Workup of Recurrent Early Pregnancy Loss

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Medical Problems of Pregnancy

Case

- 35 year old woman presents to your clinic for recurrent pregnancy loss (RPL)
- G5P1A4
  - 1st pregnancy: Delivered healthy 11 pound boy
  - Four subsequent miscarriages at 6 weeks
  - Used ASA 81 QD and Progesterone IM during last pregnancy
  - Non smoker, no alcohol
- No prior medical history
- No family history
- On Review of Systems: intermittent diarrhea and bloating- told she had IBS by GI
Ten questions we hope to answer

1. What is included in its definition?
2. How common is RPL?
3. What are the associated risk factors?
4. What are potential causes of RPL?
5. How does it differ from infertility?

Ten questions (continued)

6. What questions to ask on history?
7. What are pertinent findings to look for on physical exam?
8. What investigations would you like to ask for?
9. Which of these will change management?
10. What guidelines exist on the subject?
1. Definition of Recurrent Pregnancy Loss

- Various definitions used in the literature,
- Traditionally defined as three or more consecutive miscarriages occurring before 20 weeks.
- Sometimes includes pregnancy losses up to week 28 and after only two miscarriages.

2. Epidemiology

- 12-15% of clinically recognizable pregnancies result in miscarriage
- No valid estimate of incidence because denominator variable (=individuals at risk) not clear.
- Around 1% of fertile couples have RPL
- Prevalence ranges between 0.6% and 2.3%
- In nearly 50% of patients with RPL, the underlying cause remains unknown.
3. Risk Factors

- Previous miscarriage
- Found to be the strongest prognostic parameter
  - Chance of subsequent live birth among untreated pts with RPL
  - With 3 miscarriages => 42-86%
  - With 4 miscarriages => 41-72%
  - With 5 miscarriages => 23-51%

3. Risk Factors (continued)

- Maternal age above 40
  - Next strongest predictor
- ?Partner specificity (assumed, never proven)
- ?Genetic risk (family risk as part of multifactorial model)
- Lifestyle factors: obesity, high caffeine intake, alcohol, stress
4. Causes of RPL

- Anatomical
- Genetic
- Hematological
- Endocrinological
- Immunologic
- Infectious
- Environmental
- Unexplained

Chromosomal abnormalities
- 50-80% of first trimester abortions show chromosomal abnormalities (trisomy, polyploidy, monosomy X).
- In comparison, chromosomal abnormalities account for 5% of stillborn (third trimester) losses.
- Also, the incidence of chromosomal aberrations is lower in recurrent compared to spontaneous abortions.

Structural uterine anomalies, eg Uterine fibroids*, septate uterus, cervical incompetence
Role of Endocrine causes

- Estimated to be the cause of 8-12% of pregnancy losses
- Progesterone essential for successful implantation and maintenance of pregnancy.
- Luteal phase deficiency, hyperprolactinemia, PCOS = inadequate progesterone secretion
- Treatment with bromocriptine therapy associated with higher rate of successful pregnancy

Endocrine (continued)

- *Uncontrolled* diabetes:
  - several studies have found high HA1c >8% to be associated with increased rates of miscarriage
- *Insulin resistance => impairment of the fibrinolytic response => difficulties with embryonic implantation
  - Role of metformin not yet found to decrease incidence of miscarriage.
Endocrine (continued)

- Poorly controlled thyroid disease – hypothyroidism and hyperthyroidism
- ?subclinical hypothyroidism= recent cochrane review found a non-significant trend
- Presence of thyroid autoantibodies
  - anti TPO even among euthyroid has been associated with RPL
- ?Hypoparathyroidism

Role of Thrombophilias

- Hereditary thrombophilias:
  - Antithrombin, protein C, protein S deficiencies
  - Factor V leiden
  - G20210A mutation in factor II (prothrombin)
  - Homozygosity in MTHFR gene with high homocysteine and low folate
- From increased bleeding risk:
  - Factor XIII deficiencies (homozygous)
  - Fibrinogen deficiency
Thrombophilies (continued)
- Attributed to placental infarcts and vascular thrombosis leading to placental insufficiency vs. Inhibition of trophoblast invasion and differentiation vs. Autoimmune phenomenon
- Large and contradictory literature on the benefits of unfractionated heparin and ASA in inherited thrombophilia on reducing pregnancy loss

Anti-phospholipid syndrome
- Only immune condition for which pregnancy loss is part of the diagnostic criteria
- 5-15% of patients with RPL have been found to have Antiphospholipid syndrome
- aCl prevalent in 0-11% of uncomplicated pregnancies
- Cochrane review 2005 pts with aPL=> potential for a 54% reduction
HepASA Trial

- Prophylactic LMWH + ASA vs. ASA alone
- Pt population:
  - 18-44yrs
  - History of 2 or more pregnancy losses prior to 32 weeks
  - Presence of ANA (1/80), aPL or inherited thrombophilia (protein C, S, APCR, factor V leiden, PT, MTHFR)
- Excluded pts with SLE, prior VTE, anatomic or genetic or hormonal causes found to explain RPL

HepASA Trial (continued):

- Of 859 eligible, 112 eligible and consented
- 24 Failed to conceive
- 88 randomized
- Results:
  - 35/45 treated with LMWH&ASA = 78% had a live birth
  - 34/43 treated with ASA alone = 79% had a live birth
  - Neither number of prior losses nor aPL status was correlated with pregnancy outcome.
Role of Autoimmune diseases

- Role of natural killer cells in uterine mucosa?
- Lupus = added risk if presence of antiphospholipid antibodies + can predispose to preeclampsia
- Untreated celiac disease
- Previous studies have shown that the use of steroids to suppress autoantibody titres do not improve the livebirth rate and have been found to increase the risk of preterm delivery.

