Recurrent pregnancy loss

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Recurrent pregnancy loss

- **Defined** as ≥ 2 losses prior to 20 weeks
- Ectopic, molar, and biochemical pregnancies are not included.
- RPL affects about 2% of women in reproductive age.
- Very heterogeneous disorder (no fixed pattern).
- The etiology can be reached in about ⅔ of couples after thorough investigations.
- RPL causes fear and anxiety in couples seeking parenthood

RECURRENT PREGNANCY LOSS

- Pregnancy loss is a significant negative life event and the repetitive nature of RPL may intensify the grief experienced.
- Studies have mostly focused on women, and there is a need for studies on the emotional impact of RPL on men.
- Clinicians and clinics should take the psychosocial needs of couples faced with RPL into account when offering and organizing care for these couples.

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RECURRENCE RISK

- ***Risk of recurrence of PL depends on:***

1. Maternal age
2. Stress
3. Occupational Or Environmental Exposure
4. Cause of pregnancy loss
5. Number of previous miscarriages
6. Number of previous term deliveries

Recurrence risk

- Women should be sensitively informed that the risk of pregnancy loss is lowest in women aged 20 to 35 years.
- Women should be sensitively informed that the risk of pregnancy loss rapidly increases after the age of 40.

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RECURRENCE RISK

- Stress is associated with RPL, but couples should be informed that there is no evidence that stress is a direct cause of pregnancy loss.
- Couples with RPL should be informed that smoking could have a negative impact on their chances of a live birth, and therefore cessation of smoking is recommended.

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RECURRENCE RISK

- Couples with RPL should be informed that maternal **obesity** or **being significantly underweight** is associated with obstetric complications and could have a negative impact on their chances of a live birth and on their general health.
- Striving for a healthy normal range body mass index (BMI) is recommended.

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RECURRENCE RISK

- Couples with RPL should be informed that excessive alcohol consumption is a possible risk factor for pregnancy loss and proven risk factor for fetal problems (Fetal alcohol syndrome). (strong)
- Couples with RPL should be advised to limit alcohol GPP consumption.

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RECURRENCE RISK

Risk of recurrent early pregnancy loss in **young** women

	Number of prior miscarriage	% of risk of miscarriage in next pregnancy
Women with ≥ 1 live born infant	**0**	**12%**
	1	**24%**
	2	**26%**
	3	**32%**
	6	**53%**
Women with no live born infants	**≥2**	**40-45%**

ROLE OF TVS IN PREDICTING MISCARRIAGE

- Appearance of fetal heart tone (FHT) on TVS decreases global miscarriage risk from 12-15% to 3-5%.
- However, in patients with past history of RPL, the miscarriage rate after embryonic heart activity is still 3-5 times higher (15-25%) than those with no such history .
- The prognostic value of FHT declines with increasing maternal age.

ETIOLOGY OF RPL

1-**Genetic** :

