Recurrent Foetal Loss

Tears stream down your face, when you lose something you cannot replace.

- Coldplay

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The stories that end badly are sad, sadder still are the ones that never began....
OUTLINE....

- What we know: KNOWN KNOWN
- What we now know we do not know: KNOWN UNKNOWN
- What we know but do not do: UNKNOWN KNOWN
- What we do not know that we don't know: UNKNOWN UNKNOWN

UNKNOWN UNKNOWN
Ohh No!
The Known Known

Recurrent foetal loss...
INTRODUCTION

- The loss of pregnancy at any stage can be a devastating experience and particular sensitivity is required in assessing and counseling couples with recurrent pregnancy loss.
- Emotionally traumatic, similar to stillbirth or neonatal death.
DEFINITION

- \( \geq 3 \) consecutive losses of clinically recognized pregnancies < 20 week gestation
  - Ectopic, molar, and biochemical pregnancies not included.

- Clinical investigation should be started after two consecutive spontaneous foetal loss, especially
  - when fetal heart activity had been identified prior to the pregnancy loss
  - when the women is older than 35 yrs of age
  - when the couple has had difficulty conceiving
RPL - SUB TYPES

- All pregnancy losses, no viable pregnancy
- Viable pregnancy followed by pregnancy losses
- Pregnancy losses interspersed with viable pregnancies
RPL-TYPES

- Primary recurrent pregnancy loss" refers to couples that have never had a live birth,

- While “Secondary RPL" refers to those who have had repetitive losses following a successful pregnancy
INCIDENCE

- 50% of all conceptions fail (most unrecognized)
- 13-15% of recognized pregnancies are lost, 90% of these before 12-14 weeks
- 10-20% of pregnant women have one sporadic spontaneous abortion
- 2% have 2 consecutive Spontaneous Abortion
- 0.4-1% have 3 consecutive Spontaneous Abortion
Recurrence suggests a persistent cause (not just a bad luck) which must be identified and treated
Causes - Biggest DILEMMAS

- Uterine Causes
  - Anatomical Causes

- Infectious Causes?
  - TB, vaginosis, Viral

- Genetic Causes

- Auto Immunologic Causes
  - APLA syndrome

- Thrombophilia

- Endocrine causes?
  - Environmental Causes
    - Oxidative stress
    - Psychological
    - Unknown aetiology

- Allo-munity
RPL - When To Start Investigating?

- Ideally after 3 losses but earlier if high risk pt, elderly, with medical disorders and known family history.

- How to Investigate?

- Investigate commoner and treatable causes first

- Do not order a blind screen
RPL _1st STEP_

- Detailed history – Clarify and Document RPL
  - Recurrent Spont. Abortions
  - Chemical Pregnancy Loss
  - Early Pregnancy Loss ..... Before 8wk.s & After 8 wk.s
  - 2nd Trimester Abortions
  - Still Births
- **Past Obstetric History**
  - Full term birth, premature birth
  - Malformed fetus
- Term of pregnancy at the time of abortion
- Location of fetal heart / anembryonic pregnancies
Environmental factors can be diagnosed by history only:

- Smoking
- Anesthetic gases
- Toxins, chemicals

High risk factors – Life Style:

- Obesity
- Daily caffeine intake > 300 mg
- Alcohol consumption
- Use of NSAIDs
Three Independent risk factors

- **Gestational Age** at abortion
- **Age** of the patient. Both Husband / Wife
- History of **previous abortions**
Is Gestational Age of any importance?

Yes

Gest. Age at abortion guides us of underline cause

- 4 - 6 wks *Alloimmunity & LPD*
- 5 - 7 wks - *Genetic causes*
- 8 - 10 wks - *Immunological Causes*
- Mid trimester - *Anatomical Causes, APLA*
Advanced parental age

- **MATERNAL AGE:** increased risk of chromosomal abnormality (Trisomy 13, 18, 21, 47XXY, 47XXX)
- **PATERNAL AGE:** increased risk of Autosomal dominant, X-linked recessive Ds

