Recurrent Pregnancy Loss Protocol

Authors : A Haken/F Hodge

Ratified in gynae forum: February 2021

Due for review: February 2024.

Contents

1. Introduction

1.1 Definitions and terminology

Pregnancy loss (PL) is defined by the European Society of Reproduction and Embryology (ESHRE) as spontaneous demise of an embryo or fetus before reaching viability (24 weeks gestation from last menstrual period); where pregnancy is confirmed by positive serum or urinary beta human chorionic gonadotrophin (βhCG).

ESHRE define recurrent pregnancy loss (RPL) as the loss of 2 or more pregnancies and in contrast to other definitions does not require the losses to be consecutive, with the aim of increasing research in the area and the support available to couples. The definition includes pregnancy of unknown location and excludes known ectopic and molar pregnancies.

The term primary RPL should be used when a couple have not had a previous pregnancy reaching the level of viability, whereas secondary RPL should be used to describe couples who have had one or more pregnancies reaching 24 weeks gestation, regardless of birth outcome. It is recommended to use the term "recurrent miscarriage" only if all PLs have been confirmed as intrauterine miscarriages.

In addition, certain terminology can evoke negative emotions and dissatisfaction with care. The following terms should therefore be avoided in caring for couples experiencing RPL: "*spontaneous abortion", "chemical pregnancy", "blighted ovum", "products of conception", "incompetent cervix", "pregnancy failure".*

1.2 Epidemiology

Miscarriage rates vary between 5-15% depending on the population studied, and RPL has been shown to affect 1-3% of couples if a definition of 3 or more consecutive pregnancy losses is used. It is likely that the recommended definition in section 2.1 will result in an increase in this figure in the coming years.

1.3 Impact

The psychological impact of RPL is significant with feelings of loss and grief escalating with each loss. This has been shown to be irrespective of pregnancy order or gestational age at the time of the loss. The effect of RPL on males is often overlooked but should be considered as equally important in the care of a couple as it can put strain on personal relationships, further increasing anxiety and low mood.

Most couples are anxious about subsequent pregnancies and want an explanation before conceiving after RPL. Evidence shows a plan for the next pregnancy or treatment to prevent a further PL is important to couples in this situation; some may choose not to attempt further pregnancies depending on their investigation results.

Care of couples with RPL should include investigations and treatment options, but should also focus on emotional support, understanding and acknowledgement of their reactions as normal. All couples should be given the option of professional counselling.

2. Guideline Summary

2.1 Investigations

Routinely test	Imaging for uterine anomalies (3D US if available / hysteroscopy) APS antibodies (LA + ACA) TPOAb and TSH levels (+T4 if abnormal)	
Consider testing depending on patient factors	Fetal karyotype Parental karyotype Hereditary thrombophilia screen APS antibodies (β-glycoprotein I) Prolactin levels Ovarian reserve HLA determination ANA levels	
Do not test	*Immunological tests* *PCOS / insulin resistance* *Luteal phase insufficiency*	*Vitamin D* *Homocysteine levels* *Androgens / LH levels*

2.2. Prognosis

Maternal age (years)	**2 PL**	**3 PL**	**4 PL**	**5 PL**
20	92%	90%	88%	85%
25	89%	86%	82%	79%
30	84%	80%	76%	71%
35	77%	73%	68%	62%
40	69%	64%	58%	52%
45	60%	54%	48%	42%

Table 1 – predicted live birth rate (%) in subsequent pregnancy in couples with recurrent pregnancy loss (RPL), depending on maternal age and number of previous pregnancy losses (PL)

