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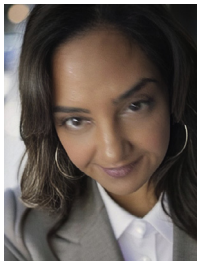
AFFILIATED SOCIETY GUIDELINE

The investigation and management of recurrent early pregnancy loss: a Canadian Fertility and Andrology Society clinical practice guideline



BIOGRAPHY

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KEY MESSAGE

Recurrent early pregnancy loss (REPL) should be considered after two pregnancy losses. Although lacking high-quality evidence to establish a standard of care, consistent pregnancy monitoring, pre-conception counselling and case-specific patient-centered treatment strategies should be considered. Despite uncertainties in diagnosis, patients with REPL have a positive prognosis.

ABSTRACT

This guideline defines recurrent early pregnancy loss (REPL) as two or more losses that occur before 10 weeks gestational age and includes non-consecutive and biochemical losses. Investigations should be considered on an individual basis and may include an evaluation of genetic, anatomical, endocrinological, structural and male-associated factors. Based on the findings and available resources, options for management may include preimplantation genetic testing (PGT) for aneuploidies or PGT for chromosomal structural rearrangements, progesterone supplementation and supportive care. This guideline emphasizes a personalized approach to the problem of REPL, recognizing an overall promising prognosis for this patient population and the avoidance of treatment options that have not been shown to be of benefit.

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KEY WORDS

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INTRODUCTION

Pregnancy loss is a common yet difficult experience for many patients. Early studies in the natural history of conception and pregnancy loss describe the inefficiencies of human reproduction, with over 50% of all conceptions resulting in early pregnancy loss (*Edmonds et al., 1982*). Most of these losses occur prior to the recognition of pregnancy (*Edmonds et al., 1982*; *Wilcox et al., 1988*).

Further cohort studies found that 15% of all recognized pregnancies result in pregnancy loss and as many as 2.6% of patients trying to conceive will present with a history of two or more recognized early losses (*Quenby et al., 2021*). With increased numbers of losses, there is evidence of an increased risk of a further pregnancy loss (*Brigham et al., 1999*; *Clifford and L Regan, 1997*; *Quenby et al., 2021*), even after adjustments for advancing maternal age (*Lund et al., 2012*).

Given the increased risk for subsequent loss and the significant psychological consequences of pregnancy loss for patients (*Farren et al., 2020*; *Kersting and Wagner, 2012*), investigation and management of recurrent pregnancy loss (RPL) is indicated. However, variance in the definition of RPL and a lack of high-quality evidence for evaluation and management leave both clinicians and patients navigating widely accessible, often conflicting and potentially harmful solutions that lack proven efficacy.

The purpose of this guideline is to define recurrent early pregnancy loss (REPL) and provide recommendations for the investigation and management of patients with REPL in a Canadian context. Relevant recommendations were made based on the evaluation of the best available level of evidence and the consensus of the guideline committee.

EPIDEMIOLOGY AND RISK FACTORS FOR PREGNANCY LOSS

Combined data from nine large cohort studies reporting on over 4.6 million pregnancies described an overall pregnancy loss rate of 15.3%. The average prevalence of patients having two pregnancy losses was 1.9% and for three or more pregnancy losses was 0.7% (*Quenby et al., 2021*).

Both reproductive ageing and the number of previous losses are independent and strong predictors of future loss. Aneuploidy increases with age due to a decline in oocyte spindle function, which predisposes ova to random meiotic and further mitotic errors that can result in an abnormal number of chromosomes (*Hassold and Chiu, 1985*). Several cohort studies have reported an increasing risk of pregnancy loss with increasing age at conception from less than 15% under age 35 years and approximately 20% at age 35–39, to 37% at 40–44, and 65% at 45 and older (*Quenby et al., 2021*).

Prior reproductive outcome is also a significant, independent risk factor for future pregnancy loss. The risk of pregnancy loss is lowest in women with no prior loss (11%), increasing by approximately 10% with each additional loss, and reaching 42% for women with three or more losses (*Quenby et al., 2021*).

Summary statements:

1. Due to increased oocyte aneuploidy, reproductive ageing is the most significant risk factor for both sporadic and recurrent early pregnancy loss.

2. With increasing numbers of pregnancy losses, the risk of euploid pregnancy loss increases.

TERMINOLOGY AND DEFINITIONS

A clear definition of RPL is required to guide diagnosis, inform investigations and evaluate treatments. Traditionally, the term 'recurrent pregnancy loss' has been defined as three or more consecutive pregnancy losses (*Rai and Regan, 2006*; *Stirrat, 1990*). However, recently the number of losses has been debated, with no consensus on the inclusion of biochemical losses, pregnancies of unknown location or non-consecutive losses.

