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Review

Current management of recurrent pregnancy loss

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Key content
- Referral criteria to recurrent pregnancy loss (RPL) services vary, owing in part to a lack of consensus on the definition of RPL.
- Good quality evidence is limited, and controversies exist on recommendations for investigations and management of RPL.
- People with RPL will most likely achieve a live birth in their next pregnancy but should have an individualised approach that identifies and corrects any modifiable risk factors and offers appropriate psychological support.

Learning objectives
- To look at the variations in definition and aetiology of RPL and use current evidence available for recommendations towards investigations and management of RPL.
- To be familiar with evidence-based guidelines published by the Royal College of Obstetricians and Gynaecologists, the American Society for Reproductive Medicine and the European Society of Human Reproduction, as well as recently published data, which will help to improve clinical outcome utilising the interventions with proven efficacy.

Ethical issues
- Differences in referral criteria and the controversies around RPL mean there can be considerable variation in how these patients are managed between services.
- The lack of good quality evidence can result in patients opting for management strategies with unproven efficacy.

Keywords: live birth / miscarriage / pregnancy / progesterone / recurrent pregnancy loss

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Introduction

The management of recurrent pregnancy loss (RPL) is a challenging clinical scenario with associated psychological trauma. It can be frustrating for both patients and clinicians. It is based on various limited evidence and several controversies exist. International evidence-based guidelines have been separately published in recent years by the Royal College of Obstetricians and Gynaecologists (RCOG) in 2011,[1] the American Society for Reproductive Medicine (ASRM) in 2012[2] and the European Society of Human Reproduction (ESHRE) in 2017;[3] however, they all have significant differences. The RCOG is in the process of updating the Green-top Guideline[1] on the topic; the updated version is to be published soon. This article provides a systematic and evidence-based evaluation of the current management of RPL.

Definition of recurrent pregnancy loss

In the UK, RPL has been traditionally defined as the loss of three or more consecutive pregnancies before 24 weeks of gestation. It affects 1–3% of all people trying to conceive.[3] However, there is a lack of consensus on this definition.

A miscarriage is the spontaneous demise of a pregnancy in utero before the fetus reaches viability. In the UK, this definition applies up to 23 weeks and 6 days of gestation; however, some countries use a definition of up to 20 weeks of gestation. While the RCOG, in their Green-top Guideline published in 2011,[1] defines RPL as the loss of three or more consecutive pregnancies, the updated RCOG draft guideline states the miscarriages do not necessarily have to be consecutive to be defined as recurrent miscarriage. ASRM defines RPL as two or more failed clinical pregnancies.[2] The

ESHRE definition is the loss of two or more pregnancies and, although it does not specify whether these should be consecutive, it acknowledges that this definition may need extending or constricting.[3]

Another important difference between the definitions is whether biochemical pregnancies are included. The ASRM guidance only includes clinical pregnancies and requires either ultrasound or histological confirmation of a pregnancy,[2] whereas the RCOG guidance considers pregnancy from conception, so includes biochemical pregnancies as well.[1] This could be an important consideration because the risk of losing three biochemical pregnancies is higher than losing three clinical pregnancies (22% versus 0.3%).[4]

Table 1 shows a comparison of the definitions used for RPL in the RCOG, ASRM and ESHRE guidance.

While there is variation in the definitions for RPL, patients experience considerable distress regardless of whether they have lost two or three pregnancies, or whether the losses are consecutive or non-consecutive. Further, the proportion of positive test results in RPL investigations and management options remain the same regardless of the definitions used.[5]

Epidemiology

Considering the differences in definitions, it is difficult to accurately calculate the prevalence of RPL. While one in eight recognised pregnancies end in pregnancy loss, the prevalence of RPL is about 1–3%.[3]

Table 1. Summary of recurrent pregnancy loss definitions used in different guidance.

Parameter	RCOG 2011[1]	ASRM 2012[2]	ESHRE 2017[3]
Pregnancy	All pregnancy losses not further defined	Clinical pregnancy defined by ultrasound/ histological examination	Serum/urinary human chorionic gonadotrophin (HCG) + ectopic/ molar pregnancies not included in definition
Weeks of gestation	Up to 24 weeks	Only mentions that majority is lost prior to 10th week	Up to 24 weeks
Recurrence	3	2	2
Consecutive	Consecutive	Consecutive	Consecutive or non-consecutive

Most spontaneous pregnancy losses are caused by embryonic aneuploidy, which in turn is mainly associated with chromosome segregation errors in oocytes.[6] Potentially, multiple interconnected factors cause these errors, such as a reduction in activity of the spindle activity checkpoint, cohesion deterioration resulting in nondisjunction during meiosis and telomere shortening, to name a few. However, all their incidences increase with the prolonged arrest of human oocytes, which is the reasoning behind maternal age having such a strong influence and being an independent risk factor for RPL.[6] Table 2 shows the age-related risk of miscarriage taken from the RCOG 2011 guidance.[1] The incidence of RPL occurring by chance for women in the age group 20–24 is 0.13% compared with around a 100-fold increase for the age group 40–44 (13.3%).[4] This suggests that for women over 40 years of age, the most likely causative risk factor is untreatable. It is strongly recommended that this information is provided sensitively to RPL patients, as this could affect choices of further investigations or treatments.