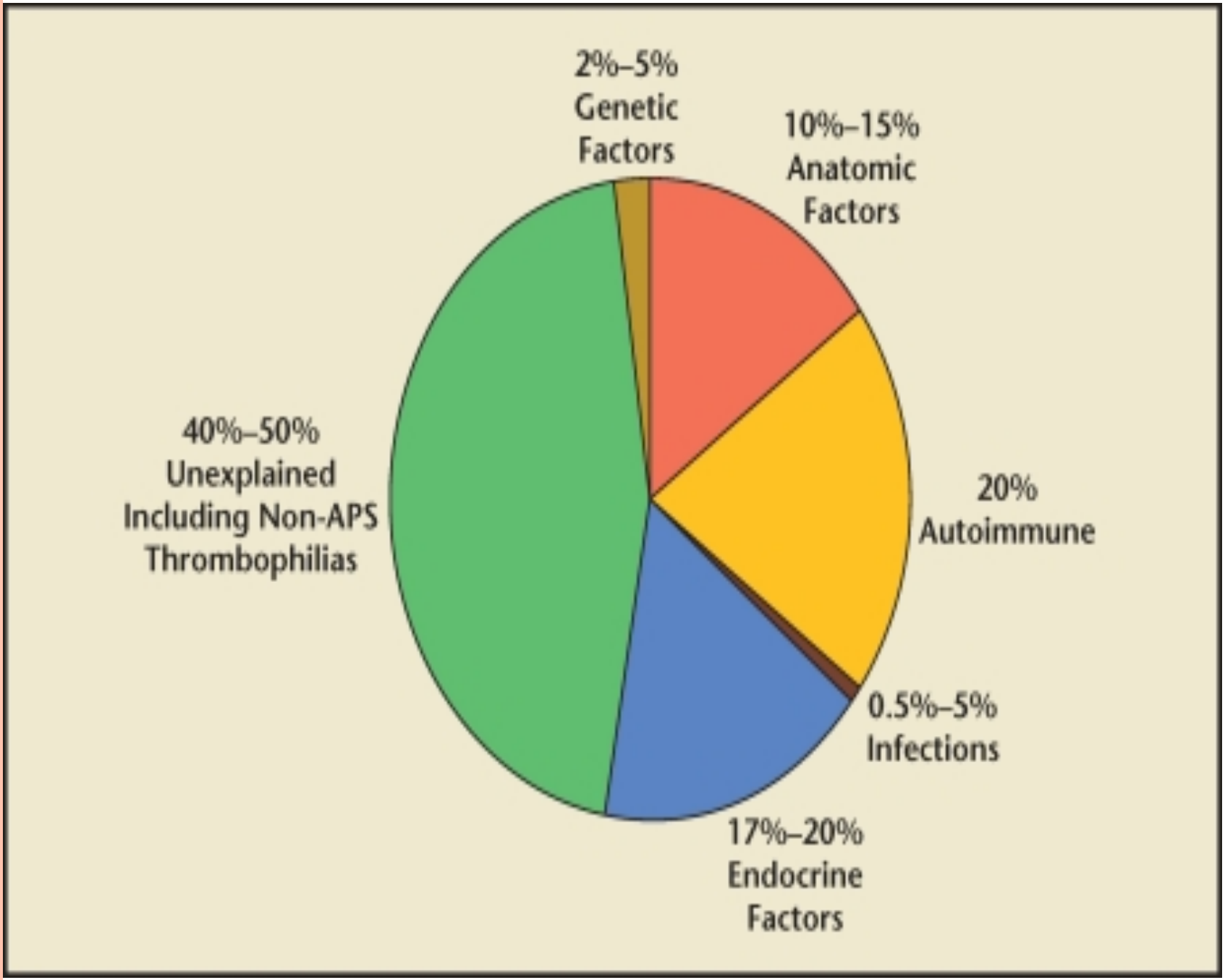
- chromosomal abnormalities in embryo (structural or numerical)
- parental chromosomal abnormalities

2- **Anatomic**:

- congenital uterine malformation
- leiomyoma : submucous
- intrauterine adhesions

3- **Immunologic**:

- Autoimmune : SLE, APLA
- Alloimmune: abnormal maternal response to fetal or placental antigens.


2%–5%
Genetic
Factors
10%–15%
Anatomic
Factors
40%–50%
Unexplained
Including Non-APS
Thrombophilias
20%
Autoimmune
0.5%–5%
Infections
17%–20%
Endocrine
Factors

ETIOLOGY OF RPL (CONT.,)

4- Endocrine:

- Thyroid disease - Diabetes mellitus

- PCOS - LPD

5-Inherited thrombophilias:

Type II: over-activity of coagulation factors (most common):

- **Factor V leiden mutation**
- **Prothrombin G20210A mutation**

Type I: deficiency of natural anticoagulants:

- **anti-thrombin III deficiency - Protein C deficiency**
- **Protein S deficiency - Factor XIII mutation**
- **Familial dysfibrinogenemia**

6- Infectious

7- Environmental: Smoking, alcohol, heavy coffee consumption

8- Unexplained

INVESTIGATIONS OF RPL

- Medical and family history could be used to tailor diagnostic investigations in RPL.
- The ESHRE guideline development group recommends to base prognosis on the number of *preceding pregnancy losses* and *female age*.