Oocyte quality and ovarian reserve Decline starts after 35 yrs
Remember
Women who have had at least one live born infant :- Good Prognosis

a. with no prior fetal losses - recurrence risk is 12 % for next preg
b. With atleast 1 prior fetal loss - recurrence risk is 24 % for next preg
c. With two prior fetal losses - recurrence risk is 26 % for next preg
d. With three prior fetal losses - recurrence risk is 32 % for next preg

WOMEN WHO HAVE NOT HAD ATLEAST ONE LIVEBORN infant with 2 or more fetal losses –
Recurrence Risk for the next pregnancy is 40 - 45 %.
GENETIC FACTORS

- Repetitive first trimester losses
- Anembryonic pregnancies
- History of malformations or mental retardation
- Advanced maternal age
About 5% of the couples with RM are carriers of balanced translocations. They themselves are healthy but during gametogenesis there is malsegregation of chromosomes, resulting in either monosomy or trisomy.

The chances of RM with one partner with balanced translocation is 30%

Difficult to convince patients – Cost
Aneuploidies of conceptus are a well recognised cause of sporadic abortion.

Trisomies affecting chromosomes 13, 16, 18, 21, 22 constitute the largest group. Strong association with advanced maternal age.

Monosomy X is the single most common chromosomal abnormality in sporadic abortions. No age association.
May be advised
Not always successful to culture
FISH can be done
Often reveals aneuploidy which is not a cause of RPL
Does have a role in directing the management.
Women who abort chromosomally normal pregnancies should be investigated for causes other than genetic.
If abortus does show unbalanced translocation then could point to parents being balanced carriers

Genetic in Male

- Both abnormal *sperm morphology* and ↑*DNA fragmentation* increase recurrent pregnancy loss.

- **Carrell and colleagues** found higher rates of sperm DNA fragmentation in couples with recurrent early pregnancy loss following spontaneous conception.

(Arch Androl 2003;49:49-55)
Fetal chromosomal abnormalities

- This may be due to abnormalities in the egg, sperm or both. The most common chromosomal defects are -

- **Monosomy**: in vitro fertilization
  - Viable only that of X-chromosome
- **Trisomy**: 13, 18, 21 tolerated than monosomy
- **KARYOTYPE** - Expensive
- **Karyotype (Parental)**
  - Low yield & limited prognostic value → only if the other work-up was negative
  - Karyotyping of blood cells misses abnormalities of meiosis, which can be found in sperm cells

- **Karyotype (Embryonic)**
  - Not really needed
  - May consider after 2nd loss
  - If abnormal karyotype + normal parents → “bad luck”
Management of Genetic factors

- Genetic counseling
- Assisted reproductive technologies, including PGD (preimplantation genetic diagnosis)
- Use of either donor oocyte or donor sperm
  - Depending on the affected partner

Acquired or congenital anomalies

Congenital anomalies: 10 - 15 % in women with RPL vs. 7 % in all women.

Abnormal implantation:
- ↓ vascularity (septum)
- ↑ inflammation (fibroid)
- ↓ sensitivity to steroid hormones
Septate Uterus

- Most COMMON anomaly 55%
- May be complete/ incomplete

- 25% early abortions
- 5 - 7% late abortions & Premature labors
Bicornuate Uterus

- 10% of anomalies
- Incomplete fusion of Uterine horns at level of fundus
- Two separate but communicating endometrial cavities
- Abortion rate 30%
- Preterm labour 20%
- Strassman Metroplasty ??

Successful Pregnancy are well known
Unicornuate Uterus

- 20% of anomalies
- Agenesis or hypoplasia of one Mullerian duct
- May be alone or accompanied by Rudimentary horn
- With presence / absence of cavity Communicating / Non-communicating
- Associated Renal anomalies occur in 40% patients Ipsilateral to hypoplastic horn

Successful Pregnancy are well known
Uterus Didelphys

- Least common anomaly -5-7%
- Abortion rate 43%, Premature birth rate 38%

Arcuate Uterus
No role
Cervical Incompetence
CERVICAL INCOMPETENCE

- Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should only be considered in women who are likely to benefit.

- Transabdominal cerclage has been advocated as a treatment for second-trimester miscarriage and the prevention of early preterm labour in selected women with previous failed transvaginal cerclage and/or a very short and scarred cervix
When do you think it is advisable to give a cerclage?