A summary of epidemiological factors and their potential effects on the risk of pregnancy loss are shown in Table 3.[7–10]

Aetiology

A 2018 study[11] into RPL aetiology showed only 26% of the patients reviewed had an explained cause, with the rest not given an aetiology or a causative reason.

Chromosomal abnormalities of the fetus

Chromosomal abnormalities are the commonest cause of pregnancy loss. They account for around 70% of early pregnancy losses, although only around 20% of those occurring between 13 and 20 weeks of gestation.[12] Numerical chromosomal abnormalities are commonest and

Table 2. Age-related risk of miscarriage[1]

Maternal age (years)	Miscarriage risk (%)
12–19	13
20–24	11
25–29	12
30–34	15
35–39	25
40–44	51
≥45	93

Table 3. Epidemiological factors and their potential effects on the risk of pregnancy loss

Factor	Effect on risk of pregnancy loss	Additional notes
Alcohol	No evidence as direct cause for RPL	Sensible to avoid excessive intake
Caffeine	No evidence as direct cause for RPL	Sensible to avoid excessive intake
Exercise	High-intensity occupation activity poses a risk	Sensible exercise levels encouraged
Family history of pregnancy loss	Women who miscarry are more likely to have a family history of pregnancy loss[7]	Further research is still needed
Maternal age	Risk increases as age advances (see Table 2)	Aneuploid pregnancy loss number specifically increases
Occupational / environmental exposures	No evidence as direct cause for RPL	Avoid exposure to possible hazardous substances during pregnancy
Paternal age	Risk increases in advanced paternal age, significantly after age 40[8]	Less pronounced effect than maternal age
Previous pregnancy loss	Increases with the number of previous pregnancy losses[9]	Percentage of pregnancy losses with euploidy increase
Smoking	No evidence as direct cause for RPL	Associated with poor obstetric outcomes if either partner smokes
Stress	No evidence as direct cause for RPL	RPL can cause significant stress
Weight/BMI	Risk increases as BMI increases above 25 Evidence from assisted reproductive treatments[10]	Associated with obstetric complications

include trisomy (52%), polyploidy (21%) and monosomy (13%).[13] A trisomy is believed to occur as a result of nondisjunction during maternal meiosis I. The risk of a chromosomal abnormality of the fetus is higher in women older than 35 years of age,[12] which supports the association of aneuploidy and increasing maternal age.

A recent meta-analysis showed no difference in the percentage of chromosomal abnormalities found in pregnancy loss tissue between those with sporadic pregnancy losses and those with RPL.[14]

Parental chromosomal abnormalities

Parental carriership of a chromosomal abnormality occurs in 2–6% of patients with RPL.[2,13] Most commonly, these are balanced reciprocal or Robertsonian translocations, so have a high chance of a healthy live birth in a future pregnancy.

Congenital uterine anomalies

Congenital uterine anomalies (CUAs) are frequently associated with RPL patients, with a prevalence of 13.3% in those with a history of miscarriage compared with 5.5% in an unselected population. In high-risk populations, uterine septae are commonest.[15,16] Most people with a CUA experience a normal reproductive outcome.[17]

Acquired uterine anomalies

Although some acquired uterine malformations such as fibroids,[18] polyps[19] and uterine adhesions[20] have been found in people with RPL, there is a lack of evidence of a direct association.

Chronic endometritis

Chronic endometritis (CE) has been associated with RPL in several studies; however, the actual prevalence is hard to describe because there is lack of consensus on the best diagnostic method.[3] In a 2020 observational prospective longitudinal study, [21] which included a systematic review and meta-analysis, use of immunohistochemistry to quantify $CD138^{+}$ cells was helpful in the diagnosis of CE and for predicting further reproductive outcomes. The continuing Chronic Endometritis and Recurrent Miscarriage (CERM) trial[22] will hopefully provide more evidence when it is completed. In this trial, women with a history of two or more consecutive pregnancy losses and who test positive for chronic endometritis, will be treated either with 100 mg doxycycline twice daily or a placebo for 14 days and their pregnancy outcomes will be compared.

Cervical insufficiency

Cervical insufficiency is associated with RPL more commonly in the second trimester. There are no recommended investigations for cervical insufficiency outside of pregnancy, so further discussion is outside the scope of this review.