In 2012, the Practice Committee of the American Society for Reproductive Medicine (ASRM) defined RPL as 'two or more failed clinical pregnancies', with a clinical pregnancy defined as one documented by ultrasonography or histopathological examination. Evaluation was recommended after two consecutive clinical pregnancy losses (*Practice Committee of the American Society for Reproductive Medicine, 2012*).

The more recently published European Society of Human Reproduction and Embryology (*Becker et al., 2022*) guideline suggests that RPL could be considered after the loss of two or more pregnancies. The inclusion of biochemical losses acknowledges their prognostic value for subsequent pregnancies in patients with recurrent losses (*Kolte et al., 2014*) as well as the significant emotional impact that any early pregnancy loss can have (*Kolte et al., 2015*). This same guideline (*Becker et al., 2022*) defines pregnancy by at least serum or β-human chorionic gonadotrophin, therefore including non-visualized pregnancy losses (biochemical pregnancy losses or resolved pregnancies of unknown location). Ectopic and molar pregnancies are excluded, and implantation failure is also excluded from the definition.

A Canadian retrospective cohort of almost 2000 patients also found that the odds of live birth decreased by 23% with each additional non-visualized or biochemical loss compared with a 25% decrease with each visualized loss (*Bedaiwy et al, 2023*).

A systematic review of 21 studies including 8301 couples with RPL examined the frequency of aetiological factors in those with two compared with three or more prior losses (*van Dijk et al., 2020*). There were no differences in the prevalence of abnormal test results for chromosomal abnormalities (10 studies), uterine anomalies (7 studies), antiphospholipid syndrome (APS; 4 studies), inherited thrombophilia (7 studies) or thyroid disorders (2 studies) between the two groups.

For the purposes of this Canadian Fertility and Andrology Society (CFAS) guideline, REPL is defined as two or more losses that occur before 10 weeks gestational age and includes non-consecutive and biochemical losses. Ectopic and molar pregnancies will be excluded as these aetiologies are distinct, and historically have not been included in any published studies of RPL.

This definition of REPL includes pregnancies before 10 weeks gestational age, and therefore the number of patients eligible for investigation and potential management will be increased. Furthermore, some of the evidence reviewed may have limited generalizability given the varying definitions of RPL used.

However, this definition recognizes the relevance of these early losses on the risk of further loss and the emotional experience of affected patients, while the decision of when to investigate and initiate options for management should ultimately be determined by patient and physician together, taking into account personal experience, maternal age and emotional state.

Summary statement:

3. REPL is defined as two or more losses occurring at less than 10 weeks gestational age, including biochemical and non-consecutive losses.

4. The prevalence of abnormal findings is similar in patients with two early losses compared with those with three or more losses; however, there are no definitive data to suggest that consultation and investigation after two losses increases live birth rate.

Recommendation:

1. Consultation and investigation of a patient for REPL can be initiated after two losses (as the desirable effects probably outweigh the undesirable effect).

INVESTIGATIONS AND TREATMENT OPTIONS IN REPL

Aneuploidy

Approximately 50–70% of sporadic early losses at less than 10 weeks gestational age result from aneuploidy, including trisomy, monosomy and polyploidy (*Hassold and Chiu, 1985*; *Ohno et al., 1991*). The frequency of aneuploidy increases with reproductive ageing and decreases with the gestational age at the time of loss (*Simpson, 1990*).

However, aneuploidy is less commonly found in RPL. A case series of cytogenetic analyses of 234 recurrent (2–20 prior losses) compared with 114 sporadic losses reported a higher proportion of aneuploidy in specimens from first losses (72.3 versus 51.3%; $P < 0.05$) (*Ogasawara et al., 2000*). Similarly, another group reported on 364 pregnancy loss specimens, finding a lower probability of aneuploid loss in recurrent compared with first losses (adjusted odds ratio [OR] 0.48, 95% confidence interval [CI] 0.27–0.85) (*Ozawa et al., 2019*). The probability of a euploid loss also increased with increasing number of losses (*Ogasawara et al., 2000*).

Summary statement:

5. In patients with RPL, the risk of subsequent euploid loss increases with increasing numbers of pregnancy losses.

Cytogenetic analysis of products of conception

An algorithm initiated by the cytogenetic analysis of products of conception (POC) from a second pregnancy loss has been proposed as a cost-effective alternative for the investigation and management of recurrent early loss (*Bernardi et al., 2012*). As opposed to initiating a complete workup after a second pregnancy loss, cytogenetic results can be used to triage patients for further investigation. Aneuploid POC would not warrant further investigation and patients could be reassured that the loss was likely to be secondary to a sporadic genetic event as opposed to an aetiology requiring diagnosis and management.