Celiac disease

- Associated with menstrual disorders, pregnancy loss and infertility
- No study has shown celiac disease to cause repeated pregnancy loss
- Two non-randomized studies have demonstrated an associated between untreated celiac disease and pregnancy loss
Infections and RPL

- Pathogenic or opportunistic?
  - It is now believed that in order for an infective agent to be responsible, it must be capable of persisting in the women’s genital tract undetected and must cause few symptoms.

Infections (continued)

- **Tuberculosis** (pelvic): affects mostly fertility
- **Listeriosis**: rarely associated with fetal loss
- Little evidence for role of **chlamydia**
- **Syphilis** seroreactivity associated with spontaneous abortion, perinatal morbidity and morbidity to viable infant
- **Bacterial vaginosis** 2nd to role on inhabitation of uterus and role in premature delivery (but mostly 2nd trimester loss and evidence inconsistent)
Infections (continued)

- TORCH infections
  - Toxoplasmosis, Rubella, CMV and herpes simplex
  - Can be associated with individual pregnancy loss but as they are only contracted once, unlikely to be associated with RPL
  - Routine screening for these diseases no longer recommended by most
- HIV => protease inhibitors can cause hyperglycemia
- Parvovirus => associated with 2nd trimester miscarriage or pre-term birth
- Hepatitis B, C => placentitis?

5. Causes of Infertility

- Definition= failure of a couple to conceive after 12 months in women less than 35 yrs and after 6 mos in women 35 and older.
- Share some common causes:
  - Karyotype abnormalities
  - Luteal phase defects
  - Thrombophilies
  - SLE
  - Celiac disease
6. What questions to ask on history?

- Age, previous pregnancies, weeks at miscarriage, any problems during pregnancy
- Family history of miscarriages, pre-eclampsia, gestational diabetes, VTE and thrombophilias
- Habits: smoking, coffee, alcohol, workplace and stress levels
- Medications including natural supplements
- Review of systems for bloating, diarrhea, mucus in stool, floating stool, joint pain, rashes, polydipsia, polyuria, nocturia, fatigue, cold intolerance, palpitations, thyroid masses

7. What are pertinent findings to look for on physical exam?

- Focused physical depending on review of systems
- Vitals: check BP, heart rate
- Cardiac exam for presence of flow murmur (hyperdynamic state)
- Thyroid exam of any goitre or nodules
- Joint exam if + on review of systems
- Acanthosis nigricans, obesity
8. Complete workup at the RVH?

- Parental peripheral blood karyotype
- Early follicular-phase FSH
- Pelvic ultrasound scan
- CBC
- Antiphospholipid antibodies (lupus anticoagulant, IgG and IgM anticardiolipin antibodies)
- Factor V leiden and prothrombin gene mutations, protein C and S, Antithrombin III, factor VIII, MTHFR, folate, homocysteine
- TSH, thyroid antibodies, OGTT, LH, FSH, Prolactin, progesterone
- ANA, RF, anti-TTG
- Vaginal/cervical cultures, HIV, hep B/C, parvovirus, syphilis, toxoplasmosis, rubella, CMV

9. Which of these will change management?

- Presence of LA or aCL antibodies => ASA, LMWH
- *Presence of a thrombophilia (+/- history) => LMWH
- TSH, FT4 => treatment
- Oral glucose tolerance test => better glucose control
- Syphillis => rx
- *Anti-TTG antibodies (+ symptoms) => change in diet
- *Elevated homocysteine and low folate => folic acid supplementation
10. Medical Investigations of RPL - Guideline Statements

- Royal College of Obstetricians (RCOG)
  - Guidelines updated: 2003

- American College of Obstetricians (ACOG)
  - Guidelines updated: ?

- European Society of Human Reproduction and Embryology (ESHRE)
  - Guidelines updated: 2006

Investigations for RPL

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Treatment to decrease risk of RPL

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<tr>
<td>Folic acid for hyperhomocysteinemia</td>
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Conclusion

- Recurrent Pregnancy Loss is defined differently in EBM but generally refers to 2+ consecutive pregnancy loss before 28 weeks.
- Exhaustive protocols searching for underlying cause not supported by the literature.
- Although associations and causations have been found for a select few, further studies documenting benefit of treatment conflicting.
- Guideline statements between specialists also conflicting.
- Strongest evidence for testing for aPL, thyroid abnormalities, uncontrolled diabetes, prolactinomas, syphilis, uterine malformations and karyotype.
- Patient specific approach best by weighing risks and benefits.
- Don’t forget the patient and underestimate the impact of TLC (i.e. Tender Loving Care).
References

2. ACOG 2010 Education Module
5. Reid et al. Interventions for clinical and subclinical hypothyroidism in pregnancy. Cochrane Database Systematic Reviews. 2010 (July 7).