Hydrosalpinx

A 2019 systematic review and meta-analysis[23] suggested that the presence of a hydrosalpinx can increase the risk of pregnancy loss and that treatment can reduce this risk. However, a caution: most of the women included in the review were specifically undergoing in vitro fertilisation (IVF), so the findings should not be generalised to people conceiving naturally.

Hereditary thrombophilia

Hereditary thrombophilias include Factor V Leiden gene mutations, prothrombin gene mutations and deficiencies in antithrombin, protein C and protein S. Although they may be associated with adverse pregnancy outcomes, the evidence is weak for any association with RPL.[3] A 2019 review[24] showed no evidence that treatment of hereditary thrombophilia improves pregnancy outcomes in RPL.

Acquired thrombophilia

Antiphospholipid syndrome (APS) is the commonest acquired thrombophilia, with a prevalence of 5–20% in RPL patients compared with 2% in those with a low-risk obstetric history.[2,3] It has been described as the most important treatable cause of RPL.[1]

Thyroid disorders

It has been known for some time that overt hypothyroidism causes an increased risk of RPL, so should be treated.[25] There is no link known between hyperthyroidism and RPL;[3] however, the picture has been less clear for subclinical hypothyroidism (elevated thyroid-stimulating hormone [TSH] and normal free thyroxine) and thyroid autoimmunity. Some of this lack of clarity appears to come from newer guidelines suggesting a new upper limit of normal for TSH of 4.0 mIU/L rather than the previous 2.5 mIU/L.[26]

A systematic review and meta-analysis in 2020[27] showed no association between subclinical hypothyroidism and RPL. Although there is an association between RPL and thyroid autoimmunity, evidence suggests that treatment of these patients does not alter their outcome.

Diabetes mellitus

Diabetes mellitus is associated with pregnancy loss: a high haemoglobin A1C (HbA1C) in the first trimester increases the risk of pregnancy loss and fetal malformation.[1] Well-controlled diabetes mellitus is not a risk for RPL.

Prolactin disorders

There is no clear evidence on the effect of either prolactin deficiency or hyperprolactinaemia on RPL. However, there is evidence that bromocriptine treatment of hyperprolactinaemia increases the live birth rate.[28]

Polycystic ovary syndrome

There is some association between polycystic ovary syndrome (PCOS) and pregnancy loss risk. This is potentially related to hyperinsulinemia and hyperandrogenaemia, but there is no evidence to suggest PCOS predisposes to RPL.[29]

Ovarian reserve

A 2020 systematic review and meta-analysis[30] showed an association between diminished ovarian reserves and RPL. However, this review suggests more evaluations are needed for any prognostic value of carrying out anti-müllerian hormone (AMH) or antral follicle counts (AFC).[30]

Luteal insufficiency

There is no clear definition for luteal insufficiency, and it could be caused by several pathologies, including prolactin disorders. There are no evidence-based investigations to identify a prognostic value for luteal insufficiency, nor any evidence of a direct association between it and RPL.

Male factors

There is a growing body of evidence to suggest an association between RPL and poor-quality sperm; however, this remains a controversial subject. A 2020 systematic review and meta-analysis[31] showed that an increased sperm DNA fragmentation index (DFI) was associated with RPL but studies on treatment and prognosis are still lacking.

Unexplained recurrent pregnancy loss

Some RPL patients will never identify a reason for their pregnancy losses. Several adjuvant treatments have been considered for these groups, with mixed outcomes. A retrospective cohort review published in 2018[11] specifically looked at adjuvant treatment in RPL. It concluded that more than two-thirds of those with RPL will have a live birth in a subsequent pregnancy, and empirical adjuvant treatment for these patients does not appear to offer any additional benefit.[11]

Who should be referred for review?

In the UK, referral to an RPL service is common after a minimum of three consecutive pregnancy losses, and this has been the case ever since the publication of the RCOG guidance in 2011.[1] More recent guidance, such as that published by ESHRE in 2017,[3] has suggested that referral could be considered after the loss of two or more pregnancies, but the need for further research is recognised.

Setting too low a threshold number of pregnancy losses needed for a referral to a RPL service can lead to large numbers of referrals. It can also cause additional anxiety and stress to people who have an otherwise high chance of a successful outcome in a subsequent pregnancy, as well as potentially subjecting patients to unnecessary investigations. However, setting a threshold too high could mean people experience avoidable pregnancy losses. The rate of abnormal test results for people undergoing RPL investigations is not altered by whether the pregnancy losses are consecutive or not, or even if there is a past history of live birth.[32]

A systematic review and meta-analysis looking at performing diagnostic investigations after either two or three pregnancies losses was published in 2020.[5] It included 8301 couples with recurrent pregnancy loss from 21 different

studies. This review looked at the prevalence of abnormal test results and showed no overall difference between the two groups, although the quantity and quality of some evidence was poor, so any recommendations should be drawn with care. While the study supports the notion that investigations may be carried out after only two pregnancy losses, the overall low prevalence of abnormal test results, as well the limited amount of evidenced-based treatment available for most abnormal test results, warrant caution in recommending this routinely. Consideration should also be given to both the financial and research implications of including large numbers of low-risk couples with an overall good prognosis for future pregnancies, in a group subjected to investigations and treatments for RPL.