This algorithm was applied to a cohort of 100 patients who had POC testing of a second or subsequent loss and RPL investigations recommended by the ASRM (*Popescu et al., 2018*; *Practice Committee of the American Society for Reproductive Medicine, 2012*). In this cohort, 67% had abnormal POC testing. Of those with euploid POC, 85% (28/33) had at least one abnormal result on the RPL workup. Alternatively, in those with aneuploid POC, 25% (17/67) had an abnormality in the RPL workup (*Popescu et al., 2018*). When documented aneuploidy and other identified potential aetiologies were combined, only 5% of losses were unexplained in this cohort, which is much lower than the frequently cited figure of 50% (*Practice Committee of the American Society for Reproductive Medicine, 2012*). Following the algorithm, only 33% of patients would have undergone both POC testing and a full RPL workup, resulting in less need for further testing, and significant cost savings (*Popescu et al., 2018*). It was also concluded that the specificity of the full RPL workup was improved over testing the entire cohort.

In Canada, the collection and testing of POC has been difficult in most community settings. Conventional cytogenetic evaluation can only be carried out on fresh tissue, so it is important to consider genetic testing at the time of the pregnancy loss and have a plan in place for POC collection, including the separation and washing of products. Decidual cell contamination of POC may lead to false-negative (46,XX) results (*Bell et al., 1999*). To increase the likelihood of accurate results, uterine evacuation of viable tissue should be performed promptly, with manual removal of POC from the surrounding endometrial curetting and rinsing of POC with sterile saline (*Lathi and Milki, 2002*). It should be noted that approximately 10–40% of tissue fails to grow in culture to allow for cytogenetic analysis (*Benkhalifa et al., 2005*; *Stephenson et al., 2002*).

Commercial kits for the analysis of self-collected POC including sampling materials (buccal swabs) to rule out maternal contamination are also available. While the benefits of commercially available tests include convenience, home-based testing, easy shipping and timely result reporting, these kits come at a cost to the patient.

Recommendation:

2. Patients who experience an early pregnancy loss with a history of one or more previous losses should be informed about the option of cytogenetic analysis of POC (for diagnosis and guidance of further management).

Preimplantation genetic testing for aneuploidies

Since more than half of early pregnancy losses are due to aneuploidy, IVF with preimplantation genetic testing (PGT) for aneuploidies (PGT-A) has been considered in the setting of REPL to increase the efficiency of achieving an ongoing pregnancy by embryo selection and transfer into patients with proven fertility.

A comparative retrospective study analysed outcomes of frozen embryo transfer (FET) cycles with and without PGT-A in individuals with RPL (*Bhatt et al., 2021*). Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) registry data were extracted for patients with a history of three or more pregnancy losses and autologous FET for whom complete pregnancy outcomes were available. A total of 4116 IVF–FET cycles from the PGT-A group were compared with 4288 cycles from the control group (FET without PGT-A). Higher live birth rates (48% versus

34%; $P < 0.001$) and lower spontaneous abortion rates (11% versus 13%; $P = 0.02$) were observed with PGT-A. The benefits of PGT-A on live birth rates increased with maternal age. However, no significant benefit was found for reducing spontaneous abortion across all age groups. Limitations include the retrospective nature of the study and the exclusion of cycles without euploid embryos for transfer in the PGT-A group.

In a prospective case-control study, PGT-A did not improve live birth rates per patient or pregnancy loss rates in RPL patients undergoing IVF (*Sato et al., 2019*). The PGT-A group included 41 patients undergoing 64 retrievals with 21 having an embryo transfer of a single euploid or mosaic embryo. The control group consisted of 38 matched patients undergoing 37 untested embryo transfers. However, there was a higher live birth rate with PGT-A per embryo transfer (52.4 versus 21.6%; $P = 0.028$).

A retrospective cohort study compared PGT-A with expectant management in 300 patients with two or more pregnancy losses between 6 and 20 weeks and normal parental karyotypes (*Murugappan et al., 2016*). While there were no differences in live birth rates or clinical pregnancy loss rates between the groups, patients undergoing expectant management had shorter median times to conception. Additionally, live birth rates per attempt were higher in patients with euploid embryo transfer compared with those conceiving naturally. The treatment group consisted of 112 patients who had an oocyte retrieval with the intent of performing PGT-A. A total of 168 oocyte retrievals were performed, with 77% of cycles proceeding to PGT-A. Of these, 74% had at least one euploid blastocyst available for transfer. The control group included 188 patients who chose to try to conceive naturally, with supportive early pregnancy care that often included progesterone suppositories.

