Recurrent Early Pregnancy Loss

Background

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

Pathophysiology

1. Etiology of recurrent early pregnancy loss
   - 50-60% of cases have one or more etiologies
   - 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
   - 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
   - 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
   - Endocrine
     - Poorly controlled DM Type 1
     - Assoc w/Polycystic Ovarian Disease
     - Thyroid disorders
   - 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
        - Methylene tetrahydrofolate 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

- Previous pregnancy outcome
  - Successful live birth decreases risk for miscarriage in the subsequent pregnancy
- 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
- Medications
  - NSAIDs, etc
  - Related to increased risk of spontaneous miscarriage

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

Diagnostics

1. History
   - Prior pregnancies, time of gestation at loss
   - Prior cervical procedures
   - Prior diagnostic workup including lab and imaging
   - Other medical problems
   - Social history
2. Physical examination
   - Pelvic exam
     - Including assessment of uterine size (fibroids), cervical appearance and length
3. Diagnostic testing
   - 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

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