Recurrent Pregnancy Loss

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CREOG - Educational Objectives

• Describe the most common causes of recurrent 1st- & mid-trimester pregnancy loss
• Elicit a pertinent history in a patient with RPL
• Perform a focused physical exam to identify possible causes of RPL
• Perform and interpret the results of selected diagnostic tests to determine the etiology of RPL
• Treat patients with a history of RPL with surgical or nonsurgical methods depending on etiology
• Counsel patients about the prognosis for successful treatment of RPL
Introduction

• RPL is frustrating and difficult
  – Often no etiology found
  – Few evidence based diagnostic and treatment strategies

• Definitions
  – Spontaneous abortion
    • Involuntary termination of a pregnancy before 20 weeks gestation or below an EFW of 500g
    • Losses after 20 weeks are considered stillbirths or premature births and often have different causes
  – Recurrent Pregnancy Loss
    • ASRM and ACOG defines RPL as 2 or more failed pregnancies
    • Each loss deserves a careful review to decide whether a specific evaluation is appropriate
    • After 3 or more losses, a thorough evaluation is warranted
case

- 28 yo G3P0030 comes into your office after a 3\textsuperscript{rd} spontaneous abortion.
  - When is an evaluation for RPL indicated?
Who should be evaluated?

Etiology of RPL

- Genetic
- Anatomic
- Endocrine
- Thrombotic
- Immune
- Microbes

2 Losses

3 Losses

Just as likely to come up with a diagnosis in patients with 2 consecutive losses when compared with those with 3 consecutive losses.

Also, the risk of abortion after 2 losses (30%) is similar to that with 3 losses (33%).
The Epidemiology of Pregnancy Loss

• 12-15% of *clinically* recognized pregnancies result in miscarriage
• Clinically recognized + unrecognized = 2-4 times higher (age dependant)
• 30-60% of all conceptions abort in the first 12 weeks gestation
• RPL occurs in approximately 1% of reproductive-aged women
Factors that influence recurrence rates

• Cause of pregnancy loss
• Maternal Age
  – <30 → 7-15%
  – 30-34 → 8-21%
  – 35-39 → 17-28%
  – >39 → 34-52%
• Increasing parity
• Previous pregnancy outcomes
• Gestational age at the time of prior pregnancy losses
case

• 28 yo G3P0030 comes into your office after a 3rd spontaneous abortion.
  – How do you counsel this patient?
## Recurrent Pregnancy Loss: Prognosis

<table>
<thead>
<tr>
<th>Number of Prior Miscarriages</th>
<th>% Risk of Miscarriage in Next Pregnancy</th>
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</thead>
<tbody>
<tr>
<td>Women who have had at least one live-born infant</td>
<td></td>
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<tr>
<td>0</td>
<td>12%</td>
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<tr>
<td>1</td>
<td>24%</td>
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<tr>
<td>2</td>
<td>26%</td>
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<tr>
<td>3</td>
<td>32%</td>
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<tr>
<td>4</td>
<td>26%</td>
</tr>
<tr>
<td>6</td>
<td>53%</td>
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<tr>
<td>Women who have not had at least one live-born infant</td>
<td></td>
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<tr>
<td>2 or more</td>
<td>40-45%</td>
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</tbody>
</table>

- A single loss increases risk for recurrent loss
- Miscarriage risk increases with the number of losses, but very gradually, rarely exceeding 40-50%
- Risk higher for women if they have had no prior live-born child

(Speroff 2005)
Etiology of Early RPL

- Genetic Factors
  - Chromosomal, Single Gene, Multifactorial
- Anatomical Factors
  - Congenital or acquired
- Immunologic Factors
  - Autoimmune (SLE, APLS) and alloimmune
- Inherited Thrombophilias
- Endocrine Factors
  - Thyroid disease, diabetes, PCOS, luteal phase deficiency
- Infectious Causes
  - Bacterial, viral, parasitic, zoonotics
- Environmental Factors
- Other Factors
  - Environmental, stress, placental abnormalities, medical illnesses, male factor
- Unexplained RPL
Genetic Factors