Management

The management of people with RPL is multifactorial and should include lifestyle modification, psychological support and specific treatment of any identified cause.

Ideally, patients should attend as a couple to the RPL clinic. The first consultation should include a full medical, obstetric and family history with information on the lifestyle of both male and female partners, such as smoking, excessive alcohol consumption, excessive exercise, being overweight or underweight.

RPL has a considerable emotional impact on those who endure it. The feelings described after a pregnancy loss (for example, sadness, tearfulness, guilt, emptiness) can often become intensified with recurrent losses.[33] It is therefore important for clinicians who look after those with RPL to consider their psychosocial needs when planning any treatment and care plans.

The impact of looking after these patients on the staff involved should also not be underestimated. This impact includes not only that on the doctors who see the patients, but the nursing and other support staff in clinics, and the secretarial support staff – these people are often the ones answering multiple phone calls and emails from patients with heavily invested emotions.

Investigations

The differences in the investigations recommended by the guidance from the RCOG, ASRM and ESHRE are shown in Table 4.

Chromosomal analysis

Box 1 describes several different genetic techniques available for analysing products of conception (POC).[34,35]

When to analyse POC is another contentious issue within RPL management. Some differences in recommendations can be explained by the progress from karyotyping to aCGH. With referral criteria to an RPL service requiring three consecutive first-trimester pregnancy losses, often, POC analysis is not carried out until a third pregnancy loss, if at all. A proposal has been made to use the results of chromosomal analysis of POC at the time of a second pregnancy loss to assess whether further investigations are required at that point in time.[35] Such a move to refer patients after two pregnancy losses rather than three could help with the pressures put on RPL services. This proposal is illustrated in Figure 1.

Genetic testing of POCs may be of psychological benefit to patients, as it could help provide them with a reason for the pregnancy loss.

Ultrasound

Commonly, 2D pelvic transvaginal ultrasound scans are used as a first-line investigation for uterine anomalies. These, as well as hysterosalpingography, are good screening tests in low-risk women; however, 3D pelvic ultrasound is recommended to diagnose and classify CUAs accurately.[16] Magnetic resonance imaging (MRI), laparoscopy and hysteroscopy can all be considered on an individual basis for complex CUAs or acquired uterine anomalies.

Thrombophilia screening

Investigations for hereditary thrombophilias should only be carried out in the presence of additional risk factors, including a strong personal or family history of thrombosis or thrombophilia,[2,3] or in the context of research.[3]

Diagnosis of APS requires a clinical manifestation (vascular thrombosis or pregnancy morbidity) and the presence of at least one antiphospholipid antibody (aPL) on two or more occasions at least 12 weeks apart. The commonly screened aPLs are lupus anticoagulant (LA), anticardiolipin antibodies (ACA, IgG and IgM) and β2 glycoprotein I antibodies (aβ2GPI, IgG and IgM).[35]

Endocrinological and metabolic investigations

A TSH assessment is recommended to screen for hypothyroidism, followed by a thyroxine (T4) assessment if TSH levels are greater than 4.0 mIU/L. An HbA1C test should be used to investigate for diabetes mellitus, particularly if there are considerable risk factors or any clinical evidence suggestive of diabetes mellitus. If there are any clinical signs of hyperprolactinaemia (oligomenorrhea/amenorrhea), then a prolactin level test should be requested.

A summary of the current evidence and recommendations for including endocrinological and metabolic disorders in the investigation of RPL is shown in Table 5.[1,3,25,27-30]

Immunology investigations

Case–control studies have shown an association between antinuclear antibodies (ANA) and RPL, with some evidence that their presence has a negative effect on prognosis[37]

Table 4. Summary of recurrent pregnancy loss investigations used in different guidance

Disorder	RCOG 2011[1]	ASRM 2012[2]	ESHRE 2017[3]
General	–	Medical history relating to RPL, life style	Medical, obstetric and family history
Genetics	Cytogenetic analysis on POC on 3 and subsequent pregnancy loss If unbalanced structural chromosome abnormality, then parental karyotyping	Parental karyotyping. Karyotyping of POC may be useful	Parental karyotyping not on a routine basis. Analysis of pregnancy tissue for explanatory purposes, using aCGH
Hereditary thrombophilia	Only in women with 2nd trimester loss	No screening unless in context of research or in case of additional risk factors for thrombophilia	No screening unless in context of research or in case of additional risk factors for thrombophilia
APS	LA and ACA on 2 occasions 12 weeks apart	LA, ACA and aβ2GPI	LA, ACA and aβ2GPI
Endocrine	–	TSH / HbA1C	TSH and TPO-Ab, if abnormal then do T4
Uterine anomaly	TVS/assess further with hysteroscopy/3D US if abnormal	SHG/HSG/ hysteroscopy	3D US
Male factor	–	Sperm DFI not recommended	Sperm DFI can be considered for explanatory purpose
Immunology	(NK cell, HLA typing) not recommended outside a research context.		

