Recurrent Early Pregnancy Loss

Background
1. Definitions
   o 3 or more consecutive pregnancy losses confirmed by urine or blood hCG
   o Before 20 weeks estimated gestational age (EGA)
   o Synonymous with recurrent miscarriage or recurrent spontaneous abortion
   o Primary
     ▪ Without preceding successful pregnancy beyond 20 wks EGA
   o Secondary
     ▪ With preceding successful pregnancy beyond 20 wks EGA
2. General info
   o Prognosis similar with 2 or more losses, workup is the same

Pathophysiology
1. Etiology of recurrent early pregnancy loss
   o 50-60% of cases have one or more etiologies
   o Parental Structural Chromosome Abnormalities
     ▪ 2-4% of couples with recurrent pregnancy loss will have one partner with genetically balanced structural chromosome abnormality
       ▪ Most commonly a balanced translocation
     ▪ Risk of aneuploidy higher if mother is heterozygous for translocation
   o Recurrent Embryonic Aneuploidy
     ▪ 50% of embryos will have evidence of aneuploidy in women with recurrent pregnancy loss, which is no different than woman with a single miscarriage
     ▪ Incidence higher if miscarriage in first 6-8 weeks
     ▪ 95% due to maternal gametogenesis errors and 5% due to paternal errors
     ▪ 75% of aneuploid will miscarry prior to 8 weeks
   o Hormonal-ovarian
     ▪ Ovulation disorders
       ▪ Abnormal follicular development on ultrasound
       ▪ Abnormal low peri-ovulatory estradiol levels
     ▪ Luteal phase defect
       ▪ Abnormally low post ovulatory progesterone level
       ▪ Often related to ovulatory disorders
       ▪ Abnormal profiles in up to 40% with recurrent early pregnancy loss
   o Endocrine
     ▪ Poorly controlled DM Type 1
     ▪ Assoc w/Polycystic Ovarian Disease
     ▪ Thyroid disorders
   o Autoimmune
     ▪ Antiphospholipid Syndrome
       ▪ Associated with recurrent early pregnancy loss (or other clinical events related to thrombosis) and abnormal levels of antiphospholipid antibodies
Antibodies found in up to 20% with recurrent pregnancy loss
- Anticardiolipin Antibodies
- Lupus Anticoagulant
- Same antibodies should be positive on 2 separate occasions, at least 6 weeks apart
  - Natural killer cells
    - Large granular lymphocytes
    - Make up 10% of peripheral blood leukocytes
    - High concentration in uterus
    - Appear to play important role in implantation
    - Found in higher concentration and with higher activity in miscarriages of chromosomally normal pregnancies
  - Thrombophilia
    - Factor V Leiden in 8% of Caucasian women
    - Activated protein C resistance
    - Protein S deficiency
    - Prothrombin G2021A mutation in 3% of Caucasian women
    - Methylenetetrahydrofolate mutation, protein C, and antithrombin deficiencies were not significantly associated with early recurrent pregnancy loss
  - Infectious
    - No consistent evidence to support role of infectious agents in recurrent early pregnancy loss
  - Anatomic
    - Uterine:
      - 10-25% of women with recurrent early pregnancy loss have uterine abnormalities when compared to 5% of controls
    - Cervical:
      - Usually associated with pregnancy loss in 2nd trimester with associated early cervical effacement and dilatation
  - Endometriosis
    - Results in peritoneal "toxins" that may influence both follicular development and subsequent implantation and embryo development
  - Unexplained

2. Incidence, prevalence
- 1% of reproductive aged women will experience 3 or more consecutive miscarriages
- 2% of reproductive aged women will experience 2 consecutive miscarriages
  - After 2 miscarriages, woman has 30% chance of recurrent miscarriage

3. Risk factors for any miscarriage
- Age and parity: incidence of miscarriage increases with age and parity
  - Rates for 20-30 = 9-17%
  - Rates for 35 = 20%
  - Rates for 40 = 40%
  - Rates for 45 = 80%
  - Risk of aneuploidy increases with age
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o Previous pregnancy outcome
  ▪ Successful live birth decreases risk for miscarriage in the subsequent pregnancy

o Lifestyle
  ▪ Tobacco: associated with 1.4-1.8 increase risk for miscarriage
  ▪ Alcohol: consuming on average of 1 drink per day increases risk by 4.84
  ▪ Caffeine: consuming greater than 3 servings per day increases risk by 2.21

o Medications
  ▪ NSAIDs, etc
  ▪ Related to increased risk of spontaneous miscarriage