• Most spontaneous abortions result from chromosomal abnormalities
  – 50% of all first trimester losses
  – 30% of all second trimester losses
  – 3% of stillbirths
  – Likely an underestimation with a true incidence closer to 75% with newer techniques that identify single gene mutations

• 90% of chromosomal abnormalities in abortuses are numerical
  – Trisomies are most common (Chromosome 13-16, 21, 22)

• The other 10% from a structural abnormality or mosaicism
Parental Chromosomal Abnormalities

• Occurs in up to 5% of couples with RPL
• One partner will have balanced rearrangements on chromosomes
  – Most are balanced translocations
  – Chromosome inversions less common
• Evaluation with parental karyotyping and genetic counseling
• Therapeutic options include artificial donor insemination, IVF with donor oocyte, preimplantation genetic diagnosis and selected transfer or adoption
Recurrent Aneuploidy

(Hassold 1980)
Anatomic Factors

• Uterine abnormalities account for 10-15% of RPL

• Prevalence of congenital uterine anomalies is 2%
  – 3 times that in women with RPL

• RPL related to:
  – Impaired distention of the uterus
  – Abnormal implantation
Anatomic Abnormalities

- **Unicornuate – 10%**
  - Failure of devt of one mullerian duct
  - Poor outcomes (50% fail)
  - Management limited
  - Cerclage efficacy unproven

- **Bicornuate – 26%**
  - Fetal loss rate 40%
  - Strassman abdominal metroplasty
  - Cervical cerclage
  - Data lacking on management

- **Didelphys – 8%**
  - Many women have normal outcomes
  - If no other cause identified, metroplasty may be helpful, but unproven
Septate Uterus

- Incomplete resorption of the medial septum
- Poor blood supply to the septum → poor implantation
- Accounts for 35% of all uterine malformations
  - Most common uterine abnormality in RPL
- Poorest reproductive outcome – 65% miscarriage rate
- Hysteroscopic Septoplasty provides good outcomes
  - 80% term delivery, 5% PTD, 15% pregnancy loss
- Arcuate uterus is a normal variant
  - If septa is <1cm there is no adverse pregnancy outcomes
Bicornuate Uterus
DES Exposure

- DES banned in 1971
- T shaped uterine cavity, hypoplastic uterus, constriction rings, irregular filling defects
- Not amenable to surgical correction
- 2-fold higher risk of spontaneous miscarriage and 9 fold ectopic risk
- Cervical incompetence is associated with DES exposure
DES Exposure - HSG
Leiomyoma

• Especially submucosal
  – Association between RPL and intramural or subserousal fibroids less clear
• Abnormal implantation due to
  – Poor endometrial receptivity of the decidua over the fibroid
  – Degeneration with increasing cytokine production
• Myomectomy indicated if no other reason for RPL identified
Asherman’s

• Intrauterine Adhesions (Synechiae)
  – Not enough support by endometrium for fetoplacental growth
  – Main cause is curettage for pregnancy complications especially in the first 4 weeks PP
    • Trauma to basalis layer, which heals with granulation tissue
    • Opposing surfaces fuse and makes bridges of tissue
    • Filmy adhesions → dense connective tissue adhesions
    • Partial or complete obliteration of the uterine cavity
  – Menstrual irregularities, cyclic pelvic pain, infertility, RPL
• Corrected with hysteroscopic lysis and placement of intracavitary balloon
  – Antibiotics are administered while balloon is in place
  – Estradiol following surgery for about 30 days
  – Sonohystogram then repeated
Asherman’s Syndrome
Cervical Incompetence

• More a cause of second trimester fetal loss
  – Different entity than first trimester miscarriage or third trimester PTL
• Painless dilatation and effacement
• Risk Factors: prior surgery or trauma, cervical or uterine anomalies and DES exposure
Immunologic Factors

• Both autoimmune and alloimmune
  – Autoimmune – immune response directed against self (SLE, APLS)
  – Alloimmune – abnormal maternal immune response to fetal or placental antigens
Autoimmune Disorders - SLE

• Risk of pregnancy loss 20%, but most of those in the second and third trimester
• Early miscarriages are not more common in women with SLE than in the general population
• Active disease at conception, onset during pregnancy and renal disease increase risk of pregnancy loss
Antiphospholipid Syndrome