Abbreviations: aβ2GPI = β2 glycoprotein I antibodies; ACA = anticardiolipin antibodies; aCGH = array-based comparative genomic hybridisation; DFI = DNA fragmentation index; HLA = human leukocyte antigen; HSG = hysterosalpingogram; LA = lupus anticoagulant; NK = natural killer; POC = products of conception; SHG = sonohysterogram; TPO-Ab = thyroid peroxidase antibodies; TSH = thyroid stimulating hormone; TVS = transvaginal scan; US = ultrasound.

However, there is currently no evidence-based proven treatment for this group.

A systematic review and meta-analysis[38] explored associations between RPL and NK cells in both peripheral blood and endometrial samples. However, any prognostic value or treatment options remain unclear and should only be offered in the context of clinical research.[38] Several other immunological tests, including those for human leukocyte antigen (HLA), anti-histocompatibility (anti-HY) antibodies and cytokines also have various weak associations with RPL, but no evidence-based proven prognostic value or treatment is available.[39]

Infection investigations

Severe infections have been associated with spontaneous pregnancy losses, but their role in RPL is unclear.[40] Investigations for infection would be prudent if clinical signs and symptoms are present. Routine screening for chronic endometritis has no evidence base, but samples taken for research is reasonable.

It is advisable to offer rubella immunity screening to RPL patients, as it is to patients undergoing infertility investigations.

Male factors

There is a growing body of evidence to suggest an association between RPL and poor-quality sperm; however, this remains a controversial subject. A 2020 systematic review and meta-analysis[31] showed that an increased sperm DNA fragmentation index (DFI) was associated with RPL, but studies on treatment and prognosis are still lacking.

Summary of investigations

A summary of the current recommended investigations for patients presenting with RPL are shown in Table 6.

Treatments

Like investigations, the different treatment recommendations differ between published guidelines. A summary of the guidance published by the RCOG, ASRM and ESHRE is shown in Table 7.

While evidence-based treatments are limited for RPL, patients prefer to have a plan for the next pregnancy. Such

Box 1. Genetic techniques available for analysing products of conception (POC)

Karyotyping

- Limited by:
  - failure of cell culture (rate of 20%)
  - maternal cell contamination (MCC) (rate of 22%)

Fluorescence in situ hybridisation (FISH)

- In practice, out of the 24 chromosome probes, only the 5–7 commonly involved in aneuploidy are selected.

Array-based comparative genomic hybridisation (aCGH)

- avoids the limitations of cell culture failure and MCC
- most recommended if genetic analysis of POC is to be performed.

Next generation sequencing (NGS)

- currently no evidence to replace any other technique

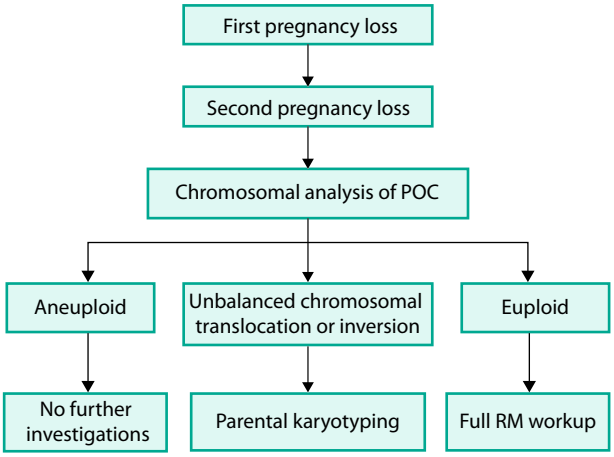

Figure 1. Proposed testing algorithm for recurrent pregnancy loss based on chromosomal analysis of products of conception. Adapted with permission from Popescu et al.[35]Abbreviations: POC = products of conception; RM = recurrent miscarriage

plans are usual dependent on if any modifiable causes are found.

