Fertility Associates – Leaders in Fertility
Recurrent Pregnancy Loss

Current diagnosis and management

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Classical definition: Recurrent Miscarriage

- **3 or more consecutive losses of clinically recognised pregnancies prior to 20 weeks gestation**
  - (ectopic and molar pregnancies are not included)
  - RPL typically occurs at similar gestational age subsequently
  - Recurrence risk increases as gestational age at loss increases
Alternative definition: Recurrent Early Miscarriage

• 3+ consecutive pregnancy losses <10 weeks
  – Includes biochemical pregnancies
  – Includes PUL (pregnancy of unknown location)
  – Includes ectopic pregnancy

  – Retrospective cohort study suggesting these pregnancy losses had the same negative impact on future live birth RR=0.9 (Kolte et al, 2014)
Recurrent Pregnancy Loss

• 2 consecutive pregnancy losses (including biochemical)
  – Often used in setting of:
    • Subfertility
    • Advanced age
    • IVF pregnancies
  – If used in general population, >30% may experience due to chance alone

– Why?
  • If pregnancy is hard to come by, best make sure you are not missing anything!
Prevalence

• 15% experience sporadic loss of clinically recognised pregnancy

• 2% experience 2 consecutive losses

• 0.4-1% experience 3 consecutive losses
  – 3 is Higher than expected by chance alone
    • 0.15x0.15x0.15 = 0.3%
  – 2 is as expected by chance
    • 0.15x0.15 = 2.25%
Other numbers

• 15% = miscarriage rate at 6-10 weeks

• Miscarriage at <6 weeks = 22-57%

• Miscarriage after 10 weeks = 2-3%

• Miscarriage rate increases with maternal age
  - <=29 = 11%
  - 30-34 = 15%
  - 35-39 = 25%
  - 40-44 = 51%
  - >= 45 = 93%
RPL Rates occurring by chance (%)

<table>
<thead>
<tr>
<th>Age</th>
<th>1 Miscarriage</th>
<th>2 Miscarriages</th>
<th>3 Miscarriages</th>
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<tbody>
<tr>
<td>20-24</td>
<td>11</td>
<td>1.21</td>
<td>0.13</td>
</tr>
<tr>
<td>25-29</td>
<td>12</td>
<td>1.44</td>
<td>0.17</td>
</tr>
<tr>
<td>30-34</td>
<td>15</td>
<td>2.25</td>
<td>0.34</td>
</tr>
<tr>
<td>35-39</td>
<td>25</td>
<td>6.25</td>
<td>1.56</td>
</tr>
</tbody>
</table>

- If RPL = 3%
  - For 30-34yr, $2.25/3 = 75\%$ are due to chance
- If RM = 1%
  - For 30-34yr, $0.34/1 = 34\%$ are due to chance
Why still so much uncertainty?

• Disagreement concerning diagnostic criteria

• Numerous methodological pitfalls that threaten validity of research into RPL
  – Some general
    • e.g. historical controls
  – Some specific to RPL
    • e.g. changes to immune system due to previous term pregnancy, change in biomarkers with menstrual cycle

• Few RCTs
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Causes – 50% will be unexplained

- Chance
- Uterine (anatomic)
- Immunologic
- Genetic (egg, sperm, embryo)
- Endocrine
- Thrombophilic
- Environmental
- Other
Uterine Factors

- Congenital Anomalies
- Leiomyomas (fibroids)
- Endometrial polyps
- Intrauterine adhesions
- Cervical insufficiency
- Defective endometrial receptivity
Uterine anomalies

• Congenital anomalies
  – 10-15% of RPL vs 7% all women
  – Septate uterus = poorest outcome (80% miscarriage)
    • Surgical correction → 80% live birth rate
      – BUT: Associated with cervical insufficiency and preterm delivery
  – Typically associated with second trimester loss
• Fibroids
  – Those that distort cavity associated with RPL and infertility
  – Evidence that myomectomy improves outcomes is less clear