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1-Screening For Genetic Causes

- **Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purpose.**

- **For genetic analysis of the pregnancy tissue, Array-based Comparative Genomic Hybridization (array-CGH) is recommended based on a reduced maternal contamination effect.**

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1-Screening For Genetic Causes

- **Parental karyotyping is not routinely recommended. It could be carried out after individual assessment of risk or analysis of products of conception reports an unbalanced structural chromosomal abnormality.**

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2- THROMBOPHILIA SCREENING

- **Screen for hereditary thrombophilia is not recommended unless for research, or in women with additional risk factors for thrombophilia .**

- **Screening for antiphospholipid antibodies is recommended :**

1-lupus anticoagulant [LA],

2- anticardiolipin antibodies [IgG and IgM])

3- anti-B2 glycoprotein-I antibodies).

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Antiphospholipid antibody syndrome

- **Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.**

- **It is association between antiphospholipid antibodies (LA, ACL and anti-B2 glycoprotein-I antibodies) – and adverse pregnancy outcome or vascular thrombosis**

RCOG 2011

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- ***Adverse pregnancy outcomes include:***

1. ≥ 3 **consecutive miscarriages before 10 weeks of gestation.**
2. **one or more morphologically normal fetal losses after the 10th week of gestation.**
3. **one or more preterm births before the 34th week of gestation owing to placental disease.**

RCOG 2011

3-IMMUNOLOGICAL SCREENING

- **HLA determination is not recommended. Only HLA class II determination could be considered in Scandinavian women with secondary RPL after the birth of a boy, for prognostic purposes.**

- **Measurement of anti-HY is not recommended**

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3-IMMUNOLOGICAL SCREENING

- **All the following tests are not recommended**

1. **Cytokine testing**
2. **Cytokine polymorphisms**
3. **Antinuclear antibodies (ANA) testing**
4. **Natural killer (NK) cell testing of either peripheral blood or endometrial tissue**
5. **Anti-HLA (anti-human leukocyte antigen) antibodies**

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4- SCREENING FOR ENDOCRINE/ METABOLIC ABNORMALITIES

- Thyroid screening [TSH] and thyroid peroxidase [TPO]-antibodies is recommended

- Abnormal (TSH) and thyroid peroxidase [TPO]-antibody levels should be followed up by (T4) testing.

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4- SCREENING FOR ENDOCRINE/ METABOLIC ABNORMALITIES

- Assessment of PCOS, fasting insulin and fasting glucose is not recommended.
- Prolactin testing is not recommended in the absence of clinical symptoms of hyperprolactinemia (oligo-amenorrhea)
- Ovarian reserve testing is not routinely recommended

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4- SCREENING FOR ENDOCRINE/ METABOLIC ABNORMALITIES

- Luteal phase insufficiency testing is not recommended.
- Androgen testing is not recommended.
- LH testing is not routinely recommended.
- Measurement of homocysteine plasma levels is not routinely recommended.

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4- SCREENING FOR ENDOCRINE/ METABOLIC ABNORMALITIES

- There is no report of an association between vitamin D status and miscarriage, and hence testing of vitamin D status is not recommended.

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5. Infective agents (TORCH)

- **Any severe infection that leads to bacteremia or viremia can cause sporadic miscarriage.**
- **The role of infection in recurrent miscarriage is unclear. So TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus) screening is not recommended.**

RCOG 2011

6. Uterine Anatomy

- All women with RPL **should** have an assessment of the uterine anatomy
- Transvaginal 3D ultrasound (3D US), has a high sensitivity and specificity, and can distinguish between septate uterus and bi-corporeal uterus. It is the preferred technique in evaluation of uterine abnormality

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6. Uterine Anatomy

- Sonohysterography (SHG) is more accurate than hysterosalpingography (HSG) in diagnosing uterine malformations. It can be used to evaluate uterine morphology when (3D US) is **not** available, or when tubal patency has to be investigated
- MRI is not recommended as first line option but can be used when 3D US not available.