In the intention-to-treat analysis, the live birth rate (32% versus 34%; $P < 0.05$) and clinical pregnancy loss rate (20% versus 24%; $P < 0.05$) were similar between the treatment and control groups. Median times to conception were significantly shorter in the expectant management group (3.0 versus 6.5 months). In patients who had an euploid embryo transfer, the live birth rate per attempt was significantly higher than those conceiving naturally (57% versus 34%; $P < 0.05$); however, the clinical pregnancy loss rate was not significantly different (14% versus 24%; $P = 0.12$).

PGT-A has been promoted in the treatment of REPL to improve outcomes by deselecting aneuploid embryos and reducing the chance of loss. While some retrospective and cohort studies show an improvement in live birth rate when transferring euploid compared with untested blastocysts in patients with REPL, there are no randomized controlled trials (RCT) of PGT-A that have randomized patients at the start of an IVF cycle. Also, a benefit of the application of IVF to an otherwise fertile population has not been demonstrated to date (*Chan et al., 2021*).

Recommendation:

3. Patients with REPL should be counselled that there is no clear benefit for PGT-A over natural conception to improve live birth rate, reduce early loss or decrease time to live birth.

Structural chromosomal rearrangements

Parental chromosomal rearrangements are found in 2–5% of patients with RPL (*Clifford et al., 1994*; *De Braekeleer and Dao, 1990*; *Franssen et al., 2006*; *Stephenson, 1996*; *Stephenson et al., 2002*). The most common structural genetic factor is a balanced reciprocal or Robertsonian translocation. Other less frequent parental polymorphisms include inversions, insertions, deletions, duplications or, rarely, a ring chromosome. Although balanced carriers are usually phenotypically normal, their pregnancies are at increased risk of pregnancy loss and may theoretically result in a live birth with phenotypic abnormality secondary to an unbalanced chromosomal arrangement.

If cytogenetic analysis of the POC reveals a structural chromosomal rearrangement, it is widely acknowledged that karyotyping of both partners should be offered before attempting another pregnancy. Genetic counselling should be provided when a parental structural genetic factor is found because the likelihood of a subsequent healthy live birth depends on the chromosome involved and the type of rearrangement.

In patients with RPL associated with a structural genetic factor, limited cytogenetic data suggest that approximately 36–39% of pregnancy losses have an unbalanced structural rearrangement (*Goddijn et al., 2004*; *Stephenson and Sierra, 2006*; *Sugiura-Ogasawara et al., 2004*). A recently published systematic review of 11 studies reported outcomes of natural conception in couples with RPL and abnormal compared with normal parental karyotypes (*Li et al., 2022*). Those with abnormal karyotypes had a lower live birth rate in the first pregnancies following diagnosis (58.8% versus 71.9%; OR 0.55, 95% CI 0.46–0.65, $P < 0.01$), specifically for translocation carriers. Pregnancy loss rates were higher among those with abnormal karyotypes (53.0% versus 34.7%; 95% CI 1.69–2.89, $P < 0.01$); however, this was based on a single small cohort study of 126 patients (*Ikuma, 2015*). Cumulative live birth rates were similar (81.4% versus 74.8%; OR 0.96, 95% CI 0.90–1.03, $P = 0.26$) between the groups.

Recommendations:

4. REPL patients may be offered parental karyotype analysis (for diagnosis and guidance of further management).

5. If there is a known family history of structural polymorphism, or if the same is found in the analysis of POC, patients should be offered karyotype analysis (based on good clinical practice).

6. If an abnormal karyotype is documented, genetic counselling should be offered (based on good clinical practice).

PGT for structural rearrangements

PGT for chromosomal structural rearrangements (PGT-SR) for patients with a known karyotype abnormality has been proposed to improve pregnancy loss risk. In this setting, again PGT often involves the application of IVF to already fertile patients.

A recent systematic review of retrospective cohort studies reported that the pregnancy loss rate in patients with RPL and a parental karyotype abnormality ranged from 25.0% to 55.6% following spontaneous conception (*Iews, 2018*). After PGT-SR, pregnancy loss rates were reportedly lower, at 5.3–39%.

