2 = 7+4 week loss

Is this recurrent pregnancy loss?
Do you send the products for karyotype?
Do you proceed with an evaluation?

Definition

• Historically, defined as 3+ consecutive spontaneous miscarriages

• Now, defined as 2 failed clinical pregnancies
  — Histologic or ultrasound confirmation

Epidemiology

• Early loss is common
  — 30-60% all conceptions
  — 15% clinically recognized pregnancies
    • Risk varies by prior OB hx
    • Even with >6 losses, risk = 50%
    • Maternal age: < 30 = 6%; 35-39 = 25%; >40 = 30-75%

5% of women will have 2 miscarriages
1% ≥ 3 miscarriages
Definition

- **2 failed clinical pregnancies**
- No specific number that justifies evaluation or defines the scope of evaluation
  - Consider female partner’s age
  - Timing, circumstances of losses
  - Personal, family history

ASRM Committee Opinion, 2013

Epidemiology

- Recurrent pregnancy loss is a disease
- RPL is a type of infertility
  - Longer time to conception
    - Number of prior miscarriages
    - Median time to live birth was 2 years
- Increased risk of placental dysfunction
  - Preeclampsia, stillbirth, SGA, abruption, preterm birth (aOR = 2)
- Risk factor for cardiovascular complications

Sapra, Hum Reprod, 2014
Kaandorp, Hum Reprod, 2014
Gunnarsdottir, AJOG, 2014
Kharazmi, Heart, 2011
Kessous, AJOG 2014

When to evaluate?

- >3 spontaneous losses
- Consider if 2 consecutive losses
  - Especially if
    - Cardiac activity prior to loss
    - Normal karyotype on prior loss
    - Female partner >35
    - Infertility

ASRM Committee Opinion, 2013
Case #2

- 32 yo G3P1021 with subfertility
- 1 full term delivery after 8 months of clomiphene
- 2 biochemical losses

FSH = 13
Estradiol = 42
Normal uterine cavity
Normal TSH, PRL
46 XX

Is this RPL?
Do the biochemical losses "matter"?
Do you do an evaluation?

Epidemiology

- **Biochemical losses are important**
  - Important prognosis for live birth
    - Danish retrospective cohort study
    - Self reported losses vs clinical losses
    - Similar RR for live birth

Case #3

- 38 yo with severe male factor infertility, conceived on her 4th cycle of letrozole, donor insemination; spontaneous abortion at 11 weeks
  - 46 XY
Case #1

- 28 yo G2P0020 with RPL
- G1 = 6 week loss, D&C
- G2 = 7+4 week loss; D&C
  - Products = trisomy 18

Evaluation

- Genetic testing on POC is not helpful
  - Newer techniques (eg SNP microarray)
    - Less test failure
    - Increased detection of abnormality
    - Identify MCC
- Early losses
  - Paraffin preserved samples
- Identify parent of origin

Lathi, Fertil Steril, 2014
Dhillon, BJOG, 2014
Levy, Obstet Gynecol, 2014
Maslow, Obstet Gynecol, 2015

Evaluation: Products of conception

- Second loss
- Infertility
- Second trimester loss
- Female partner age >35
Evidence based evaluation

Clinical criteria:
• Vascular thrombosis
• Complication of pregnancy
  > 1 unexplained fetus death after 10 weeks (morph. normal fetus)
  > 1 premature births before 34 weeks (morph. normal fetus)
  > 3 unexplained consecutive spontaneous abortions before 10 weeks of gestation

ASRM Committee Opinion, 2013

Evaluation

• *Inherited thrombophilias cause miscarriage*
  – Association between inherited thrombophilias, but prospective trials have failed to confirm or show low absolute risk
    • FVL homozygous
    • Prothrombin
Testing for inherited thrombophilias in women who have experienced recurrent fetal loss is not recommended.

ACOG Practice Bulletin, 2013

Routine testing of women with RPL for inherited thrombophilias is not currently recommended.

ASRM Committee Opinion, 2013

American College of Chest Physicians; Chest, 2012
Evaluation

- Maternal immune hyperactivation causes miscarriage – Studies are conflicting – Unclear if association or causation – No effective, safe treatments to date
  - IVIG (randomized prospective trial, 2015) – No difference in live birth rates vs placebo
  - IVIG (meta-analysis, 2015) – No difference in live birth rate – Increased adverse events – Should not be used outside of a clinical trial

Christiansen, BJOG, 2015
Egerup, PLoS One, 2015

Evidence based evaluation

- Parental karyotypes
- Uterine cavity assessment
- TSH, PRL, consider hemoglobin a1c
- Consider APLS
  - B2 glycoprotein, lupus anticoagulant, anticardiolipin
- Screen for personal, family history of thrombophilia

ASRM Committee Opinion, 2013

Evidence based treatment

- Endocrinopathy
  - Thyroid disease, hyperprolactinemia, glucose control
- APLS
  - Aspirin 81mg and anti-thrombotic agents
- Uterine septum
  - Resection
- Parental translocation
  - IVF with PGS/PGD vs donor gametes
Treatment

• Supplemental progesterone does NOT reduce further miscarriage
  – Meta-analysis (Cochrane review, 2013)
    • No difference vs placebo/no treatment
    • Small benefit in couples with 3 prior consecutive unexplained losses (OR 0.39, 95% CI 0.21 – 0.72)
  – RCT; placebo controlled, double blinded
    • 1568 women with RPL
    • 400 mcg micronized progesterone vaginal suppositories BID
    • No difference in live birth > 24 weeks between groups
      – RR = 1.04 (0.94-1.15)

Coomarasamy, NEJM 2015

Treatment

• Anti-thrombotic therapy does NOT reduce miscarriage in women with unexplained RPL
  – RCT
    • Placebo controlled, double blinded
    • 258 women enrolled
    • No difference in live birth rates
  – Multicenter controlled trial
    • 449 women
    • No difference in ongoing pregnancy at 24 weeks or live birth

Pasquier, Blood, 2015
Schleussner, Ann of Int Med, 2015

Treatment

• Aspirin does NOT reduces the risk of miscarriage in unexplained RPL
  – Randomized trial
    • aspirin vs heparin + aspirin vs placebo
    • No difference in live birth rate
  – RCT (EAGeR trial)
    • Double blind, placebo controlled
    • Preconception aspirin vs placebo
    • No difference in live birth rates, nor in % euploid loss

Kaandorp, NEJM 2010
Mumford, Hum Reprod 2016
Treatment

- Preimplantation Genetic Screening increases live birth rate in women with unexplained RPL
  - No randomized trials
  - Prospective trials
    - Reduced miscarriage rates
    - Shorter time to live birth
  - Meta-analysis (2011)
    - Similar live birth rates compared to natural conception
    - Lower miscarriage rates (9% vs 28%)

Sher, F&S, 2009
Fragouli, F&S, 2010
Musters, F&S, 2011

Evidence based treatment

- Unexplained RPL
  - Supportive care (TLC)
    - Prospective trial (n = 158 couples)
      - Weekly visits
      - 36% live birth in standard vs 85% TLC
    - Prospective trial (n = 201 couples)
      - Frequent ultrasounds
      - 26% miscarriage vs 51% in supportive care

Stray-Peterson, AJOG, 1988
Clifford, Hum Reprod, 1997

Counseling

Kaandorp, Hum Reprod, 2014
Summary

2 confirmed pregnancy losses
Evaluation determined by clinical scenario
  – Cavity evaluation
  – Parental karyotypes
  – Consider APLS if clinical criteria met
  – TSH, PRL, diabetes screening
Consider karyotype or microarray on POC
If workup negative, supportive care

Questions?