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6. Uterine Anatomy

- If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered.

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7. Male factor

- In the male partner, it is suggested to assess life style factors (smoking, alcohol consumption, exercise pattern, and body weight).

- Assessing sperm DNA fragmentation can be considered for explanatory purposes,

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TREATMENT TO INCREASE LIVE BIRTH RATE IN RPL

- It is recommended to base prognosis on the number of preceding pregnancy losses and female age.
- Prognostic tools (Lund, Brigham) can be used to provide an estimate of subsequent chance of live birth in couples with unexplained RPL.

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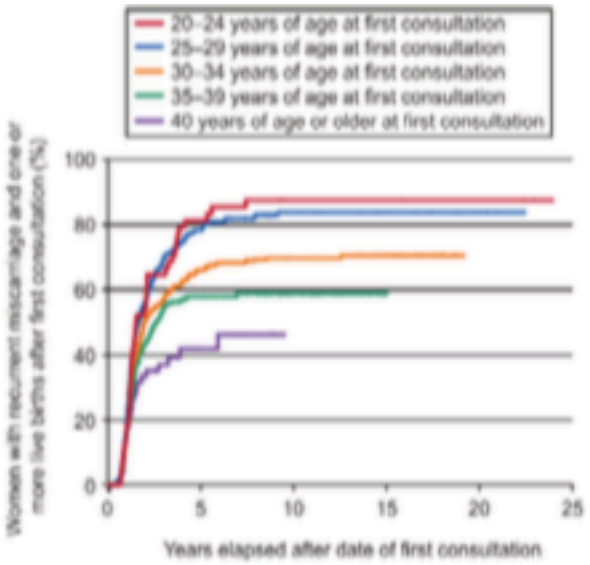

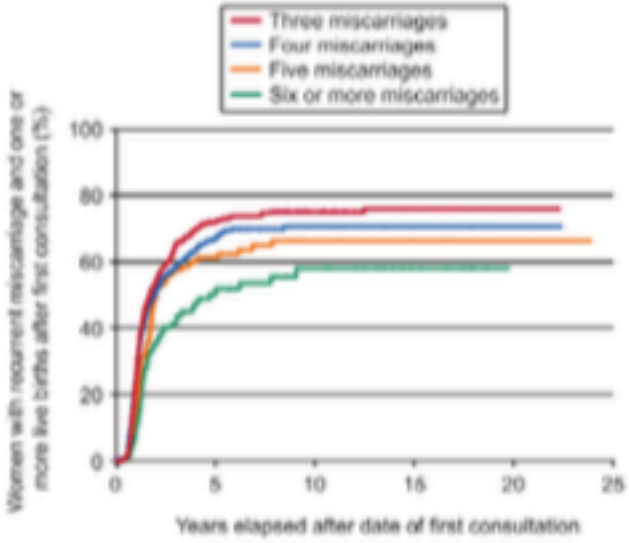

Table 1: Hazard Ratio (95% CI) of Achieving a Live Birth After Referral According to Age at First Consultation and Number of Previous Miscarriages (Lund *et al.*, 2012) (reproduced with permission).

No. of Previous Miscarriages	Age at First Consultation (y)				
	20–24	25–29	30–34	35–39	40 or Older
3	1.28 (0.78–2.11)	1.50 (1.15–1.96)	1 (reference group)	0.81 (0.60–1.10)	0.48 (0.26–0.89)
4	1.93 (1.20–3.11)	0.99 (0.72–1.36)	0.95 (0.72–1.26)	0.67 (0.47–0.95)	0.88 (0.46–1.68)
5	0.48 (0.18–1.29)	1.51 (0.92–2.48)	0.79 (0.53–1.18)	0.76 (0.50–1.17)	0.32 (0.10–1.00)
6 or more	NE	0.80 (0.49–1.30)	0.55 (0.34–0.88)	0.51 (0.29–0.91)	NE

NE, not estimable.