A meta-analysis was recently published comparing expectant management and PGT in patients with RPL and an abnormal parental karyotype (*Li et al., 2022*). Data

were limited to two retrospective studies including 50 patients undergoing PGT, primarily using fluorescence in-situ hybridization performed at the cleavage stage, and 75 patients managed expectantly. Outcomes of interest were live birth and pregnancy loss rates following diagnosis of an abnormal karyotype. No difference was found in cumulative live birth rate (60% versus 68%; OR 0.55, 95% CI 0.11–2.62, $P = 0.45$), but pregnancy loss rates were lower after PGT (24.0% versus 65.3%; OR 0.15, 95% CI 0.04–0.51, $P < 0.01$) (*Li et al., 2022*).

The Japan Society of Obstetrics and Gynecology conducted a nationwide prospective cohort to assess the pregnancy outcomes in PGT-A or PGT-SR including 2993 patients with REPL, 7650 egg retrievals with 5282 PGT-A/SR cycles and 1663 embryo transfer cycles. The euploidy rate in the entire patient population was 25.5%, including individuals with pregnancy loss or implantation failure. In the REPL group, the pregnancy rate per embryo transfer was 74% (1243/1663), with an ongoing pregnancy rate of 60.7%. Pregnancy losses occurred in 126 of 1009 ongoing pregnancies (12.5%). These rates remained relatively constant across all maternal ages. The study suggests that PGT-A/SR may enhance pregnancy rates per embryo transfer and lower pregnancy loss rates per pregnancy, particularly among individuals of advanced maternal age. These results are, however, limited in the absence of a control group (*Iwasa et al., 2023*).

Until a well-designed RCT comparing natural conception with PGT-SR is reported in this patient population, clinicians will need to base their patient counselling on the limited data available, including a discussion on limited proven benefit with respect to cumulative live birth. Any potential benefit of PGT-SR should be balanced against the emotional and financial cost of a failed IVF cycle. Patients need to be counselled about their chance of conception and risk of pregnancy loss with or without IVF and PGT-SR.

Recommendation:

7. Patients with REPL should be counselled that there is no clear benefit to PGT-SR in comparison to expectant management to improve live birth rate. However, PGT-SR may reduce pregnancy loss due to structural chromosomal abnormalities if a balanced, euploid embryo is available for transfer and a pregnancy occurs.

Endocrine factors

Diabetes mellitus, insulin resistance and polycystic ovary syndrome

The prevalence of diabetes mellitus in patients with RPL is similar to that in the general population (*Bussen et al., 1999*). Although well-controlled diabetes is not a risk factor for RPL (*Mills et al., 1988*), individuals who have high glycated haemoglobin (HbA_{1c}) concentrations in the first trimester are at a higher risk of pregnancy loss and fetal malformation (*Hanson et al., 1990*).

Insulin resistance, measured through varying markers of insulin metabolism, has been reported more commonly in women with RPL compared with fertile controls in several case-control and cohort studies (*Craig et al., 2002*; *Ispasoiu et al., 2013*; *Wang et al., 2011*; *Zolghadri et al., 2008*). A systematic review reported that patients with RPL had significantly higher rates of insulin resistance as defined by abnormal fasting plasma insulin, homeostasis model assessment for insulin resistance values, and glucose to insulin ratio (*Cai et al., 2022*).

Similarly, retrospective studies have also reported a more frequent finding of polycystic ovary syndrome (PCOS) in individuals with RPL compared with fertile control participants (*Sagle et al., 1988*; *Watson et al., 1993*). PCOS is associated with several pregnancy complications, including gestational diabetes, pregnancy-induced hypertension and pregnancy loss (*Homberg, 2006*). Retrospective studies have also described higher markers of insulin resistance in RPL patients with PCOS than those without it (*Chakraborty et al., 2013*). However, cohort studies of RPL patients found similar live birth rates in women with and without PCOS (*Liddell et al., 1997*; *Rai et al., 2000*).

Metformin and insulin-sensitizing agents

Treatment with insulin sensitizers has been proposed to reduce risk of pregnancy loss in individuals with PCOS. Two small cohort studies reported reductions in pregnancy loss risk in patients with PCOS who took metformin during pregnancy compared with those who did not (*Jakubowicz et al., 2002*; *Khattab et al., 2006*). In one study, the reduction in loss rates was maintained in a subset of patients with at least one prior early pregnancy loss. A single RCT of 320 PCOS patients compared the impact of metformin (started before conception and continued to the 12th week of pregnancy) or placebo on pregnancy loss rates in infertile patients. The intention-to-treat analysis did not show an improvement in pregnancy loss rate with metformin (15.2% versus 17.9%; $P = 0.8$) (*Morin-Papunen et al., 2012*).

