Recurrent Pregnancy Loss
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Learning Objectives
> Definitions
> Miscarriage Basics
> Recurrent Pregnancy Loss: Evidence Based
  – Etiologies
  – Workup
  – Treatment
Classic Definition of Recurrent Pregnancy Loss (RPL):

3 or more consecutive pregnancy losses before 24 weeks.

RPL: Psychological Burden

> 1/3 of patients attending a specialist clinic are clinically depressed

> 1/5 have levels of anxiety similar to psychiatric outpatient population

Rai and Regan Lancet 2007
12-15% of clinically recognized pregnancies

50% of all conceptions

Sporadic Miscarriage

Ongoing Pregnancy
Pregnancy Loss

Causes of Miscarriage

Euploid 40%
Aneuploid 60%
Age and Miscarriage

% Pregnancies Miscarried

- 20-24: 9%
- 25-29: 11%
- 30-34: 15%
- 35-39: 25%
- 40-44: 51%
- >45: 75%

Prevalence of RPL

- Sporadic: 25-50% of women will experience
- RPL: 1%
- Expected rate by chance alone: 0.34%
### Characteristics of Patients with Recurrent Miscarriage

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 miscarriages</td>
<td>100% (n=500)</td>
</tr>
<tr>
<td>Conception delays</td>
<td>32%</td>
</tr>
<tr>
<td>Late miscarriage</td>
<td>22%</td>
</tr>
<tr>
<td>Stillbirth or neonatal death</td>
<td>6%</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>5%</td>
</tr>
<tr>
<td>Abortion for fetal aneuploidy</td>
<td>2%</td>
</tr>
<tr>
<td>Previous livebirth</td>
<td>45%</td>
</tr>
<tr>
<td>Pregnancy with prematurity/IUGR</td>
<td>20%</td>
</tr>
</tbody>
</table>

Strobino Am J Public Health 1986

### RPL: Prognosis

- Brigham et al
- Prospective longitudinal study
- 325 patients with ideopathic recurrent miscarriage. Most eval after three losses (24% after 2)
- Exclude: APLS, PCOS, Translocation

Brigham et al Human Reproduction, 1999
RPL: Prognosis (contd.)

Result:

> Overall 70% (226/325) conceived

> Success Rate: 75%
(pregnancy beyond 24 weeks)

Chance of future success in subsequent pregnancy by age and # of SAB’s

Brigham et al Human Reproduction, 1999
Factors associated with recurrent pregnancy loss

RPL and Aneuploidy

> Stephenson et al 2002
> 420 Specimens karyotyped
> 285 Couples with RPL
> Compared to historical controls (Hassold and Chiu)

RPL and Aneuploidy


Age and Rates of Aneuploidy

273 Karyotypes of products of conception analyzed

Age | % Aneuploid
---|---
<35 | 52%
35-40 | 69%
>40 | 72%

Frequency of Specific Chromosomal Trisomies found in miscarriages

Lathi et al F and S2008
RPL and Aneuploidy

Finding
> In patients <36 with RPL, incidence of aneuploid loss is lower than control.

Implication
> Incidence of aneuploidy high – karyotype useful to avoid unnecessary workup
> Younger patients have proportionately more euploid losses – a group to focus on for other causes

Factors associated with Recurrent Pregnancy Loss

- Anatomic 18%
- Translocation 4.4%
- Anti-phospholipid Antibody 19%
- Factor V Leiden 7%
- Endocrine 7%
- Unexplained 45%


Jaslow et al F&S 2009
Causes of Recurrent Miscarriage

Parental Translocation 4%

Balanced reciprocal  Robertsonian

- Exchange of genetic material across two chromosomes
- Fusion of two long arms at the acrosome
- Loss of short arms

May result in:
(1) normal karyotype  (2) balanced karyotype  (3) abnormal and unbalanced
Causes of Recurrent Miscarriage: Translocations

> Typical patient: Hx of miscarriages, livebirths, possibly child with abnormalities
> Diagnosis: karyotype both parents
> Referral to genetic counselor
> Risk of unbalanced offspring depends
  – on sex of the carrier
  – type of rearrangement
  – method of ascertainment -> RPL may have better prognosis

Parental Translocations: Natural History

1893 RPL couples

41 live births (71%)

Amnio on 14: All balanced or diploid

51 structural rearrangement (2.7%)

58 monitored pregnancies

17 Miscarriages (29%)

Stephenson et al Human Reproduction 2006
Parental Translocations: Natural History

> Goddijn et al: 1234 couples
> 41 carrier of translocation
> Following ascertainment of carrier status:
  – 43 pregnancies in 25 couples
  – 30 were live births (70%)
> Amnio in 26: 58% normal karyotype and 42% balanced
> One Dandy Walker malformation (unrelated)
> No other known unbalanced progeny