2.3 Management Flowchart

History from couple + examination in RPL clinic
Advise lifestyle changes:
- Smoking cessation
- Limit alcohol
- Avoid recreational drug use
- Aim BMI 20-25
- Regular gentle exercise
- Consider folic acid and Vitamin D if planning conception
Consider testing couples for:
- Parental / fetal karyotype (if previous child with congenital anomaly)
- Hereditary thrombophilia (if VTE risk factors or family hx)
-Prolactin (if oligo-amenorrhoea)
- Ovarian reserve (if suspect premature ovarian insufficiency)
- ANA levels (if auto-immune conditions)
- HLA determination (if Scandinavian and previous male child)
- Sperm DNA fragmentation (if unhealthy male lifestyle)
ACA + LA
(consider β-glycoprotein I)
Positive APS Ab
Re-test 6 weeks later
If remain positive
Aspirin and LMWH in next pregnancy
TSH + TPOAb
(+T4 if abnormal)
Treat hypo and hyperthyroidism
Test early next pregnancy
Ultrasound pelvis
(3D if available)
Congenital anomaly
Assess renal tract, consider MRI
Fibroids, polyps, adhesions
Surgery not recommended

3. Organisation of care

3.1 Clinic requirements

- Longer first visit with prior information provided in writing. This has been shown to reduce anxiety levels in couples. Furthermore, it helps in managing expectations on arrival regarding information to be discussed and treatment options. Information should include incidence of RPL, causes and investigations relative to patient history.
- Timeframe estimate for investigations, including how results will be discussed
- Treatment plan - include possibility of no treatment depending on history / investigation results, and the consideration of participating in clinical trials if couples wish to.

3.2 Considerations for care

Couples should be treated with kindness, compassion and respect at all times. There should be ample time to listen to their history, choices and wishes for the future with recognition that their situation is individual to them. Time for questions and further discussion should be allowed for and conversations should use clear but sensitive language. Certain terminology should be avoided – see section 2.1. It is important to be honest and avoid falsely reassuring couples, whilst maintaining a positive and supportive outlook for future pregnancies should they choose to conceive again.

Patients can be offered early reassurance scans fortnightly from around 6 weeks gestation. They can contact EPU once they have a positive pregnancy test to arrange these.

4. Risk factors and health behaviours

4.1 Risk factors

Age

The biggest known risk factor for PL is advancing female age, with the lowest risk of PL in 20-35 year olds. Studies have shown that the risk of PL rapidly increases over the age of 40 years.

Stress

Stress is often associated with RPL however no studies to date have found a direct causative link, as it is difficult to ascertain whether stress is a result of RPL rather than a cause.

Environmental

Environmental factors such as exposure to heavy metals, pesticides and radiation have been studied, and although pregnant women are advised to avoid contact with the above in general, there is not enough data at present to recommend protection against any specific factor to improve outcomes in future pregnancies.

Other

There is insufficient evidence to screen for chronic endometritis or to assess endometrial decidualisation in patients with RPL.

4.2 Health behaviours

Smoking

Smoking cessation is advised for all pregnant women, due to the negative impact on pregnancy and general health. There has been no directly studied link between smoking and RPL, however as cessation is known to improve pregnancy outcomes and live birth chances it should be recommended to all couples.

Weight

Extremes of weight such as obesity and being significantly underweight are associated with obstetric complications and could impact the chance of a live birth in addition to the effect on general health. In addition, maternal obesity is a significant independent risk factor for RPL. The recommendation is to strive for a healthy weight (BMI 20-25).

Alcohol and other substances

Excessive alcohol intake in pregnancy is associated with significant adverse fetal effects – most notably fetal alcohol spectrum disorder. It is also a potential risk factor for PL and therefore women should be advised to limit their alcohol intake to 1-2 units per week and avoid alcohol completely when pregnant, in line with NHS guidelines from the Chief Medical Officers. Cannabis has not been directly linked with RPL, however it is recommended that pregnant women or those attempting to conceive avoid using substances such as cannabis.

Exercise

There have been no studies on exercise and RPL, however general recommendations for pregnant women regarding gentle, regular exercise should be followed.

Caffeine

Some studies have shown an association between excessive caffeine intake and late pregnancy loss. It is unclear from current evidence if caffeine is a risk factor for RPL.

Sex

There is no evidence that sexual intercourse in early pregnancy increases risk of PL. Couples should be reassured of this fact, as they may assume they are to blame for previous PL and struggle with feelings of guilt as a result.

Radiation

Although high dose radiation during pregnancy has been associated with congenital malformations and fetal death, current evidence suggests that there is no increased risk of PL with exposure to diagnostic radiological procedures which use low doses.