• Polyps
  – No data on RPL, but are associated with infertility
• Intrauterine adhesions
  – Insufficient endometrium for normal fetoplacental growth

• Cervical insufficiency
  – Causes recurrent mid-trimester loss
  – NOT associated with recurrent early pregnancy loss

• Defective endometrial receptivity
  – Currently just a theory
Immunologic factors

- **Antiphospholipid Syndrome**
  - 5-15% of patients with RPL
  - Antibodies have several detrimental effects on the developing trophoblast (not thrombosis)

- **Other immunologic factors**
  - Normal complex immunologic mechanism at the feto-maternal interface becomes dysregulated
    - A likely cause
    - No evidence
Endocrine Factors

- **Diabetes**
  - Poorly controlled diabetes associated with pregnancy loss
  - No increased risk if well controlled

- **Polycystic Ovarian Syndrome**
  - Overall, increased risk of pregnancy loss
  - More recent studies suggest associated with obesity and insulin resistance rather than PCOS per se.
    - Not associated with LH or androgens as previously thought
• Obesity
  – BMI >30 →
    » increases chance of miscarriage by 20%
    » triples risk of RPL development
    » increases risk of euploid miscarriage
  – Insulin resistance is an independent risk factor for miscarriage (through elevated levels of PAI-1)
• Thyroid Antibodies
  – Anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-Tg)
  – Associated with doubling of miscarriage rate

• Subclinical hypothyroidism
  – Normal T4 with TSH >2.5
  – Significant increase in thyroid hormone demand in pregnancy
    • E2 mediated increase in TBG, increased peripheral metabolism of T4, placental de-iodination of T4, increased renal iodide clearance
• Hyperprolactinaemia
  – Normal prolactin may be important in maintaining early pregnancy
  – May reflect luteal phase insufficiency
  – Small RCT found bromocriptine improved outcome
• Luteal phase defect
  – Controversial – difficult to diagnose
  – May reflect underlying
    • Hyperprolactinaemia
    • PCOS
    • Abnormal thyroid function
    • Hypogonadotrophic hypogonadism
      – Stress, exercise, extreme weight loss
    • Poor ovarian reserve
Genetics

- Chromosomal rearrangements
  - 3-5% of couples with RPL
    - c.f. 0.7% general population
  - Mostly balanced translocations
    - 60% reciprocal
    - 40% Robertsonian
    - More common in females
    - Those of maternal origin more likely to cause RPL

- More likely if:
  - Young maternal age at second miscarriage
  - Family history of RPL
Inherited Thrombophilia

• Very controversial

• Most (but not all) prospective studies show NO association with early or Late fetal loss

• Case-control and cohort studies have generally reported an association, particularly with late fetal loss
• Meta-analysis of case-control, cohort and cross-sectional studies (Rey et al, 2003)

<table>
<thead>
<tr>
<th></th>
<th>OR (Early Loss)</th>
<th>OR (Late Loss)</th>
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<tbody>
<tr>
<td>FVL</td>
<td>2.01</td>
<td>7.83</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>2.56</td>
<td>2.30</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>~</td>
<td>7.39</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>~</td>
<td>~</td>
</tr>
<tr>
<td>ATIII deficiency</td>
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• Several similar studies since this have failed to show association with RPL
• European prospective cohort on thrombophilia
  – Fetal loss of 29.4% vs 23.5%
    • OR Only significant for stillbirth = 3.6

• Roque et al 2004, cohort study
  – Presence of thrombophilia **protective** against recurrent early pregnancy loss (OR = 0.55)
  – Thrombophilia associated with increase loss >10/40 (OR = 1.76)
Screening for inherited thrombophilia in women with recurrent early (<10 week) pregnancy loss is NOT recommended