Goddijn et al Human Reproduction 2004

Parental Translocations: Natural History

> Chance of unbalanced offspring may be lower in patients ascertained by RPL compared with personal history.
> Findings need to be confirmed in larger studies

Goddijn et al Human Reproduction 2004
Preimplantation Genetic Diagnosis (PGD) for Translocation

- Verlinsky et al
- Multicenter, retrospective
- 469 cycles for translocation
- Take home baby rate:
  - 23%/cycle
  - 34%/transfer
- Conclusions for PGD:
  - May decrease miscarriage/abnormality rate
  - May not increase live birthrate

Verlinsky et al, Fert & Stert 2004

Translocation: Summary

- Small but important cause of RPL
- Referral to genetic counselor
- In RPL patients: live birth rate appears relatively good, with low chance of unbalanced/abnormal offspring
- PGD can be used to lower risk of miscarriage or unbalanced offspring
Anatomic Factors associated with Recurrent Pregnancy Loss

Anatomic 18%

Uterine Malformation
- Septum
- Bicornuate
- Fibroids
- Adhesions

RPL & Anatomic Factors: Diagnosis

- HSG
- Saline Sonogram
- Hysteroscopy
RPL & Anatomic Factors: Diagnosis

> 509 women with RPL
> 1976 low risk controls
> Uterine malformation (including arcuate) ascertained by 3D ultrasound
> Results: diagnosis of uterine anomaly:

<table>
<thead>
<tr>
<th>Uterine Anomaly Found</th>
<th>Control</th>
<th>RPL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Distribution of anomalies

- Arcuate
- Septate
- Bicornuate
- Unicornuate

Salim et al Human Reproduction 2003
RPL & Anatomic Factors

Treatment

Septum

Unicornuate/Bicornuate

Hysteroscopic Metroplasty

No treatment indicated

No prospective trials
Summary of retrospective series: LBR of 85%

Grimbizis Human Reprod.Up 2001

RPL & Anatomic Factors: Diagnosis

> Fibroids, Polyps, Adhesions
  – Strongest link between:
    • Submucosal fibroids
    • Polyps > 1

Treatment:
> No strong randomized data exists
> Hysteroscopic removal of submucosal polyps, fibroids, adhesions indicated in patients with recurrent pregnancy loss
Causes of Recurrent Miscarriage

Auto-antibodies
> Thrombotic abnormalities
> Pregnancy complications

Anti-phospholipid Antibody Syndrome (APS) 15%

Clinical:
> One or more confirmed episodes of vascular thrombosis of any type:
  - Venous
  - Arterial
  - Small vessel

Myakis et al Journal of Thrombosis and Haemostasis, 2006
International Consensus Criteria 2006 (contd.):

Pregnancy complications:
> Three or more spontaneous pregnancy losses at less than 10 weeks EGA, other causes excluded (genetic, hormonal, anatomic)
> 1 or more pregnancy losses at greater than or equal to 10 weeks EGA
> One or more premature deliveries at less than 34 weeks EGA secondary to severe pre-eclampsia or placental insufficiency

Myakis et al Journal of Thrombosis and Haemostasis, 2006

The Antiphospholipid Syndrome

Laboratory:
> Lupus anticoagulant
> Anticardiolipin antibodies
  – IgG or IgM isotype
  – Medium to high levels
> Anti-b2 glycoprotein I antibody
  – IgG or IgM
  – >99% percentile titer

**Antibody testing must be positive twice, 12 weeks apart**
Antiphospholipid Syndrome

Pathogenesis:
- Thrombosis of maternal vessels
- Inflammation/inhibition of trophoblast invasion
- Heparin and ASA may function as anti-coagulant as well as anti-inflammatory agents

Antiphospholipid Syndrome: Treatment

Live birth rates in patients treated for APS

Rai et al 1995, 1997; Stephenson 2007
Factors associated with Recurrent Pregnancy Loss

Endocrine 7%

Jaslow et al F&S 2009

RPL: Endocrine

> Thyroid
> Uncontrolled Diabetes – Check Glucose

Other endocrine?
PCOS
Day 3 FSH/Anti-mullerian Hormone
Factors associated with Recurrent Pregnancy Loss

Factor V Leiden 7%

Jaslow et al F&S 2009

Factor V Leiden

The Evidence
- Multiple small retrospective studies
- 2 small prospective
- 3 meta-analyses
Inherited Thrombophilia

> Inquiry into connection between thrombophilia and RPL based on:
  – Antiphospholipid syndrome
  – Connection between late pregnancy complications and inherited thrombophilias

Clotting versus inflammation?