Table 2: Predicted percentage success rate of subsequent pregnancy according to age and previous miscarriage history (Brigham *et al.*, 1999) (reproduced with permission).

Age (years)	Number of previous miscarriages			
	2	3	4	5
20	**92 (86–98)**	**90 (83–97)**	**88 (79–96)**	85 (74–96)
25	**89 (82–95)**	**86 (79–93)**	**82 (75–91)**	79 (68–90)
30	**84 (77–90)**	**80 (74–86)**	**76 (69–83)**	71 (61–81)
35	**77 (69–85)**	**73 (66–80)**	**68 (60–75)**	62 (51–74)
40	69 (57–82)	64 (52–76)	58 (45–71)	52 (37–67)
45	60 (41–79)	54 (35–72)	48 (29–67)	42 (22–62)

Values are percentages with 95% confidence intervals (CI) shown in parentheses. Where the CI <20%, the values are shown in bold print.

1- GENETIC/CHROMOSOMAL CAUSES

- All couples with results of an abnormal fetal or parental karyotype should receive genetic counselling.

- All couples with results of an abnormal fetal or parental karyotype may be informed about the possible treatment options available including their advantages and disadvantages.

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1- Genetic/Chromosomal causes

- For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research, or if indicated for venous thromboembolism (VTE) prevention

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2- Antiphospholipid Antibody Syndrome

- For women who fulfill the laboratory criteria of APS and a history of 3 or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (Unfractionated heparin [UFH] or Low molecular weight heparin [LMWH]) starting at date of a positive pregnancy test, over no treatment.

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3- Endocrine / Metabolic

- Overt **hypothyroidism** arising before conception or during early gestation should be treated with levothyroxine in women with RPL.
- There is conflicting evidence regarding treatment effect of levothyroxine for women with subclinical hypothyroidism (SCH) and RPL. Treatment of women with SCH may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks.

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3- Endocrine / Metabolic

- Women with ***subclinical hypothyroidism*** or ***thyroid autoimmunity*** and RPL when become **pregnant again**, TSH level should be checked in early gestation (7-9 weeks), and hypothyroidism should be treated with levothyroxine.

- There is **insufficient evidence** to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL outside a clinical trial.

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3- Endocrine / Metabolic

- There is **insufficient evidence** to recommend the use of **progesterone** to improve live birth rate in women with RPL and luteal phase insufficiency.

- There is **insufficient evidence** to recommend the use of human chorionic gonadotrophin (hCG) to improve live birth rate in women with RPL and luteal phase insufficiency.

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3- Endocrine / Metabolic

- There is **insufficient evidence** to recommend **metformin** supplementation in pregnancy to prevent PL in women with RPL and glucose metabolism defects.
- Bromocriptine treatment **can be considered** in women with RPL and hyperprolactinemia to increase live birth rate.
- Preconception counseling in women with RPL **could include the general advice** to consider prophylactic vitamin D supplementation

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4- Uterine anomalies

- Whether hysteroscopic septum resection has beneficial effects (improving live birth rates, and decreasing miscarriage rates, without doing harm), should be evaluated in the context of surgical trials in women with RPL and septate uterus.
- Metroplasty is **not recommended** for bicorporeal uterus with normal cervix and RPL.

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4- Uterine anomalies

- Uterine reconstruction is not recommended for hemi-uterus (unicornuate uterus) and RPL.
- There is **insufficient evidence** in favor of metroplasty in women with bicorporeal uterus and double cervix (didelphic uterus) and RPL.
- There is insufficient evidence supporting hysteroscopic removal of submucosal fibroids or endometrial polyps in women with RPL.

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4- Uterine anomalies

- Surgical removal of intramural fibroids is not recommended in women with RPL. There is **insufficient evidence** to recommend removing fibroids that distort the uterine cavity.