- Lack of evidence of causation
- Lack of evidence that anticoagulants improve outcomes
• Screening women with recurrent or non-recurrent pregnancy loss after 10 weeks associated with histological evidence of placental ischaemia and infarction and maternal vessel thrombosis is still CONTROVERSIAL
  – Recurrence risk is low
  – No high quality data that anticoagulation improves outcome
• Screening for high homocysteine levels or the presence of MTHFR variant is NOT recommended in ANY setting
  – Benefit from reducing homocysteine levels is unproven
  – All pregnant women should be taking folate supplementation anyway
Environmental

- No high quality data

- Chemicals associated with spontaneous loss include
  - Arsenic, aniline dyes, benzene, ethylene oxide, formaldehyde, pesticides, lead, mercury, cadmium

- Association with obesity, smoking, alcohol, caffeine unclear
  - May act synergistically and/or in dose dependent manner
Other causes

• Male Factor
  – Advanced paternal age
  – Sperm DNA fragmentation
  – Semen abnormalities (esp abnormal morphology)
  – Varicocele

• Decreased ovarian reserve
  – Associated with poorer quality oocytes
• Coeliac disease
  – Untreated disease associated with RPL and infertility
  – Rare presentation of the condition

• Wilson’s disease
  – Untreated disease fatal and associated with RPL
  – Rare, autosomal recessive
    • 1 in 10000-50000 general population
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Evaluation

• History
  – Characteristics of previous losses and other pregnancies
    • Gestational Age
      – Chromosomal and endocrine tend to occur earlier
      – Anatomic and immunologic tend to occur later
    • Anembryonic versus live embryo
      – Loss prior to FH suggests chromosomal
    • Pregnancy complications
  – Uterine instrumentation
  – Menstrual cycle abnormalities / galactorrhoea
– Environmental exposures
– Lifestyle
– Venous or arterial thromboembolism

– Family history
  • RPL
  • VTE

– Consanguinity
- Physical examination
  - General examination
    - BMI
    - Signs of endocrinopathy (hirsutism, galactorrhoea)
  - Pelvic examination
    - Cervical abnormalities
    - Obvious pelvic mass/fibroids

- Mental Health evaluation
  - Screen for depression
    - 8.6% of women vs 2%
Investigations

• Karyotype Parents
  – To detect balanced reciprocal or Robertsonian translocations or mosaicism
  – Prevalence 2.9% (5 times higher than general popn) Thrapel 1985
    • 50% reciprocal
    • 25% Robertsonian
    • 10% sex chromosome mosaicism in females
    • 15% inversions etc
• Karyotype Products of Conception
  – Normal = suggests maternal environmental factor
  – Abnormal = usually explains nonviable pregnancy

  – Karyotypes may be normal, but array CGH may demonstrate major abnormalities
  – Cells from chromosomally abnormal abortuses are less likely to grow in culture (esp Trisomy 7 and triploidies)
• Uterine assessment
  – Sonohysterography
    • Delineates internal contours of cavity and provides concomitant sonographic visualisation of the outer surface
    • Often difficult to access in NZ
  – Hysterosalpingography (HSG)
    • Delineates internal contours and tubal patency
    • Does not evaluate outer contour
      – Can’t distinguish septate from bicornuate
- **Hysteroscopy**
  - Gold standard for intrauterine pathology
  - Cannot distinguish some septate from bicornuate
  - Can be performed as office procedure

- **Ultrasound**
  - Can miss small septae and other intrauterine pathology
  - 3D very accurate for uterine anomalies

- **MRI**
  - Useful for clarifying uterine anomalies
  - Often easier to access than 3D USS
• Exclude Antiphospholipid syndrome  
  – Clinical criteria  
    • Vascular thrombosis  
    • Pregnancy morbidity  
      – 1+ unexplained loss >10/40  
      – 1+ delivery <34/40 related to preeclampsia or placental insufficiency  
      – 3+ unexplained loss <10 weeks  
  – Laboratory criteria  (Positive on two occasions, 12 weeks apart)  
    • Lupus anticoagulant  
    • Anticardiolipin antibodies IgG or IgM  
    • Anti-B2 glycoprotein-1
• Thyroid function and antibodies
  – TSH, T4
  – Anti-TPO
  – Anti-Tg