- Cervical length < 2.5 cms
- Internal os width > 1.5 cm
- Available closed cervical length > 1/2

Timing of cerclage:
Any time between 12 wks to 28 wks
Do FIBROIDS cause Recurrent pregnancy loss?
Submucosal fibroids may be associated with RPL and should be removed hysteroscopically. Intramural and subserous fibroids do not require removal.
UTERINE ASSESSMENT

- Sonohysterography (SIS)
  - More accurate than HSG
  - Differentiate septate & bicornuate uterus

- Hysterosalpingogram (HSG)
  - Does not evaluate outer contour
  - Not ideal for the cavity

- Hysteroscopy
  - Gold standard for Dx + Rx intrauterine lesions
  - Reserved for when no Dx is made
UTERINE ASSESSMENT

- **Ultrasound**
  - Presence and location of uterine myomas
  - Associated renal abnormalities

- **MRI**
  - Differentiate septate from bicornuate

- Hysteroscopy, laparoscopy, or MRI → second-line tests when additional information is required
TREATMENT

Surgery

- **Hysteroscopy**
  Procedure of choice
  Septum excision, polypectomy
- **Laparoscopic myomectomy**
  For fibroids
- **Laparotomy**
Organisms implicated in causing Recurrent Abortion include:

- Chlamydia
- Mycoplasma
- Ureaplasma
- Coxakie
- Parvo virus

TORCH is a useless Investigation

Cochrane Review has categorically proven in multiple meta-analysis that none of the “TORCH” group of infections are responsible for recurrent spontaneous abortions.
Concluded “infections of the maternal and/or paternal genitourinary system may be the causal factor for recurrent pregnancy loss and can also pre-determine women that are of greater susceptibility to preterm pregnancy”

Bacterial Vaginosis

- **Commonest cause of vaginitis**
- **Amsel's criteria** for diagnosis of BV
  - Thin, homogeneous discharge
  - Release of an amine (putrescine, cadaverine, & trimethylamine) or fishy odor on addition of KOH is to vaginal discharge
  - "Clue cells" (Vaginal epithelial cells coated with coccobacilli)
  - Vaginal pH > 4.5
- **Nugent score**: Gram Stain of vaginal swab

Bacterial Vaginosis: 50%

<table>
<thead>
<tr>
<th>Trichomonas vaginalis</th>
<th>Candida albicans</th>
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<tbody>
<tr>
<td>25%</td>
<td>25%</td>
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</table>
BV and RSA

- BV one of the most frequently founded cause of spontaneous abortions and prematurity birth
- Diagnostics is easy and not expensive
- High vaginal pH is diagnostic
- Treatment is simple using Metronidazole/Clindamycin

The influence of Chlamydia trachomatis infection on RSA

Specific anti-chlamydial antibodies in 3 groups of women

- **IgA class**
  - 7.9% (p=0.082) in group 1 (RSA group),
  - 4.5% (p=0.236) in group 2 (1 abortion)
  - 0% in group 3 (no abortions)

- **IgG class** in 21.1% (p=0.024), 36.4% (p=0.000) and in 4.4%, respectively.

**CONCLUSIONS:**

- C.t. infection is an important causative agent in RSA
- Anti-Chlamydial antibodies included in screening tests

*Kavalier F, BMJ. 2005 Jul 16;331(7509):121-2.*
Hattori Y, Nakanishi T.

- Uterine cervical inflammatory cytokines, interleukin-6 and -8, as predictors of RSA

- Both IL-6 and IL-8 in cervical mucus were significantly higher in patients who miscarried subsequently than in those who had a live birth.
In Tubercular Endometritis (TVS)

- Endometrium hardly 2-3 mm.
- Endometrial lining appears broken, bright echogenic.
- Peri ovarian inflammation and spec’s of calcification on ovarian surface.
- T-O mass are seen as unilocular or multilocular thick walled mass with diffuse internal echoes.
- Layering effect seen when debri settles down.
- Outer margins poorly delineated if adhesions present.
- Restricted mobility (Frozen pelvis)

Diagnosis :- TB Gold Test, MTBC, TB PCR
IMMUNOLOGIC FACTORS

Autoimmune
(directed to self
tissues/cells)
- Systemic Lupus Erythmatosus
- Antiphospholipid Syndrome

Alloimmune
(directed to foreign
antigen)
An abnormal maternal immune response to fetal or placental antigen.
Autoimmune

- Systemic Lupus Erythmatosus (SLE)
  - Risk for loss is 20%, mostly in 2nd and 3rd trimester of pregnancy and associated with antiphospholipid antibodies.

