Recurrent Pregnancy Loss
2018
William G Dodds MD

RPL Definition
Classic: >3 Consecutive
ASRM: >2 Consecutive
RC OB/GYN: <3 Consecutive
**Miscarriage Frequency**

- 1.3% had ≥3 consecutive losses

60,000 pregnancies Parkland Hospital 1999

**Theoretic AB Rate**

- 2 consecutive losses – 2%
- 3 consecutive losses – 0.15% 6/2000
- 4 consecutive losses – 0.05% 1/2000

**AB and Age**

<table>
<thead>
<tr>
<th>AGE</th>
<th>AB Rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>10-15</td>
</tr>
<tr>
<td>30-34</td>
<td>15-20</td>
</tr>
<tr>
<td>35-39</td>
<td>25-30</td>
</tr>
<tr>
<td>40-44</td>
<td>50-55</td>
</tr>
</tbody>
</table>
RPL and Maternal Age

<table>
<thead>
<tr>
<th>Age</th>
<th>RPL Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1/85</td>
</tr>
<tr>
<td>30</td>
<td>1/45</td>
</tr>
<tr>
<td>40</td>
<td>1/4</td>
</tr>
</tbody>
</table>

Aneuploidy in ART embryos

<table>
<thead>
<tr>
<th>Aneuploidy risk (%)</th>
<th>Maternal age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>&lt;35</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>100</td>
<td>45</td>
</tr>
</tbody>
</table>

Random chance vs actual RPL

<table>
<thead>
<tr>
<th>3 consec. AB</th>
<th>Random</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.34% (1)</td>
<td>1.3% (2)</td>
</tr>
</tbody>
</table>

1) Women age 30-34
2) Kutteh WH, Pasquautte NM 1995
What is pregnancy loss?

- Confusing with different definitions between ACOG, ASRM, and RC OB/GYN
- Most accepted: Any loss <20 weeks with initial rising hCG level.

RPL Evaluation

- Karyotype (both)
- Uterine cavity evaluation (SIS, HSG, HS)
- Immune anti B2 glycoprotein, LA, ACA
- TSH, TPO, mid-luteal progesterone, HgA1C
- PCO evaluation
- Thrombophilia evaluation only with personal or family thrombosis history

Positive test results for RPL

<table>
<thead>
<tr>
<th>2 losses</th>
<th>3 losses</th>
<th>&gt;4 losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=447</td>
<td>N=343</td>
<td>N=230</td>
</tr>
<tr>
<td>41%</td>
<td>40%</td>
<td>42%</td>
</tr>
</tbody>
</table>

per evidence based tests
Etiologies of evidence-based tests when evaluating recurrent pregnancy loss

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control Frequency (%)</th>
<th>Abnormal test result (%)</th>
<th>P value (2 vs. 3 vs. &gt;3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental genetics</td>
<td>2.8%</td>
<td>3.4%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Uterine anatomy</td>
<td>18.7%</td>
<td>18.2%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Lupus anticoagulant antibodies</td>
<td>5.0%</td>
<td>2.9%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>15.6%</td>
<td>13.1%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>8.1%</td>
<td>6.5%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>4.2%</td>
<td>8.1%</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

The most common genetic abnormality in RPL:

- Balanced translocation 85%
  - Reciprocal translocation 59%
  - Robertsonian translocations 27%
- Inversions 9%
  - Sex chromosome aneuploidies 4%
  - Supernumerary chromosomes 1%

RPL and POC Genetics

Cytogenetic abnormalities in POC are lower in RPL patients compared to woman (<35 years old) with sporadic loss:

- Sporadic loss women 50% aneuploidy
- RPL women 35% aneuploidy
Chromosome Abnormalities in AB

- Most common in POC: 16, 22, 21, 15.
- Most common in PGS is an essentially equal distribution of all 23 chromosomes
- Most “biochemical losses” are aneuploidies

Anatomic Causes of RPL

- Congenital 6.2%    Acquired 13.3%
  Most common congenital – septate uterus 4.8%
  Most common acquired – fibroids 6.2%

Immune Factors RPL

- Autoimmune (against self)
- Alloimmune (against another)
Unproven RPL Immune Theories

- HLA similarity
- Natural killer cells
- Embryo toxic factors

Unwarranted Immune Tests

- Natural killer cell assays
- T-helper cell 1 and 2 cytokine ratios
- Embryo toxic factor testing

Approved Autoimmune RPL Testing

- ACA
- LA
- B2 glycoprotein antibodies
- Antiphosphatidyl serine (possible)
**Antiphospholipid Antibody**

- Inhibits hCG release
- Inhibits trophoblast migration, invasion, and trophoblast cell adhesion molecules
- Activates complement on trophoblast surface causing inflammation
- Heparin known to reverse these actions

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**Unexplained RPL**

- 50% of all AB can be explained with complete chromosomal tissue evaluation
- 60-70% RPL patients should have an identifiable cause
- Lifestyle issues – tobacco, alcohol, marijuana, maternal obesity.

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**What is the chance of successful pregnancy in unexplained RPL patients?**

- 3 miscarriages: 75% success in 2 years if <30 years of age
  40% success in 2 years if ≥40 years of age
- ≥6 miscarriages: 45% success in 2 years including all ages
Aneuploid Karyotype Translocation or inversion

- No evaluation unless a third loss
- RPL evaluation
- Get karyotypes on parents and offer PGD

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