Factor V Leiden

- Factor V Gene
- Factor V
- Prothrombin
- Thrombin
- APC

- 2-5% Caucasians
- 3-8x increased risk of thrombotic event
**Rey et al The Lancet 2003**

### FVL and RPL <13 weeks:
- **OR 2.01 (CI: 1.13, 3.58)**

### FVL and RPL >19 weeks:
- **OR 3.26 (CI: 1.82, 5.83)**

**Rai et al Human Reproduction 2002**

**Factor V Leiden:**

- Analysis of patients with recurrent early loss (>3; <12 w)
- Factor V Leiden heterozygote: n=16, median age 32
- Controls; n=153; median age 33

**Live Birth Rate (LBR):**
- FVL carrier: 37.5%
- Non-carrier: 69.3%
- **OR 3.7**
  - (95% CI: 1.3-10.9)
**Factor V Leiden: Meta-analysis**

> Rey et al
> Seven studies evaluating FVL loss before 13 weeks
> Excluded studies with poor methodology

Rey et al Lancet 2003

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**Prothrombin G20210A:Meta-analysis**

> Rey et al
> 4 studies of recurrent loss before 13 weeks
> OR 2.32 (1.12,4.79)

Rey et al Lancet 2003
MTHFR Gene Mutation

Methylene tetrahydrofolate reductase (MTHFR)

- C677T mutation
- A1298C mutation

Low dietary Folate, B6 and B12 → May lead to Elevated Homocysteine

Treatment: Anticoagulation

No Randomized Controlled Trials

- Younis 2002
- Brenner 2000 → No control group
- Carp 2003
- Folkineringa 2006
- Gris 2004 → Controlled, but not randomized

Late Losses
**Treatment with Anticoagulation**

> Randomized control trial
> Patients with at least one loss >10 weeks
> FVL, PTgene, Protein S (+)
> Patients received either lovanox (n=80) or baby aspirin (n=80)

![Live birth rate graph](Gris et al Blood 2004)

- **Gris et al Blood 2004**

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**Treatment with Anticoagulation**

- 37 female carriers of Protein C, Protein S or Antithrombin III derived from cohort study
  - Offered prophylaxis for pregnancies
  - 26 opted for prophylaxis (med age 28)
  - 11 declined (med age 23)

<table>
<thead>
<tr>
<th>Prophylaxis:</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>Fetal Loss</td>
<td>2%(1)</td>
<td>58% (11)</td>
</tr>
</tbody>
</table>

![Miscarriage Rate graph](Folkeringa et al 2006)

- **Folkeringa et al 2006**
Treatment with Anticoagulation

Women with inherited thrombophilia and RPL
N=85

Treated
n=37
Mean age: 30.0

Not treated
n=40
Mean age: 31.7

Live Birth Rate

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Not treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>.02</td>
<td></td>
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Note: 56% of treated and 35% had MTHFR mutation

Carp et al J Thrombo Haemost 2003

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Thrombophilias: Summary

> FVL, PT gene and hyperhomocysteinemia may have a small association with RPL

> Folic Acid and Vitamin B supplementation

> No current role for checking MTHFR
Inherited Thrombophilia: Treatment Strategies

- No randomized controlled trials with anticoagulants
- Multiple small series suggesting benefit, but small in size and lacking controls
- Consideration of treatment should be done in a research setting with discussion of risks and benefits
- Results may be confounded by possibility that heparin prevents pregnancy loss through alternative (non-anticoagulant) methods

Factors associated with Recurrent Pregnancy Loss

- Anatomic 18%
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Mainly Genetic

Jaslow et al F&S 2009
Management of Unexplained Recurrent Pregnancy Loss

- Counseling
- Attempt at Karyotype
- Encouragement to try again
- Pre-implantation Genetic Diagnosis
- Egg Donation

Unexplained RPL

Patient presenting with second or third pregnancy loss

Karyotype if possible

- Aneuploidy
  - Try again
  - ? PGS
  - Eg donation

- Euploid
  - RPL Workup
Cost Effectiveness of Karyotyping Products of Conception

Figure 2: Cost Difference Between Karyotype of POC vs. RPL Workups

- APS, Saline sono, TSH, Glucose, FVL, Parental Karyotypes
- Evidenced Based Workup + Thrombophilia

- $0
- $200
- $400
- $600
- $800
- $1,000
- $1,200
- $1,400
- $1,600
- $1,800

- < 35 years
- 35-40 years
- >40 years
Summary

> RPL causes patients significant distress

> A basic workup can be initiated, but patient should be advised of strong chance of negative findings.

> Most can be reassured of a good prognosis if they continue to try

Evidence Based Treatment

> Karyotype POC’s -> Counseling

> Parental Karyotype -> Genetic counseling, PGD?

> Anatomic -> Hysteroscopic correction

> ACA, LAC, anti-beta2 glycopro - > Low dose ASA and heparin

> TSH, PRL, Glucose -> Correction

>
Summary

If initial workup is negative, consider:

> Inherited thrombophilia
  – FVL mutation
  – Fasting homocysteine
  – PT gene mutation
  – Protein C and Protein S

Thank you