5. Investigations

5.1 Genetic screening

Fetal / embryological

Approximately 90% of embryos that miscarry are phenotypically abnormal. They may also be genetically abnormal. It is also known that the prevalence of chromosomal abnormalities in spontaneous miscarriage is around 45% - this is the same in RPL cases. **Genetic assessment of pregnancy tissue from RPL is therefore not recommended routinely** as it does not impact prognosis or provide any treatment options. It may be requested by couples for explanatory purposes of a current PL and could be considered for this reason.

Parental

Certain karyotype abnormalities in parents are associated with increased rates of PL. These include reciprocal translocations and inversions. However even if an abnormality is found in parental karyotype, the cumulative birth rate and chance of a healthy child are very good. As it does not predict outcome in next pregnancy and there is a low incidence of such anomalies in the general population**, it is not recommended to test parental karyotype routinely in RPL**. There may however be cases when it is considered, such as if couples have had a previous child with a congenital abnormality, offspring in the family have an unbalanced chromosomal abnormality, or if a translocation has been detected in analysis of pregnancy tissue.

5.2 Thrombophilia

Subdivided into hereditary and acquired, thrombophilias are conditions associated with an increased risk of venous thromboembolism (VTE).

Hereditary

Includes conditions such as Factor V Leiden mutation, prothrombin gene mutation, Protein C Protein S and antithrombin deficiencies. There is no clear evidence of an association with RPL in studies to date and therefore routine screening of all women is not recommended. **Testing should be considered only if a woman has additional risk factors for thrombophilia** (e.g. previous VTE, family history of hereditary thrombophilia) – and in these

cases testing should be performed >6 weeks after PL to avoid false positives due to physiological changes occurring in pregnancy.

Acquired

A diagnosis of antiphospholipid syndrome requires evidence of persistent antibodies in serum, plus a history of vascular thrombosis or pregnancy complications such as pre-eclampsia and other placenta-mediated complications. The associated antibodies are lupus anticoagulant (LA), anticardiolipin IgG and IgM (ACA), and β-glycoprotein I IgG and IgM. **In women with RPL, screening for LA and ACA is recommended**. The association with PL and β-glycoprotein I antibodies is weaker, however testing for this could also be considered in women with RPL. As for hereditary thrombophilia screening, tests should be performed >6 weeks since last pregnancy and confirmatory tests performed a further 6 weeks later.

5.3 Immunological

Human leukocyte antigen (HLA) determination

In most women, there is weak or inconclusive evidence of an association between HLA class and RPL. There are a few cohort and case control studies of Scandinavian women showing higher prevalence of a specific HLA type (presence of DRB1*03 allele) in women with RPL compared to a control population. Testing for HLA determination could therefore be considered in Scandinavian women with RPL as it is thought to have some prognostic value.

Anti-nuclear antibodies

Anti-nuclear antibodies (ANA) are positively associated with auto-immune conditions. Some studies have shown an association with RPL, though this does not necessarily imply causation. Testing could be considered however it is important to inform patients that the information provided by the result would not be useful for prognosis.

Other

There is no strong evidence for an association with RPL and any of the following: anti-HY antibodies, cytokines, natural killer cells, and anti-HLA antibodies. Testing for these immunological markers is therefore not recommended.

5.4 Metabolic and endocrine

Thyroid

Elevated levels of thyroid peroxidase antibodies (TPOAb) is associated with PL, and subclinical hypothyroidism is associated with RPL (one study found rates as high as 27% in women with RPL). As thyroid conditions are common and treatable**, testing for thyroid**

stimulating hormone (TSH) and TPOAb is recommended in all RPL patients. If these initial results are abnormal, patients should also have their thyroxine (T4) levels checked.

Polycystic ovarian syndrome (PCOS) and insulin resistance

There is an association with RPL though it is unclear if this is causative. In addition, studies have shown live birth rates in future pregnancies are not significantly different between patients with PCOS and controls, meaning the results of testing would not be helpful for prognosis. **Testing for PCOS is not routinely recommended in RPL**.