A systematic review also showed that, in most studies, it has been reported that the most beneficial effects of metformin were found in obese women with PCOS who experienced RPL compared with those without PCOS (*Wartena and Matjila, 2023*).

There are no RCT examining the benefit of metformin in an patient population with RPL.

Obesity

A systematic review and meta-analysis of 25 studies and 7916 patients examined the association between body mass index (BMI) and RPL. The mean BMI in the RPL group ranged from 20.3 to 29.3 kg/m^2 and in the control group from 20.1 to 26.93 kg/m^2. Patients with RPL had a significantly higher BMI than control participants, with a mean difference of 0.7 kg/m^2 (95% CI 0.2–1.3) (*Eapen et al., 2021*). A meta-analysis of two studies demonstrated an increased risk of RPL among obese individuals (BMI ≥30 kg/m^2; OR 1.75, 95% CI 1.24–2.47, $P < 0.05$) but not overweight patients (BMI 25–29.9 kg/m^2; OR 1.15, 95% CI 0.87–1.51, $P = 0.33$) when compared with normal weight controls (*Cavalcante et al., 2019*).

A cohort study evaluated 117 pregnancy losses with cytogenetic analyses in a population with two or more prior losses. Euploid pregnancy loss was more frequent in obese participants (BMI ≥30 kg/m^2) (58% versus 37%; Relative Risk [RR] 1.63, 95% CI 1.08–2.47, $P = 0.02$) (*Boots et al., 2014*).

Obesity is well known to be a risk factor for poor reproductive outcome (*Mahutte et al., 2018*). Although there is little published evidence demonstrating the efficacy of weight reduction on REPL, the promotion of weight management is reasonable given the reproductive and other significant adverse health associations.

Recommendations:

8. Patients with REPL should be screened with an HbA_{1c} measurement, and elevated concentrations should be managed prior to

conception (based on good clinical practice).

9. In individuals with PCOS, there is insufficient evidence to recommend metformin for the prevention of pregnancy loss in patients with REPL.

Thyroid disorder

It is postulated that overt thyroid disease is associated with REPL, although there are few data to support the supposition (*Dong et al. 2020*). A study of over 19,000 women in 49 centres in the UK showed that the prevalence of overt hypo- or hyperthyroidism occurs in fewer than 1% of patients with REPL and infertility (*Dhillon-Smith and Coomarasamy, 2020*), similar to the proportion found in an unselected population (*Canaris et al., 2000*). Overt thyroid disease is generally corrected prior to conception (*Alexander et al., 2017*).

Subclinical hypothyroidism (SCH) is defined as an elevated thyrotrophin (thyroid-stimulating hormone [TSH]) concentration with normal serum concentrations of free thyroxine (FT4). The upper normal limit of TSH is typically 4.2–4.5 mIU/l in non-pregnant adults (*Maraka et al., 2018*). The association between SCH and REPL is not straightforward, in part because many studies define SCH as a TSH concentration of over 2.5 mIU/l. This 2.5 mIU/l cut-off is defined by the 2011 American Thyroid Association (ATA) guidelines as the upper normal limit of TSH in the first trimester of pregnancy based on data from US and European populations (*Stagnaro-Green et al., 2011*).

However, more recent studies from diverse populations support only a slight downward shift of the upper reference range of TSH in pregnancy, with some studies showing little difference from the non-pregnant state. Consequently, in 2017, the ATA recommended that, in the absence of population-specific reference ranges, the upper normal limit of TSH in the first trimester should be reduced by 0.5 mIU/l from non-pregnant values, or simply a value of 4.0 mIU/l used (*Alexander et al., 2017*). The prevalence of SCH using a TSH range of 4.5–9.9 mIU/l was 2.4% among women with REPL (*Dhillon-Smith and Coomarasamy, 2020*), again similar to an unselected population of reproductive-age women (*Canaris et al., 2000*). Lowering the upper normal TSH limit to 2.50 mIU/l would increase the prevalence of SCH to 19.9% in non-pregnant patients (*Dhillon-Smith and Coomarasamy, 2020*).

SCH is associated with adverse reproductive outcomes including sporadic pregnancy loss (*Maraka et al., 2016*). A recent systematic review and meta-analysis examined the association between SCH and RPL, defined as two or more losses (*Dong et al. 2020*). Five studies including 1777 patients with two or more losses at less than 20 weeks were included, with the upper limit of normal for TSH defined as 2.5 mIU/l in 53% of the patients (four studies) and 4.5 mIU/l in the remainder. The prevalence of SCH ranged from 2% to 63% across the studies, with a pooled prevalence of 12.6% (95% CI 0–32.5%). No association was found between SCH and RPL, except in one case-control study (*Triggianese et al., 2016*).

