A clinician's dilemna: Why we miscarry

Defining and Evaluating Recurrent Pregnancy Loss

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The human side

- Often as emotionally devastating as a stillborn or neonatal death
  - Treat the human first
    - Reassure the patient that nothing they did was wrong!
      - Not stress, exercise, intercourse, too little sleep, lifting a heavy item, etc…
  - Offer and support clinical counselling

Definition of Recurrent Pregnancy Loss (RPL)

- Incidence of single loss prior to 20 weeks is 15%
  - Subsequent loss rate is 15 percent
- After two losses, incidence of subsequent loss is 17-31%
- After three losses, incidence of subsequent loss is 25-46%
- Because these are similar, most experts recommend initiating an evaluation after TWO consecutive losses
  - Risks factors (including infertility and age) may even make an earlier evaluation appropriate
- However, even after 6 miscarriages, there is data to support that 50% of women will have a normal outcome
  - Clifford, K. Human Reproduction 12(2):387, 1997

Etiologies

- GENETIC
- Anatomic
- Endocrine
- Thrombophilic
- Immunological
- Infectious
- Environmental

Genetics, genetics, genetics

- At least 50% of all miscarriages have a genetic aberration
  - Many undetected by conventional G-banding (abnormal karyotypes often do not culture well)
  - CGH is reasonable and cost-effective

- 3-5% of patients with RPL have peripheral karyotypic abnormalities, and the expense tends to be excessive
- In PGD cycles, 70% of embryos from RPL patients, and 45% of non-RPL patients were aneuploid
  - Rubio C, Human Reproduction. 2003.

Structural Evaluation

- Hysterosalpingogram, sonohysterography, hysteroscopy, ultrasound, MRI
  - SHG or hysteroscopy is more definitive and accurate
  - Ultrasound advantageous because of identification of other pathology (fibroids, etc…)
  - MRI or 3D U/S for differentiation of bicornuate from sepate

What labs are helpful?

- Anticardiolipin (IgG and IgM) and Lupus anticoagulant
  - Must be repeated to confirm
- beta2-glycoprotein and possibly phoshatidyl serine
  - Kuteh, 2015
- Possibly TSH and thyroid antibodies
  - Isolated TPO tx with euthyroid state showed 50% loss reduction
    - Thangaratinam S, BMJ. 2011
- Ovarian reserve appears to be abnormal in50% of RPL (Ant F, FSH, AMH)
- PRL if oligoovulatory
- ?DNA sperm fragmentation

Not indicated by science

- Hypercoagulable testing
- Diabetes screening (other than high risk populations)
- Progesterone levels
- Endometrial biopsies
- Culture/serology for mycoplasma, toxo, chlamydia, BV

Age and pregnancy loss risk

- 20-30 y/o 9-17%
- 35 y/0 20%
- 40 y/o 40%
- 45 y/o 80%
  - Nybo Andersen, BMJ. 2000.
- Many IVF outcome-based studies suggest even higher rates of loss

Uterine anomalies

- 10-15 % of patients with RPL (4-7% of all women)
- Septate have worst outcome, and are repairable
  - 44% loss rate
    - 77-90% live birth after repair
      - Grimbizis, 2001
- Unclear causation - ?blood supply, inability to respond to steroid hormones

Leiomyoma

- Intracavitary lesions
  - Removal improves outcomes
    - Etiology of loss is likely related to implantation and inflammatory mechanisms
- Intramural not consistently associated with abnormal outcome
  - Size has been the most concerning parameter, but not held up in larger studies

Diabetes

- HgbA1C >8 associated with much greater loss rate
- Well-controlled diabetes is not associated with loss

PCOS

- Loss rate as high as 20-40%
- Mechanism of loss:
  - Endo receptivity
  - Delayed ovulation/synch timing
  - Alteration in growth factors/cytokines/hormones
  - LH superactivity
  - Insulin resistance – but Metformin likely does not improve outcomes
- Cycle length >34 days was most important predictor of RPL
  - Quenby SM, Obstet Gynecol. 1993.

Other endocrine

- Thyroid antibodies (TPO and thyroglobulin)
  - Causality and conflict in literature exist

- Hyperprolactinemia
  - Higher PRL in patients who miscarry
    - Treatment increased LB rate from 52% to 86%
      - Hirahara F, fertil Steril. 1998.

Luteal phase defect

- NO evidence that diagnosis or treatment changes ANY outcome-related variable
- EMB and progesterone levels are NOT indicated
- Treatment in the first trimester has NO convincing evidence for improved outcomes

Antiphospholid syndrome – International Consensus

- 5-15% of RPL patients
  - Diagnosis – One Lab and one Clinical Criteria
  - Clinical Criteria:
    - Vascular thrombosis
    - Pregnancy morbidity
      - >10 week loss of morphologically normal fetus
      - PTD <34 weeks with eclampsia/sever pre-eclampsia/placental insufficiency
      - > 3 SAB's <10 weeks, excluding maternal (hoemone, anatomical, karyo) and paternal (karyo)
  - Laboratory Criteria:
    - Lupus anticoagulant two or more occasionas >12 weeks apart
    - ACA IgG or IgM in medium or high titer (>40 GPL of MPL or >99%) two or more >12 wks
    - Anti-beta2 glycoprotein-I IgG or IGM > 99%ile two or more >12 weeks

Antiphospholipid syndrome

- Phosphatidyl serine may be indicate
- Effects:
  - Trophoblast effects
    - Inhibition of villous cytotrophoblast differentiation
    - Impairment of invasion of extravillous cytotrophoblast invasion into the decidua
    - Induction of syncytiotrophoblast apoptosis
    - Maternal inflammatory pathway excitation
- Treatment:
  - Low dose baby aspirin and twice daily UNFRACTIONATED heparin
  - Low molecular weight heparin has not been rigorously tested or proven

Other associations

- Inherited thrombophillias
  - Indicated with history of clot or family history of thrompbophilia
  - Treatment empiric

- Infectious causes
  - Not clearly associate with loss and treatment may not improve outcome
  - Ureaplasma, Mycoplama, chlamydia, Listeria, Toxo, CMV, herpes

Lifestyle, Environmental Factors

- OBESITY
- Alcohol
  - > 3-5 drinks/wk
- Caffeine consumption
  - >3 cups of coffee/day
- Cocaine

TLC

- Weekly ultrasounds, counselling, no heavy lifting/sex
  - 85% vs 36% live birth rates
    - Stray-Pedersen, et al expanded 1988
- Depression scores linked to lower future live birth rates
    - Sugiura-Ogasawara, 2002

Alloimmune

- HLA
- Embryotoxic factors
- Decidual cytokines
- Blocking or anti-paternal antibody levels
- HLA-G polymorphism
- Metanalysis of paternal white blood cell immunization
  - Porter, TF 2006
- Metanalysis of IVIG
  - Hutton, 2007, Ata, 2011

Evaluation Recommendations

Treatment Recommendations