Chromosomal abnormalities

Patients with chromosomal abnormalities should be referred for genetic counselling. Although the option of preimplantation genetic testing (PGT) has been shown to reduce the number of pregnancy losses, there is no overall difference in the live birth rate.[40]

The STAR (Single Embryo Transfer of Euploid Embryo) study, a multinational multicentre randomised controlled trial published in 2019, showed no improvement in pregnancy outcomes from the use of in vitro fertilisation (IVF) in combination with PGT for aneuploidy screening (PGT-A).[42]

Anatomical abnormalities

There is evidence to show improved live birth rates after treatment for fibroids that distort the uterine cavity.[18] There is a lack of evidence for a direct association, or that treatment improves outcomes, for other acquired uterine malformations such as polyps[19] and uterine adhesions.[20]

There is evidence that hysteroscopic septal division reduces pregnancy loss rates, resulting in live births. However, owing to a lack of high-quality evidence of the efficacy and safety of surgical treatment, this should only be offered on an individual basis by experienced specialists.[16]

Table 5. Summary of the current evidence and recommendations for including endocrinological and metabolic disorders in the investigation of recurrent pregnancy loss (RPL)

Disorder	Evidence	Recommended Investigation
Diabetes mellitus	Poor control associated with pregnancy loss and fetal malformations[1]	Yes
Hyperprolactinaemia	Treatment of hyperprolactinaemia is of benefit[27]	Yes if oligo/ amenorrhea
Thyroid disorders		
Hyperthyroidism	No association with RPL[2]	No
Hypothyroidism	Associated with adverse pregnancy complications[24]	Yes
Subclinical hypothyroidism	No association with RPL[26]	No
Thyroid autoimmunity	Associated with RPL but no effect from treatment[26]	No
Androgen disorders	No association with RPL[2]	No
Diminished ovarian reserve	Diminished ovarian reserves association with RPL but no prognostic value shown[28]	No
Hyperhomocysteinemia	No association with RPL[2]	No
Luteal insufficiency	No association with RPL[2]	No
Luteinising hormone	No association with RPL[2]	No
PCOS	No association with RPL[29]	No
Vitamin D deficiency	No association with RPL[2]	No

Table 6. Summary of recommended investigations for recurrent pregnancy loss

Disorder	Recommended	Individually assessed	No evidence to do
Chromosomal abnormalities	Pregnancy tissue	Parental karyotyping	–
Anatomical abnormalities	2D/3D pelvic scan	MRI, laparoscopy, hysteroscopy	–
Thrombophilia	Acquired thrombophilia - LA, ACA (IgG and IgM), aβ2GPI (IgG and IgM)	Hereditary thrombophilia	–
Endocrinological	TSH + HbA1C	T4, Prolactin	TPO-Ab, Testosterone, SHBG
Immunological	–	ANA	NK cells / HLA / AHYA /Cytokines (research only)
Infection	Rubella immunity screening	HVS / chlamydia / Endometrial biopsy	TORCH screen
Male factor	–	Sperm DNA fragmentation index	–

Abbreviations: aβ2GPI = β2 glycoprotein I antibodies; ACA = anticardiolipin antibodies; AHYA = anti-histocompatibility antibodies; ANA = antinuclear antibodies; HLA = human leukocyte antigen; HVS = high vaginal swab; LA = lupus anticoagulant; MRI = magnetic resonance imaging; SHBG = sex hormone binding globulin; T4 = thyroxine; TORCH = toxoplasmosis rubella cytomegalovirus herpes simplex; TPO-Ab = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone.

Table 7. Summary of treatment options from different guidelines

Disorder	RCOG 2011[1]	ASRM 2012[2]	ESHRE 2017[3]
Balanced chromosome abnormality	Genetic counselling IVF + PGT optional	Genetic counselling IVF + PGT optional	Genetic counselling IVF + PGT optional
APS	LDA + Heparin	LDA + UFH	LDA (starting preconception) + Prophylactic UF or LMWH (starting from first positive pregnancy test)
Thrombophilia	Insufficient evidence	–	Insufficient evidence (Not recommended unless in the context of research)
Endocrinology	Insufficient evidence	Treat maternal endocrine disorders (thyroid dysfunction, diabetes, and hyperprolactinemia) Other treatments not advised	Levothyroxine for hypothyroidism Bromocriptine for hyperprolactinemia Other treatments not advised
Uterine anatomy abnormality	Insufficient evidence	Consider surgical correction	Insufficient evidence Septum correction in the context of a trial
Unexplained	Supportive care in a dedicated EPAU	TLC, counselling, support	Supportive care No therapeutic intervention
Others	–	–	No immunological treatment No progesterone

Abbreviations: EPAU = early pregnancy assessment unit; IVF = in vitro fertilisation; LDA = low-dose aspirin; LMWH = low-molecular-weight heparin; PGT = preimplantation genetic testing; TLC = tender loving care; UFH = unfractionated heparin.

Acquired thrombophilia

The use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) combined with low-dose aspirin has been shown to improve live birth rates[36,43] and birthweights[43] in RPL patients. LMWH has the benefit of once-daily administration and a superior safety profile for thrombocytopaenia and osteopenia over UFH.[36]

A recommended treatment plan for APS patients is to start low-dose aspirin and a prophylactic dose of LMWH from a first positive pregnancy test. However, these patients should be recommended to discuss plans for pregnancy in advance with their specialist.

Immunological treatments

A systematic review and meta-analysis published in 2018[44] showed no improvement in the live birth rate when looking at the role of immunotherapy for RPL. Use only in the context of research is recommended.