A single retrospective cohort study reported the outcome of treatment with levothyroxine in patients with RPL and SCH (*Bernardi et al., 2013*). The study included patients who had two or more losses at less than 10 weeks (excluding chromosomally abnormal losses) and a TSH concentration of over 2.5 mIU/l with a normal FT4. In a subset of patients with SCH, the treatment group received pre-conceptual levothyroxine to maintain the TSH concentration under 2.5 mIU/l. There were 69 pregnancies in 39 patients, with no difference in live birth in treated or untreated pregnancies (48% versus 52%; $P = 0.83$).

Antithyroid antibodies are commonly associated with thyroid dysfunction. The prevalence of antibodies reported in one study was 9.5%, which may be higher than the normal population rate of 4% (*Dhillon-Smith and Coomarasamy, 2020*). Within the group with SCH, the likelihood of thyroid peroxidase (TPO) antibodies increased with increasing TSH. Women with a history of three or more pregnancy losses or subfertility were no more or less likely to have overt thyroid disease, SCH or TPO antibodies compared with those with one or two previous losses (*Dhillon-Smith and Coomarasamy, 2020*). A systematic review and meta-analysis reported a significant association between thyroid autoimmunity and RPL in 17 studies (OR 1.94, 95% CI 1.43–2.64) (Dong et al., 2020). A follow up of the Thyroid Antibodies and Levothryoxine (TABLET) trial (*Dhillon-Smith, 2019*) found that 7% of euthyroid antibody-positive patients developed hypothyroidism or SCH, but there was no difference in the cumulative live birth rate regardless of treatment.

Two recently published systematic reviews and meta-analyses of six RCT examining the effect of levothyroxine treatment on pregnancy outcomes in women positive for antithyroid antibodies reported no difference in live birth rates or pregnancy loss rates (*Lau et al., 2021*; *Wang et al., 2020*). However, the included RCT were not limited to RPL populations, included both euthyroid and SCH patients, and did not always start levothyroxine peri-conceptually.

A single, multicentred RCT Levothyroixin in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4Life trial) examined the effect of levothyroxine treatment on live birth rate in euthyroid RPL patients who were anti-TPO positive. Patients with two or more clinical pregnancy losses were randomized to pre-conceptual levothyroxine or placebo. The trial was concluded prematurely due to slow recruitment, with only 187 of 240 intended patients randomized. A total of 47 (50%) participants in the treatment group and 45 (48%) in the placebo group had a live birth (RR 1.03, 95% CI 0.77–1.38; absolute risk difference 1.6%, 95% CI −12.7 to 15.9). The rate of clinical loss was 23% with levothyroxine and 33% with placebo (RR 0.83, 95% CI 0.56–1.25). There were also no differences in live birth or loss rates in the per protocol analysis or in subgroup analyses comparing patients with two and three or more losses, and those with TSH concentrations under and over 2.5 mIU/l (*van Dijk et al., 2022*).

Recommendations:

10. Patients with REPL should be screened with a TSH measurement.

11. Patients with REPL may be offered TPO antibody screening to identify those at higher risk of SCH or overt hypothyroidism.

12. Patients with overt hyper- or hypothyroidism should be maintained in a euthyroid state prior to attempting pregnancy.

13. Treatment with levothyroxine is not recommended for the prevention of pregnancy loss in individuals with REPL when the TSH concentration is less than 4 mIU/l pre-conceptually, regardless of antibody status.

Hyperprolactinaemia

Hyperprolactinaemia has not been consistently associated with RPL. While a

case-control study of 84 participants reported higher pre-pregnancy prolactin concentrations and a greater proportion of hyperprolactinaemia (>16 ng/ml) in women with three or more pregnancy losses compared with nulligravid control participants with tubal or male factor infertility (35.7% versus 4.8%; $P = 0.001$) (*Bussen et al., 1999*), another small retrospective cohort study described a similar prevalence of hyperprolactinaemia (≥15 ng/ml) in individuals with two or more unexplained losses versus fertile controls (21.7% versus 16.7%) (*Triggianese et al., 2015*). In a retrospective report of 174 patients with three or more unexplained consecutive losses, only three were hyperprolactinaemic (>660 mIU/l). In the remaining patients with subsequent conceptions, prolactin concentrations were statistically higher in those who had a live birth (*Li et al., 2013*).