- Antiphospholipid syndrome (APA)
  - 5 - 15% of women with RPL may have APA
  - APA likely induce microthrombi at placentation site. Altered vascularity affects developing embryo, induces abortion
Antiphospholipid syndrome

An Autoimmune disorder having specific clinical & lab criteria.

--Sapporo criteria

Diagnosis requires at least one of each.

**CLINICAL**
1) Thrombolic events - arterial, venous, small vessel
2) Pregnancy loss - ≥3 losses at <10wks gestation, fetal death after 10wks, premature birth at <34wks associated with severe preeclampsia or placental insufficiency.

**LABORATORY**
1) Lupus Anticoagulant
2) Anticardiolipin antibodies (IgG or IgM)

Any lab test results must be observed on at least 2 separate occasions 6 wks apart.

(An International Consensus Conference held in Sapporo in 1998)
Treatment

1. Low Molecular weight Heparin
   - 3000 IU subcu twice a day
   - Expensive treatment

2. Un-fractionated Heparin is better option

3. Low dose Aspirin

4. Steroids? Mainly for anti nuclear antibodies
   - 10 – 20 mg prednisolone / day
Alloimmune mechanism

Theory: Normally pregnancy (foreign tissue graft) is tolerated by the maternal immune system through formation of antigen blocking antibodies.

Felt that in couples that share similar types of HLA, there is inadequate formation of blocking antibodies in the maternal environment.

Therefore the maternal immune system mounts an immune response to the implanting pregnancy and a spontaneous abortion occurs.
Although previous studies have concluded that there was a higher degree of HLA sharing in couples with recurrent abortion, multiple recent studies have not confirmed this.

Multiple investigators have attempted to modulate the immune response using

1) paternal WBC immunization
2) IV Immunoglobulin
3) donor seminal plasma vaginal suppositories

NONE HAVE BEEN SHOWN TO BE BENIFICIAL
ALLOIMMUNITY

**DIAGNOSIS**

- HLA crossmatching
  
  Husband’s lymphocytes + wife’s serum

**TREATMENT**

- Transfusion of husband’s lymphocytes
  
  Pure suspension of husband’s lymphocytes
  
  [ 300ml of blood = 10ml of suspension ]
  
  Inject 5ml IV, 1 ml subcu and 1ml intradermal
Immunologic Factors - Treatment

- Immunostimulating Therapies - Leukocyte Immunization
- Immunosuppressive Therapies
Immunostimulating Therapies—Leukocyte Immunization

- stimulation of the maternal immune system using alloantigens on either paternal or pooled donor leukocytes
- leukocyte immunization also poses significant risk to both the mother and her fetus

- graft-versus-host disease, severe intrauterine growth retardation, and autoimmune and isoimmune complications
Immunosuppressive Therapies

- To antiphospholipid antibodies and to inappropriate cellular immunity toward the implanting fetus
  - intravenous immunoglobulin
  - progesterone
intravenous immunoglobulin

- theory
  - an overzealous immune reactivity to their implanting fetus

- Mechanism
  - decreased autoantibody production and increased autoantibody clearance, T-cell and Fc receptor regulation, complement inactivation, enhanced T-cell suppressor function, decreased T-cell adhesion to the extracellular matrix, and downregulation of Th1 cytokine synthesis

- disadvantage
  - expensive, invasive, and time-consuming, requiring multiple intravenous infusions over the course of pregnancy

- side effects
  - nausea, headache, myalgias, hypotension, anaphylaxis
Progesterone

- **Mechanism**
  - inhibits Th1 immunity
  - shift from Th1-to Th2 type responses

- **administered**
  - intramuscularly
  - intravaginally
  - may increase local, intrauterine concentration
  - averting any adverse systemic side effects
Mild endocrine diseases are likely not causes for recurrent abortion.