• 33-75% of pregnancy losses related to APLS occur after 10 weeks gestation
• APLS is the cause of 5-10% of RPL due to:
  – Decreased platelet activity
  – Increased thrombosis
  – Decreased fibrinolysis
  – Uteroplacental thrombosis / vasoconstriction
  – Inhibit fusion of trophoblasts
• Management
  – Prophylactic anticoagulation with heparin throughout pregnancy and 6 weeks PP
  – Benefit of low dose aspirin is unknown
  – Other therapies suggested, but not well studied include corticosteroids and IVIG
Box 2. Clinical Criteria for Diagnosis of Antiphospholipid Syndrome

1. Vascular thrombosis
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ, or

2. Pregnancy morbidity
   a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or features consistent with placental insufficiency, or
   c) Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Box 1. Laboratory Criteria for the Diagnosis of Antiphospholipid Syndrome

1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart. It is interpreted as either present or absent. Testing for lupus anticoagulant is ideally performed before the patient is treated with anticoagulants, or

2. Anticardiolipin antibody of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma, present in medium or high titer (i.e., greater than 40 GPL or MPL, or greater than the 99th percentile), on two or more occasions, at least 12 weeks apart, or

3. Anti-β₂-glycoprotein I of immunoglobulin G (IgG) and/or immunoglobulin M isotype in serum or plasma (in titer greater than 99th percentile for a normal population as defined by the laboratory performing the test), present on two or more occasions, at least 12 weeks apart.

Alloimmune Disorders

• Maternal immune recognition and response to paternally-derived antigens
• Lack of immunological protection to the embryo at the maternal-fetal interface
  – Maternal cytotoxic antibodies
  – Absent maternal blocking antibodies
  – NK cell dysfunctions
• Current methods of evaluation are investigational
• No immunotherapy has proven to be effective
Inherited Thrombophilias

- Pathophysiology similar to that in APLS
- Imbalance in coagulation and fibrinolysis
- Factor V Leiden and prothrombin gene mutation are the most common, but many others
- Association more with second trimester and later losses
- Indications for screening and treatment not yet established with respect to RPL
Inherited Thrombophilias
ACOG PB 124 – Sept 2011

• Who are candidates for evaluation?
  – Personal history of VTE with a nonrecurrent risk factor
  – A first degree relative with a high risk thrombophilia or VTE before age 50 in absence of risk factors
    • High risk → Antithrombin deficiency, double heterozygousity or homozygosity for Prothrombin G20210A mutation and FVL
  – ***Testing in women with RPL or placental abruption is not recommended
Endocrine Factors - Hypothyroid

- Incidence of pregnancy loss very low in treated and controlled hypothyroid
- Markedly increased if elevated TSH
  - Untreated subclinical disease
  - Those with overt disease with inadequate treatment
Endocrine Factors - Diabetes

• If under good control no increased risk of RPL
• Risk of SAB directly proportional to level of hemoglobin A1C and blood glucose levels
• Obtaining hemoglobin A1C and blood glucose level is unwarranted unless there is known or suspected diabetes.
• Women should wait to conceive until A1C levels normalize.
Endocrine Factors - PCOS

- 30-50% increased incidence of miscarriage
- There is a correlation between elevated LH and RPL
  - Once thought to be due to adverse effects of LH or hyperandrogenism in those with PCOS
    - However, using GnRH agonist prior to ovulation did not have an effect of pregnancy outcome
  - Now thought to be more closely caused by hyperinsulinemia and elevated PAI
- Metformin (Category B) is proven for ovulation induction
  - Controversial: conflicting evidence that metformin will decrease miscarriage rate
  - Improves hormone environment and glucose utilization
  - Obesity can increase miscarriage risk especially if BMI >40
Metformin, PCOS and Pregnancy Loss