4. Morbidity / mortality for any miscarriage
  o Physical
    ▪ Anemia
    ▪ Infection in missed or incomplete miscarriage
    ▪ Surgical complications if D&C required for removal of miscarried fetus
  o Emotional: 11% risk of major depressive disorder in first 6 months after miscarriage (22% if woman is "childless")

Diagnostics

1. History
  o Prior pregnancies, time of gestation at loss
  o Prior cervical procedures
  o Prior diagnostic workup including lab and imaging
  o Other medical problems
  o Social history

2. Physical examination
  o Pelvic exam
    ▪ Including assessment of uterine size (fibroids), cervical appearance and length

3. Diagnostic testing
  o Laboratory evaluation
    ▪ Chromosomal
    ▪ Parents
    ▪ Products of conception
      • May be difficult to evaluate in very early miscarriage
      • Certain chromosome abnormalities are at a higher risk of repeating while others are more random events
      • Morphologically normal appearing fetus excludes significant chromosomal abnormality with 95% accuracy
    ▪ Hormonal-ovarian
      • Mid luteal progesterone level
    ▪ Endocrine
      • DM Type 1: HgA1C
      • Thyroid: TSH
- Autoimmune
  - Antiphospholipid Syndrome
    - Lupus anticoagulant
    - Anticardiolipin antibodies
- Thrombophilia
  - Factor V Leiden
  - Activated protein C resistance
  - Protein S deficiency
  - Prothrombin G20210A mutation
  - Anatomic evaluation
    - Intra-uterine
    - Ultrasound: 3 D or sonohysterography
    - Hysteroscopy
    - Endometriosis
    - Laparoscopy

Differential Diagnosis
1. Key differential diagnoses
   - Single etiology versus multiple etiology

Therapeutics
1. Treatment: based on recurrent pregnancy loss diagnostic workup
   - Lifestyle
     - Avoidance of tobacco, alcohol, drugs
     - Limit caffeine to <3 servings per day
     - Encourage proper nutrition
   - Medications
     - Avoiding NSAIDs, aspirin, and other potentially harmful meds
   - Parental Structural Chromosome Abnormalities
     - Counseling regarding risk for recurrence
   - Recurrent Embryonic Aneuploidy
     - Counseling regarding risk for recurrence
   - Hormonal-ovarian
     - Luteal support with progesterone
     - Document normal luteal progesterone level while on supplemental progesterone support prior to attempting conception
     - Progesterone support through 1st trimester, and through 37 weeks if prior preterm labor
   - Endocrine
     - Optimization of insulin and sugar levels in DM Type 1 prior to attempting conception
     - Normalization of TSH prior to attempting conception
   - Thrombophilia
     - Heparin when pregnancy confirmed
   - Autoimmune
     - Antiphospholipid Syndrome:
       - Heparin and low dose aspirin when pregnancy confirmed
Intravenous immunoglobulin:
  - Showed some benefit in those with recurrent early pregnancy loss who had a prior pregnancy carried to term and had unexplained recurrent miscarriage
    - Anatomic
      - Cervical
        - Cerclage
      - Uterine
        - Surgical correction of septate uterus deformity or other major intrauterine deformity
    - Other:
      - Endometriosis
        - Surgical treatment with laser with adhesion minimizing technique

Follow-Up

1. Return to office
   - Dependent upon etiology and treatment protocol
   - When pregnancy confirmed, early intervention of underlying disorder improves success for carrying pregnancy to term
2. Refer to specialist
   - Unexplained
   - Need for surgical intervention for diagnosis and treatment
   - Hysteroscopy, laparoscopy, cerclage placement
3. Admit to hospital
   - Current spontaneous abortion
4. Heavy bleeding resulting in unstable vital signs or orthostatic hypotension
5. Septic abortion
   - Need for surgical management in terms of Dx or Tx

Prognosis

1. Risk for subsequent pregnancy loss versus chance of live pregnancy
   - 30% risk for subsequent miscarriage for this groups as a whole with no treatment
   - Risk is higher with advanced maternal age, and also increases with successive losses
   - Risk is even higher when identified treatable etiologies are not treated

Prevention

1. Proper evaluation of recurrent early pregnancy loss after second consecutive miscarriage
   - Etiology may be multifactorial
2. Lifestyle management
3. Treatment of specific conditions
4. Supportive counseling and stress reduction

References


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