1) Thyroid disease

- Poorly controlled hypo- or hyper-thyroidism
  - Infertility & pregnancy loss
- ↑ thyroid antibody, even if euthyroid.
  - No strong evidence
2) Diabetes mellitus

- Poorly controlled (↑Blood glucose & HbA1c levels in 1st trimester) ➔ ↑ risk for loss.
- Miscarriage risk rises with the level of HbA1c
- Well-controlled ➔ No ↑ risk.
3) Polycystic Ovarian Syndrome

Polycystic ovary morphology itself does not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously (RCOG).

- Hyperinsulinemia & ↑ level of Plasminogen Activator Inhibitor activity – implicated as the proximate cause of incidence of loss (30-50%) among PCOS women (Br J Obst Gynecol, 1993).

- METFORMIN treatment can reduce or eliminate risk of miscarriage in PCOS women (Fertility Sterility, 2001; J Clin Endocrin 2002).
4) Luteal phase defect

- Progesterone is essential for implantation and maintenance of pregnancy
  - A defect in Corpus luteum → impaired progesterone production.
- However, LPD cannot be diagnosed during pregnancy; a consistently short luteal phase duration is the most reliable diagnostic criterion.
5) Hyperprolactinemia

- There is insufficient evidence to assess the effect of hyperprolactinaemia as a risk factor for recurrent miscarriage.

RCOG Green-top Guideline No. 17
April 2011
ENDOCRINE FACTORS

- Thyroid Function Tests- T3, T4, TSH
- S.Prolactin
- Glucose tolerance test
- HbA1c
- S.FSH
- S.LH
- S.Progesterone
TREATMENT

Luteal-phase insufficiency

- luteal-phase support with progesterone
- There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage (RCOG)

- However newer evidences is coming up as large multicentre study PROMISE is currently on the way.
- PCOS, hyperandrogenism, hyperinsulinemia
  - insulin-sensitizing agents (METFORMIN)
- overt diabetes mellitus
  - prepregnancy glycemic control
- hypothyroidism
  - thyroid hormone replacement
THROMBOPHILIA

- Thrombosis on maternal side of the placenta $\rightarrow$ impair placental perfusion
  - Late fetal loss, IUGR, abruption, or PIH
- Relationship with early loss is less clear
  - large and contradictory literature
  - May be restricted to specific defects not completely defined, or presence of multiple defects
THROMBOPHILIA

- Evaluate if loss > nine weeks + evidence of placental infarction or maternal thrombosis
- Antithrombin III, Protein C, Protein S, prothrombin gene, factor V leiden
Antithrombotic Therapy

- The combined use of low-dose aspirin (75-80mg/dl) and subcutaneous unfractionated heparin (5000unit twice daily)
Etiology - Environmental Factors

- **Confirmed association**
  - Ionizing irradiation
  - Organic solvents
  - Alcohol
  - Mercury
  - Lead

- **Suspected association**
  - Caffeine (> 300 mg/day)
  - Hyperthermia/fever
  - Cigarette smoking

- **Unknown association**
  - Pesticides

Etiology - Environmental Factors

- Diagnostic x-rays
- Air travel
- Microwave ovens
- Diagnostic ultrasounds
- Electromagnetic fields
- Video display terminals
- Aspartame
- Obesity
- Exercise

- Chocolate
- Drinking water
- BGH
- Phytoestrogens
- Phthalates
- Herbicides
- Hair dyes
- Nail polish
- Saccharin
Etiology - Idiopathic

- More than 50% of couples with RPL have no explanation despite extensive evaluation(s).
- Informative and sympathetic counseling appears to play an important role.
  - 70% live birth rates reported in couples with unexplained RPL who undertake an untreated subsequent pregnancy.