- Legro, et al. 2007 - PPCOS trial (n=626)
  - Randomized control trial of 3 groups: CC+Placebo, Metformin+Placebo and CC+Metformin
  - Trend toward a greater rate of SAB in metformin only group (40%) vs 25.8% in CC only group and 30% in the CC and metformin group
  - Not statistically significant
- Moll, et al. 2007 (n=228)
  - Randomized trial of two groups: metformin + CC or placebo + CC
  - No difference in pregnancy loss rate (11% vs 12%
- Zain, et al. 2009 (n=115)
  - Randomized trial of 3 groups: Metformin, CC, or both
  - Did not observe a difference in pregnancy loss rate
Endocrine Factors – Luteal Phase Dysfunction

• Corpus luteum is important until 7 weeks gestation

• Not clear how diagnosis of LPD should be made
  – Endometrial Biopsy
    • Incidence of abnormal biopsy similar in fertile and infertile women (33% vs 25%)
  – Measuring serum progesterone levels is unnecessary
    • Variable, pulsatile secretion by CL
  – Luteal phase duration is the most reliable diagnostic approach
    • If short (<13 days) obtain serum prolactin and TSH
Endocrine Factors – Luteal Phase Dysfunction

- Cochrane review supports supplemental progesterone starting in first trimester in patients with RPL
- Data included patients with:
  - 3 or more losses
  - 1st or 2nd trimester losses
  - Route and dose not specified
- Luteal Phase Supplementation
  - Ensure it is taken after ovulation; 3 days after LH surge
  - Unclear how long, but typically 9 weeks
  - 50-100-200 mg pv bid
  - Vaginal gels/suppositories
  - IM progesterone
  - PO suboptimal when compared to IM
Infectious Causes

• No infectious agent has been clearly proved to cause RPL

• Multiple organisms associated with miscarriage, but no data to indicate cause
  – Ureaplasma, Mycoplasma, toxiplasma, Listeria, campylobacor, herpes, CMV, bacterial vaginosis

• Not recommended to do routine serologic testing, cervical cultures for RPL evaluation
Environmental Factors

• Heavy metals: Lead, mercury
• Ionizing radiation
• Anesthetic gas
• Organic Solvents
• Ethanol
• Nicotine
• Caffeine
• Temperature
• Physical/Emotional Stress
Unexplained RPL

• More than half with RPL will have no identified risk factors
• Poorer prognosis if there is a prior second trimester loss
• 70-75% of women with unexplained RPL will achieve a successful pregnancy
case

• 28 yo G3P0030 comes into your office after a 3\textsuperscript{rd} spontaneous abortion.
  – What is your evaluation of RPL in this patient?
# Overview of Evaluation and Treatment

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<thead>
<tr>
<th>Category</th>
<th>Evaluation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Genetic</td>
<td>Karyotype, both parents</td>
<td>Counseling</td>
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<td>Preimplantation genetic diagnosis</td>
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<td>Anatomic</td>
<td>Sonohysterography or HSG</td>
<td>Hysteroscopic septoplasty</td>
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<td>MRI</td>
<td>Hysteroscopic myomectomy</td>
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<td>IVP or renal sono</td>
<td>Hysteroscopic adhesiolysis</td>
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<td>Abdominal metroplasty</td>
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<td>Cervical Cerclage</td>
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<td>Immunologic</td>
<td>Lupus anticoagulant</td>
<td>Aspirin and heparin</td>
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<td></td>
<td>Anticardiolipin antibody</td>
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<td>Anti B2 Glycoprotein</td>
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<td>Thrombophilies</td>
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<td>Prothrombin Gene Mutation</td>
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<td>Activated Protein C Resistance</td>
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<td>Antithrombin III</td>
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<td>Endocrine</td>
<td>TSH</td>
<td>Thyroxine</td>
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<td>Luteal Phase Duration</td>
<td>Clomid</td>
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<td>Blood Glucose, Hgb A1C</td>
<td>Metformin</td>
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<td>Pro lactin</td>
<td>Dopamine agonists</td>
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<td>As indicated by symptoms</td>
<td>Empiric antibiotics</td>
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<tr>
<td>Environmental</td>
<td>History</td>
<td>Behavior modifications</td>
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</tbody>
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Established tests and treatments in bold
References

- *Definitions of infertility and Recurrent Pregnancy Loss*. Practice Committee of ASRM. Fertility and Sterility Vol 90; Suppl 3; Nov 2008
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