• Ovarian reserve
  – AMH is best test
    • <5pmol/L suggests significant compromise
• Inherited Thrombophilia
  – Controversial
  – Unlikely to be associated with loss <10 weeks
  – Some heritable thrombophilias are common in community, with most having normal pregnancy outcomes
    • FVL hetero 1-15%
    • Prothrombin hetero 2-5%

  – Recommended if personal history of VTE or family history of heritable thrombophilia
  – Consider if >10 weeks and histological evidence of infarction etc
• Screening for diabetes
  – HbA1c

• Screening for Wilson’s disease
  – Hx or family hx neurologic, psychiatric, liver disorders
    • Serum copper and ceruloplasmin (low)
    • Urine copper (high)

• Screen for sperm DNA fragmentation
  – SCSA (Sperm chromatin structure assay)

• Examine male for varicocele
Summary of Investigations

– Bloods
  • Karyotype Parents and POC
  • aCL, Lupus Anticoagulant, Anti-B2 glycoprotein-1
  • TSH, T4, Thyroid antibodies
  • HbA1c
  • AMH
  • Coeliac screen and ?Wilson’s Disease screen
  • Thrombophilia screen in very selected patients

– Radiology
  • TVS
  • HSG (unless 3D USS or sonohysterogram available)

– Other
  • SCSA
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Why don’t people stick to guidelines?

• Current guidelines based on few, small and often poor-quality studies that cannot support strong, evidence based guidelines

• Pressure from desperate patients to do something
  – Although few proven therapies exist

• Doctor’s economical motives
  – I’m hopeful that in NZ this is rare
Management

• High quality data is limited

• Most couples have a good prognosis
  – If investigations normal – 77% live birth
  – If investigations abnormal – 71% live birth

• Emotional support is a priority
  – May enhance success
• Parental karyotype abnormality
  – Refer genetic counseling
    • Probability of having normal vs abnormal conception
      – Risk of miscarriage vs normal carrier vs abnormal child
    • Depends on specific chromosome rearrangement
  – Options:
    • Natural conception +/- CVS/Amniocentesis
    • IVF with Preimplantation genetic diagnosis (PGD)
      – D3 biopsy and FISH
        » Scriven et al: 83% biopsy, 26% no et, 20% LBR
      – Blastocyst biopsy and 24 chromosome screening
        » Very little data
    • Gamete donation
• Uterine anomalies
  – Surgical correction of:
    • Uterine septum
    • Adhesions
    • Submucous fibroids
  – Original data is problematic as most use self controls
  – Newer studies also support
  – NB: These women need cervical length monitoring when pregnant as increase risk of cervical incompetence
• Antiphospholipid syndrome
  – Aspirin + Heparin from positive pregnancy test
    • NB: LMWH has not been established as effective alternative

• Thyroid Autoimmunity
  – Treatment with thyroxine in antibody positive women → reduction in miscarriage RR0.48 (Meta-analysis of 2 RCT - Thangaratinam 2011)

• Subclinical hypothyroidism
  – Treat all women with TSH>2.5 with thyroxine
• Hyperprolactinaemia
  – Bromocryptine

• PCOS
  – Weight loss to normalise BMI
  – Cardiovascular exercise
  – Consider metformin

  • Observational studies suggest benefit (continued throughout 1st trimester) (Glueck 2001, Jakubowicz 2002)
  • RCT did not show benefit (stopped when pregnancy diagnosed) (Legro 2007)
• Inherited thrombophilias
  – Why did you test it????????
  – **Not** associated with recurrent first trimester loss
  – May increase risk for late losses, IUGR, abruption or preeclampsia
  – Probably no harm in aspirin
  – Discuss with obstetricians or obstetric physicians regarding heparin (need to be very up to date with literature) due to risk:benefit
• Abnormal SCSA
  – Antioxidant + Frequent ejaculation
  – Remove suspected contributing factors
    • SSRIs
    • Obesity
    • Smoking
  – IVF with ICSI/IMSI
• Coeliac
  – Exclude gluten from diet