Endocrinological treatments

If diabetes mellitus, thyroid disease, or hyperprolactinaemia are not well controlled, then gaining preconceptual advice and input from specialists with an interest in pregnancy care is recommended. A TSH level of <4.0 mIU/L should be targeted, with no additional treatment for euthyroid women with thyroid peroxidase antibodies.[27]

A 2009 systematic review and meta-analysis[45] showed no effect of metformin on the pregnancy loss risk for PCOS patients.[45]

Male factor treatments

Although no specific evidence-based treatment for male factors is available, giving lifestyle modification advice, such as on smoking, obesity and excessive exercise, to improve sperm DNA damage is recommended.[3]

A 2019 Cochrane review[46] looked at antioxidant use for male subfertility. Although this was low-quality evidence, it suggested antioxidant supplementation in subfertile males may improve life birth rates. Individual assessment for use could be consider, although this has not been directly examined with RPL.

Unexplained pregnancy loss treatments

For several years, progesterone has been given empirically for unexplained pregnancy loss. Indeed, a 2019 Cochrane review

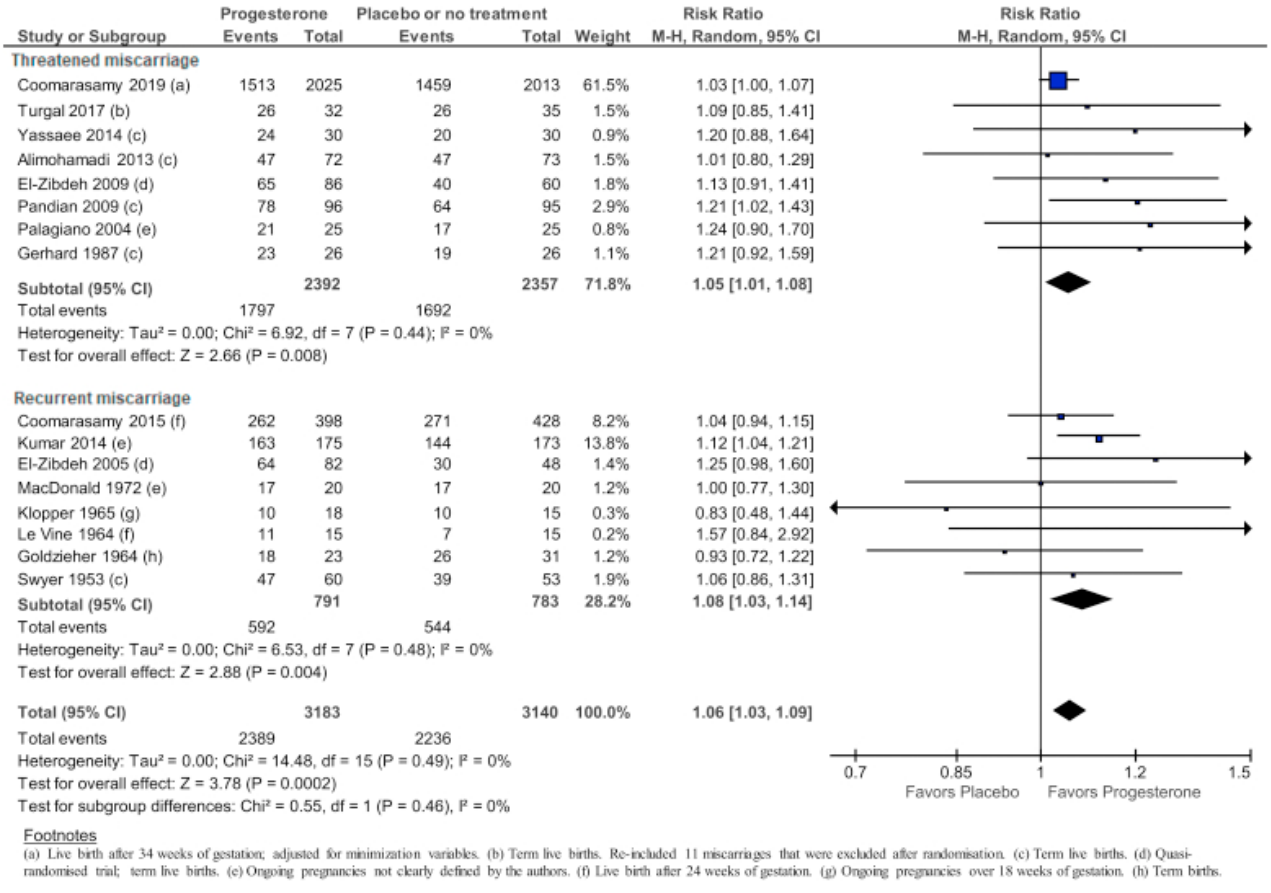

Figure 2. Live birth or continuing pregnancy outcome for all progesterone and progestogen studies.[47]

suggested that progesterone supplementation for RPL may reduce the rate of pregnancy loss in further pregnancies.[47]