Prolactin

There is contrasting evidence for an association with RPL and prolactin levels, and therefore testing should only be considered if there are additional factors suggestive of abnormality (e.g. oligo-amenorrhoea suggesting possible hyperprolactinaemia).

Ovarian reserve testing

There is insufficient evidence for an association with RPL and routine investigation is not recommended. Testing could be considered if there are additional features suggestive of premature ovarian insufficiency.

Luteal phase insufficiency

This term is used to describe low levels of progesterone in early pregnancy which is thought could affect implantation. There is inconsistent evidence for an association with RPL and therefore testing is not recommended.

Androgens and Luteinising Hormone (LH) levels

There is inconsistent evidence for an association with RPL and investigation is therefore not recommended.

Vitamin D

There has been a possible association between vitamin D deficiency and PL, however **vitamin D supplementation is recommended for all pregnant women**, and specific testing for deficiency is not required.

Hyperhomocysteinaemia

Once again there is inconsistent evidence for a role in RPL, and levels of homocysteine in serum are further confounded by lifestyle factors. Routine testing is therefore not recommended.

5.5 Anatomical

Congenital uterine anomalies have been associated with RPL, whereas acquired uterine anomalies have a less clear association. It is recommended that all women with RPL have an assessment of uterine anatomy. As 3D ultrasound is not currently available in Singleton women should be offered sonohysterography in preference to hysterosalpingogram (HSG) due to improved accuracy. Women may also be offered hysteroscopy to assess the uterine cavity further. Magnetic resonance imaging (MRI) is not a first line investigation. It could be considered if abnormalities are detected on ultrasound, to assist in reviewing the renal tract and plan potential surgery, however the accuracy in detection of uterine malformations has not been fully determined.

5.6 Male factors

Poor sperm quality has been associated with RPL. Lifestyle factors such as smoking, alcohol use, excessive exercise and weight should be assessed as these have been shown to affect sperm quality. Specific investigations such as DNA fragmentation tests may be considered if significant lifestyle factors present, though the evidence for an association with RPL is indirect.

6. Treatment

6.1 Genetic abnormalities

Couples should be referred for genetic counselling and consideration of prenatal genetic testing (PGT) if an abnormal parental or fetal karyotype is detected. There are additional options which can be discussed in these cases, including PGT for structural chromosomal abnormalities which if detected may reduce miscarriage rate, but not necessarily increase the live birth rate or time to pregnancy. Send referral forms to sw.genetics@wales.nhs.uk. If the referral is urgent call 01792 285 978. If the patient is living in South East Wales, send referral forms to: All Wales Medical Genomics Service, Institute of Medical Genetics, UHW, Heath Park, Cardiff, CF14 4XW, or contact 02921 842577 for urgent referrals.

6.2 Thrombophilia

If hereditary thrombophilia is detected there is no increase in live birth rates if treated with anticoagulants. **In antiphospholipid syndrome**, there is evidence that treating with a combination of aspirin and heparin improves outcomes if couples have had 3 or more PL. **Low-dose aspirin should be started pre-conception, and heparin (low molecular weight or unfractionated) added upon confirmation of positive pregnancy test**. Both should be continued until delivery.

6.3 Metabolic / endocrine

Thyroid

Overt hypothyroidism should be treated with thyroxine to establish euthyroidism. Treatment of subclinical hypothyroidism has conflicting evidence and should be considered on a case-by-case basis. On the one hand, treating subclinical hypothyroidism may reduce the risk of miscarriage, however a high level of free thyroxine has the potential to cause neurodevelopmental effects on the fetus. Regardless of decision chosen, thyroid function should be checked early in any future pregnancies. Treating isolated TPOAb in euthyroid patients is not recommended.

Hyperprolactinaemia

Small studies have shown that bromocriptine may improve the live birth rate in patients with hyperprolactinaemia and this can therefore be considered if elevated prolactin is detected.

Other

Although testing for elevated homocysteine levels is not recommended, if detected consideration may be given to high dose folic acid and vitamin B6 supplementation, or a combination of low dose aspirin and heparin – though evidence is from small studies only. There is insufficient evidence to recommend hCG / progesterone supplementation or the use of metformin in improving live birth rates in patients with RPL.