• Wilson’s
  – Zinc sulphate or other chelating agent
• **Unexplained** (50% of patients)
  – Lifestyle modification
    • Optimising BMI
    • Eliminating smoking
    • Reducing alcohol
    • Reducing caffeine

– **TLC** (Tender loving care)
  • Psychological supportive care in a dedicated clinic
    – Counselling, regular blood tests and USS

» (Liddell 1991)
– Progesterone
  • Meta-analysis of RCT = OR 0.4-0.5
    – Small numbers, wide confidence intervals
  • Therapeutic effect may relate to immune modulation
  • Utrogestan 200mg PV tds until 12/40

– Controlled ovarian hyperstimulation with FSH
  • Observational study suggests benefit
  • May correct luteal phase defect or prepare better implantation site due thicker endometrium
  • Typical cost = $2000-3000 per cycle
- IVF with PGS
  - Studies reveal conflicting results
    - Problems with D3 vs D5 biopsy, FISH etc
  - D5 biopsy with 24 chromosome screening (array CGH or SNP array) is probably beneficial but not cost effective

- Oocyte donation
  - Associated with 88% LBR in women with RPL

- Gestational surrogacy
  - Only after extensive investigation
– Combined therapy
  • Prednisone (20mg) + Aspirin + Progesterone + Folic Acid
  • Observational study suggested benefit (Tempfer 2006)
  • Concern regarding long term prednisone use
    – PPROM, GDM, hypertension
What does **NOT** work for unexplained RPL

- Aspirin +/- heparin
- LMWH
- Immunotherapy
- Glucocorticoids
Summary of Treatment

• Unexplained
  – Lifestyle modification
  – Folic Acid (normal dose of 800mcg)
  – Antioxidant for male partner
  – Empirical progesterone to 12-14 weeks
  – Psychological/emotional support
  – TLC
  – High quality antenatal care

• Explained
  – Directed therapy as previous
Euploid POC After ≥2 Pregnancy Losses
OR
At Least 2 Consecutive Miscarriages With No POC Diagnosis
OR
At Least 3 Nonconsecutive Miscarriages With No POC Diagnosis

Anatomic Evaluation (Ex: HSG, SHG)

Endocrinologic Evaluation (Ex: TSH, Prolactin, Hyperglycemia)

Add Progesterone Support to Future Pregnancies Until 10 Weeks Gestation

Autoimmune Factors: aPL, LAC, β2GP 1

Evaluation of Lifestyle/Environment (Ex: Caffeine, Tobacco, Alcohol, Environmental Exposures, Obesity)

Genetics: Karyotype of Parents if no POC karyotype Obtained

Targeted Surgical Correction

Targeted Medical or Surgical Correction

Start ASA, SQ heparin, Calcium, & Vitamin D preconceptionally and continue until delivery (Follow CBC)

Appropriate Alterations to Lifestyle, Nutrition, or Environment

Preimplantation Genetic Testing if Appropriate and Desired: PGS/PGD

Not included in this decision tree are more controversial types of testing and therapies such as those dealing with microbiologic factors, thrombophilic factors, immunotherapy, and other evaluations though these may be appropriate in certain clinical situations.

Fig. 2. Workup for early RPL. An algorithm for the full workup of early RPL. Arrows are provided that guide the reader through various outcomes possible during the RPL evaluation and appropriate next steps in diagnostic and therapeutic management. (From Brezina PR, Kutteh WH. Recurrent early pregnancy loss. In: Falcone T, Hurd W, editors. Clinical reproductive medicine and surgery: a practical guide. 2nd edition. New York: Springer; 2013; with permission.)
Remember

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