- There is **insufficient evidence** of benefit for surgical removal of intrauterine adhesions for pregnancy outcome. After hysteroscopic removal of intrauterine adhesions in women with RPL, precautions have to be taken to prevent recurrence of adhesions

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4- Uterine anomalies

- Women with a history of **second-trimester** pregnancy losses and suspected cervical weakness should be offered serial cervical sonographic surveillance.
- In women with a singleton pregnancy and a history of recurrent **second-trimester pregnancy loss attributable to cervical weakness**, a cerclage could be considered. There is no evidence that this treatment increases perinatal survival.

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5- Lifestyle Modification

Couples with RPL should be informed that smoking, alcohol consumption, obesity and excessive exercise could have a **negative impact** on their chances of a live birth, and therefore cessation of smoking, a normal body weight, limited alcohol consumption and a normal exercise pattern **is recommended.**

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6-Male factor management

- Sperm selection is not recommended as a treatment in couples with RPL
- Antioxidants for men have not been shown to improve the chance of a live birth.

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7. Unexplained RPL

- Lymphocyte immunization therapy should **not** be used as treatment for unexplained RPL as it has **no** significant effect and there may be serious adverse effects.
- Intravenous immunoglobulin (IvIg) is **not** recommended as a treatment of RPL.
- Glucocorticoids are **not** recommended as a treatment of unexplained RPL or RPL with selected immunological biomarkers.

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7. Unexplained RPL

- **Heparin or low dose aspirin are not recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL.**
- **Low dose folic acid is routinely started preconceptionally to prevent neural tube defects, but it has not been shown to prevent pregnancy loss in women with unexplained RPL.**
- **Vaginal progesterone does not improve live birth rates in women with unexplained RPL.**

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7. Unexplained RPL

- There is insufficient evidence to recommend *intralipid therapy* for improving live birth rate in women with unexplained RPL.
- There is insufficient evidence to recommend G-CSF *(granulocyte-colony stimulating factor)* in women with unexplained RPL.
- There is no evidence to recommend *endometrial scratching* in women with RPL.

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8- Non Conventional treatment

- Women with RPL ask about using multivitamin supplements, they should be advised on multivitamin supplements that are safe in pregnancy.
- The role of the following therapeutic modalities in RPL are **lacking evidence**:

1- Chinese Herbal treatment

2- Acupuncture

3- ICSI/IVF

4-Diet – antioxidants

5- Others including homeopathy, bioresonans therapy and naprotechnology.

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Glossary

- Homeopathy = a system of complementary medicine in which ailments are treated by minute doses of natural substances that in larger doses would produce symptoms of the ailment.
- Bioresonance therapy= is a biophysical treatment that works with the patient's own electromagnetic fluctuation spectrum i.e uses the patient's own energy field.
- Naprotechnology = (natural procreative technology) is a new women's health science that monitors and maintains woman's reproductive & gynecologic health .

MANAGEMENT OF RPL SUMMARY

Category	Evaluation	Treatment
Genetic	**Karyotype, both parents** Ovarian reserve test	**Counseling** **Donor gametes where appropriate** Preimplantation genetic diagnosis
Anatomic	**Sonohysterography or HSG** Magnetic resonance imaging IVP or renal ultrasound	**Hysteroscopic septoplasty** **Hysteroscopic myomectomy** **Hysteroscopic adhesiolysis** Abdominal metroplasty Abdominal myomectomy Cervical cerclage
Immunologic	**Lupus Anticoagulant** **Anticardiolipin Antibody**	**Aspirin and heparin**
Thrombophilias	Factor V Leiden Prothrombin Gene Mutation Activated Protein C Resistance Homocysteine Protein C Protein S Antithrombin III	Aspirin and heparin
Endocrine	**TSH** **Luteal Phase Duration** Blood Glucose, HgbA1C Prolactin	Thyroxine **Clomiphene citrate** **Metformin** **Dopamine agonists**
Infectious	**As indicated by symptoms**	Empiric antibiotics
Environmental	**History**	Behavior modification

THANK YOU