6.4 Uterine anomalies

Surgical management of septate uterus could be considered as there is some evidence for a reduction in miscarriage rate. However, there are concerns about the possible impact on fertility and therefore decision to operate should be individualised. These patients should be referred to the fertility team for consideration of this.

There is not enough evidence to recommend treatment for other congenital uterine anomalies, or acquired anomalies such as fibroids, polyps or intra-uterine adhesions. In addition, there is evidence of risk associated with uterine surgery including development of adhesions, pregnancy complications and uterine rupture in labour.

Recurrent second trimester PL may be associated with cervical weakness and patients should be offered cervical length assessment between 16 and 24 weeks in line with national guidelines (NICE). Cervical cerclage can be considered in those patients found to have a shortened cervix and previous second trimester PL.

6.5 Male factors

Modification of lifestyle factors known to impact sperm quality should be recommended. There is no evidence that antioxidant supplementation or treating varicoceles improves outcomes in couples with RPL. Sperm selection is not recommended as a treatment.

6.6 Unexplained RPL

There are limited recommended treatments for unexplained RPL. The results of the PRISM trial have shown that vaginal progesterone pessaries produce a very small improvement in outcome for women with RPL who suffer bleeding in early pregnancy – this may therefore be offered in this subgroup of women. If couples request specific information, there is no evidence that any of the following improve outcomes:

- Intravenous immunoglobulins
- Lymphocyte immunization therapy (additional risks to maternal blood pool significant)
- Glucocorticoids such as prednisolone
- Heparin / low dose aspirin
- High dose folic acid
- Intralipid
- Granulocyte colony stimulation factor (G-CSF)
- Endometrial scratch

6.7 Alternative therapies

There is insufficient evidence for an improvement in live birth rates with vitamin supplements. If asked specifically ensure recommendation is pregnancy safe. There is insufficient evidence that the following improve outcomes in couples with RPL:

- Chinese herbal remedies
- Acupuncture
- Homeopathy
- In vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI)

7. Prognosis

The live birth rate is good for most couples with RPL. On average, 75% have a subsequent pregnancy surviving to >24 weeks. If a fetal heartbeat is detected at 8 weeks gestation the outcome of pregnancy is successful in 98% (reaching >99% if seen at 10 weeks or more). The best predictors of success in a subsequent pregnancy are maternal age and number of previous PL. Table 1 (in section 2.1)) gives predicted success rate of subsequent pregnancy in terms of percentage live birth rates, dependent on number of previous PL and maternal age.

Appendix 1 – Abbreviations

ANA	Anti-nuclear antibody
ACA	Anticardiolipin antibody
Array-CGH	Array-based comparative genomic hybridization
βhCG	Beta human chorionic gonadotrophin
BMI	Body mass index
DNA	Deoxyribonucleic acid
ESHRE	European Society of Human Reproduction and Embryology
G-CSF	Granulocyte colony stimulating factor
HLA	Human leukocyte antigen
HSG	Hysterosalpingogram
ICSI	Intracytoplasmic sperm injection
IgG, IgM	Immunoglobulin G and M (antibodies)
IVF	In vitro fertilisation
LA	Lupus anticoagulant
LH	Luteinising hormone
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PCOS	Polycystic ovarian syndrome
PGT	Prenatal genetic testing
PL	Pregnancy loss
RCOG	Royal College of Obstetricians and Gynaecologists
RPL	Recurrent pregnancy loss
T4	Thyroxine
TPOAb	Thyroid peroxidase antibody
TSH	Thyroid stimulating hormone
VTE	Venous thromboembolism
3D	Three dimensional

Appendix 2 – Referral form for prenatal genetic counselling

Early Pregnancy Unit
Singleton Hospital
Sketty Lane
Swansea
SA2 8QA

Date of referral:

Patient details/addressograph:

Name: ……

Identification number: …….

Date of birth: ……

Contact number: …….

Dear Genetics team,

We would be grateful for your review of the above patient regarding her diagnosis if recurrent pregnancy loss. Clinical details can be found below.

History: Reason for referral:

Yours sincerely,

Name of referring clinician: ……..

Contact details: ……..