Male factor

- Trend toward repeated miscarriages with abnormal sperm (< 4% normal forms, sperm chromosome aneuploidy)
- Paternal HLA sharing not risk factor for RPL
- Advanced paternal age may be a risk factor for miscarriage (at more advanced age than females)
## INVESTIGATIONS

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Investigation</th>
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<tbody>
<tr>
<td>Genetic/Chromosomal</td>
<td>Karyotype both partners</td>
</tr>
<tr>
<td>Anatomical</td>
<td>HSG, hystero sonogram, ESI</td>
</tr>
<tr>
<td></td>
<td>laparoscopy &amp; hysteroscopy, MRI</td>
</tr>
<tr>
<td>Endocrine</td>
<td>TSH, prolactin, +/- GTT</td>
</tr>
<tr>
<td>Immunological</td>
<td>Anticardiolipin, lupus</td>
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<td>anticoagulant screen</td>
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<td>Thrombophylia</td>
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<tr>
<td>Infectious</td>
<td>Cervical Cultures</td>
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</tbody>
</table>
1) Anatomical distortions of the uterine cavity (surgical correction, hysteroscopically, laparotomy)

2) Control of Endocrinological diseases (control of diabetes, thyroid disease, progesterone luteal support)

3) Antiphospholipid antibodies (aspirin and heparin)

4) Thrombophilia (heparin)
Management of Patient with Idiopathic RPL

Preconception

1. Folic acid
2. Correct nutritional deficiencies
3. Prophylactic Doxycycline
4. Luteal support?
   - HCG / natural progesterone
Role of Progesterone—What is evidence?

- This benefit of progesterone could be explained by its immunomodulatory actions.
- A meta-analysis to assess progesterone support for pregnancy showed that it did not reduce the sporadic miscarriage rate.
- However, in a subgroup analysis of trials involving women with recurrent miscarriage, progesterone treatment offered a statistically significant decrease in miscarriage rate compared with placebo (PROMISE, http://www.medscinet.net/promise)
RPL - In Evident Cases Of Luteal Phase Defect....

There is definite role of progesterone.

- Allylestrenol
- Dehydro gestrenol
- Natural progesterone
  - Oral
  - Vaginal
- Injectable 17 – hydroxyl progest caproate
Summary of Cochrane Review

- **Parental Chromosomal** rearrangements
- **Anatomic** defect of the uterine fundus and cervix,
- APLA Sydr. (phospholipid antibodies)
- **Thrombophilia** activated protein C resistance, factor V and II gene mutation –
  Play definite Role
Summary of Cochrane Review

Karyotype POC

The majority of cases are due to repeated fetal chromosome abnormalities occurring consecutive by chance.
Progesterone deficiency, hypersecretion of LH, infective agents, and immune rejection are not currently considered causes of RFL.

Empirical treatment with progesterone, high LH suppression, or immunotherapies are of no proven benefit.

Subclinical/overt thyroid disorder or diabetes mellitus are rare
The use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted.

**BUT**

Some doctors give treatment like:

- Low dose aspirin
- Subcutaneous heparin
- Folic acid
- Progesterone
- Solcoseryl (increase oxygen supply)
- Nitroglycerin (increase implantation by increase uterine blood flow)
- Tocolytic

With often surprisingly beneficial outcome!
Empiric Treatment Supportive Care

Stray-Pederson

- 195 couples with RPL compared
- 1) **standard of care** - no specific treatment,
  - no recommendations or support with
- 2) **TLC** - psychological support
  - weekly follow up
  - rest as much as possible
  - avoid heavy work, travel
  - coitus prohibited
Empiric Treatment Supportive Care

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Success rate of pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>24</td>
<td>33%</td>
</tr>
<tr>
<td>TLC</td>
<td>37</td>
<td>86%</td>
</tr>
</tbody>
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Small numbers, but low risk/complication treatment
RPL

<8wk

4-6 wks Alloimmunity LPD

5-7 wks Genetic

8-10 wks Immunological

>10 wks Immunological (APLA)

>10 wks anatomical

<8wks

Hormones assay
Th1, Th2, TNF, NK

Chromosome FISH

ACLA
Lupus anticoagulant
ANA, Anti DSDNA

USG, MRI Hysteroscopy TVS

>8wks

Progesterone Paternal leucocyte

Genetic counsel Gamete donor

Aspirin/Heparin Steroids/Immunosuppressive?IVIG

Surgery
A woman who has suffered a single sporadic miscarriage has an 80% chance and a woman with three consecutive miscarriages a 40-60% chance of her next pregnancy being successful
Don't Quit.

While there's life, there's hope.

- Marcus T.
This is our hope.
Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained recurrent miscarriage does not improve the live birth rate.

Thank You