Figure 2 summarises the findings of a 2020 meta-analysis[48] showing the live birth rate or continuing pregnancy outcomes with progesterone versus placebo or no treatment, which increased significantly to 75% from 71% (RR 1.06; 95% confidence interval [CI] 1.03–1.09; P = 0.0002) with progesterone. This same paper specifically analysed the results from two trials; one exploring the use of vaginal micronised progesterone on live birth rates in RPL (PROMISE),[49] and one exploring threatened pregnancy loss (PRISM).[50] This analysis showed a small but positive treatment effect dependent on the number of pregnancy losses. The authors believed the dual risk factors of early pregnancy – bleeding and a history of one or more previous pregnancy loss(es) – identifies high-risk women for whom progesterone is of benefit.[48]

This information should be communicated to patients at high risk of pregnancy losses. If a joint decision is reached to treat with progesterone, then we propose the use of the following regimes of vaginal micronised progesterone:

- Women with vaginal bleeding and a history of one or more previous pregnancy loss(es):
  - 400 mg twice daily
  - starting at the time of presentation with vaginal bleeding and continued until 16 completed weeks of gestation
- Women with a history of three or more previous pregnancy loss(es):
  - 200 mg twice daily
  - starting at the time of presentation with vaginal bleeding and continued until 12 completed weeks of gestation;
  - but if any vaginal bleeding, then increasing to 400 mg twice daily and continued until 16 completed weeks of gestation

General treatments

Lifestyle advice should include limiting alcohol and caffeine intake, stopping smoking, and maintaining a healthy exercise

Table 8. Summary of recommended treatment options for recurrent pregnancy loss.

Disorder	Recommended	Individually assessed	No evidence to do
Chromosomal abnormalities	PGT for structural rearrangements	PGT-A	–
Anatomical abnormalities	Surgical treatment of fibroids	Surgical correction of uterine septum, polyps or adhesions	Surgical treatment to other müllerian abnormalities
Thrombophilia	UFH or LMWH and LDA for APS	–	Treatment for congenital thrombophilia
Infection	Antibiotics if evidence of infection	–	Prophylactic antibiotics
Immunological	–	–	Prednisolone, IVIg, Intralipids Partner lymphocyte transfusion
Endocrinological	Treatment of diabetes Treatment of overt hypo/hyperthyroidism Treatment of hyperprolactinaemia	–	Treatment for subclinical hypothyroidism, or thyroid peroxidase antibodies Androgens hCG
Male factor	Lifestyle modification	Antioxidants	–
Unexplained	Progesterone	–	–
General	Maintain normal BMI Stop smoking Vitamin D TLC Dedicated RPL clinic	Limit caffeine ≤3 cups a day	–

Abbreviations: APS = antiphospholipid antibody syndrome; BMI = body mass index; IVIg = intravenous immunoglobulin; LDA = low-dose aspirin; LMWH = low-molecular-weight heparin; PGT = preimplantation genetic testing; PGT-A = PGT for aneuploidy; RPL = recurrent pregnancy loss; TLC = tender loving care; UFH = unfractionated heparin.

level and healthy weight/body mass index (BMI).[3] If maternal BMI is ≥30, then high-dose folic acid should be recommended. A discussion about vitamin D supplementation is recommended, both pre-conceptually and during pregnancy.[51]

As well as offering potential treatments, it is important to discuss individualised psychological support and lifestyle advice that can be offered to both partners in an RPL couple. Planning future pregnancies should include offering early pregnancy ultrasound scans and ensuring patients have appropriate contact numbers for early pregnancy units. Patients should be reassured that, despite a diagnosis of RPL, around 70% of patients will achieve a live birth in their next pregnancy.[11]

Summary of treatments

A summary of the current recommended treatments for RPL is shown in Table 8.

Conclusion

Recurrent pregnancy loss is a challenge that causes psychological distress to patients and their partners. The paucity of evidence presents clinicians with dilemmas on what to offer patients. Referral criteria to RPL services vary, owing – in part – to a lack of consensus on the definition of RPL. Good quality evidence is limited, and controversies exist on recommendations for investigations and management of RPL.

Patients with RPL must be reassured that most will achieve a live birth in their next pregnancy. Furthermore, individualised approaches should be created to identify and correct any modifiable risk factors, as well as offering appropriate psychological support.

Disclosure of interests

MRC is on the RCOG Part 1 MRCOG examination sub-committee. KJ is an Associate Editor for *The Obstetrician & Gynaecologist*. He was excluded from editorial discussions and had no involvement in the decision to publish.

Contribution to authorship

MRC researched and wrote the article. AT wrote and edited the article, KJ instigated and edited the article. All authors approved the final version.

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