A single RCT examining treatment with bromocriptine in patients with hyperprolactinaemia and RPL has been reported to date (*Hirahara et al., 1998*). Forty-eight participants with two or more otherwise unexplained losses and elevated basal (≥10 ng/ml) or thyrotrophin-releasing hormone-stimulated (>86 ng/ml) prolactin concentrations were randomized to pre-conceptual bromocriptine continued to 9 weeks gestational age or no treatment. Treated patients had documented normalization of prolactin prior to subsequent conception. In 1 year, there were 21 conceptions in each group. The pregnancy loss rate was significantly lower with treatment (14.3% versus 47.6%;, $P < 0.005$). However, this study has been judged to provide only low-quality evidence due to its small size and methodological shortcomings (*Chen et al., 2016*).

Recommendation:

14. There is insufficient evidence to recommend for or against routine screening for hyperprolactinaemia in REPL patients in the absence of overt symptoms.

Progesterone supplementation

Progesterone is required for the maintenance of early pregnancy. However, the association between luteal phase deficiency and pregnancy loss is controversial. There is a lack of consensus in the literature on how best to detect luteal insufficiency, let alone on its optimal treatment (*Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility, 2021*). Nevertheless, the use of supplemental progesterone in the management of REPL is common.

The PROMISE (Progesterone in Recurrent Miscarriage) trial was designed to investigate whether treatment with progesterone would increase live birth rates in patients with unexplained REPL (*Coomarasamy et al., 2015*). This multicentre, double-blind, placebo-controlled trial randomized 836 participants with a history of three or more pregnancy losses to receive either twice-daily vaginal micronized progesterone (400 mg) or placebo. Treatment was commenced as soon as possible after a positive pregnancy test, and no later than 6 weeks of pregnancy. No significant difference was found in the rate of live birth in the progesterone group compared with the placebo group (65.8% versus 63.3%; RR 1.04, 95% CI 0.94–1.15). Similarly, no difference was demonstrated in a subgroup analysis comparing those with three pregnancy losses to those with four or more ($P = 0.52$) or in patients who started treatment prior to 5 weeks' gestation compared with those who started between 5 and 6 weeks' gestation ($P = 0.15$).

One of the criticisms of this well-designed and well-executed trial is that progesterone may have been started too late to improve outcomes. A small observational cohort study involving 116 patients with two or more pregnancy losses treated with vaginal micronized progesterone shortly after ovulation reported high clinical pregnancy rates compared with controls. Pregnancy success in subsequent pregnancies was higher in women who were treated compared with controls: 68% (86/126) compared with 51% (19/37) (OR 2.1, 95% CI 1.0–4.4) (*Stephenson et al, 2017*). Nevertheless, the PROMISE trial remains the best available evidence to date on the effect of progesterone treatment for REPL.

The PRISM (Progesterone in Sporadic Pregnancy loss) trial was designed to investigate whether treatment with progesterone would improve outcomes for patients who experience first-trimester bleeding (*Coomarasamy et al., 2019*) and was powered to analyse whether the benefit of progesterone is greater with a greater number of previous losses. This multicentre, double-blind, placebo-controlled trial randomized 4153 participants to receive either twice-daily vaginal micronized progesterone (400 mg) or placebo. Treatment was commenced at presentation with bleeding and continued until 16 weeks' gestation. No significant difference was found in the rate of live birth in the progesterone group versus the placebo group (75% versus 72%; RR 1.03, 95% CI 1.0–1.07). However, analysis showed a statistically significant benefit for progesterone in patients with three or more prior pregnancy losses (72% versus 57%; RR 1.28, 95% CI 1.08–1.51). Thus, twice-daily 400 mg vaginal micronized progesterone is of benefit for individuals with higher order REPL who are experiencing first-trimester bleeding.

Recommendations:

15. In patients with REPL, there is conflicting evidence regarding the routine use of progesterone supplementation; however, the best available evidence suggests there is no benefit to live birth rates.

16. In patients with three or more early pregnancy losses who experience first-trimester bleeding, micronized vaginal progesterone supplementation should be offered to increase live birth rates.

Anatomical factors

Congenital and acquired structural defects in the uterine body may predispose to pregnancy loss and can be found in up to 15% of women with REPL (*Stephenson 1996*). Assessment of the uterine cavity can include hysteroscopy with or without laparoscopy, sono-hysterography, 3D ultrasonography or magnetic resonance imaging (*Carbonnel et al., 2021*).

The presence of a uterine septum has been associated with a history of REPL in 6–16% of cases (*Carbonnel et al., 2021*), whereas other Müllerian fusion anomalies such as a bicornuate or unicornuate uterus are associated with second-trimester losses or preterm delivery (*Acién, 1997*; *Lin, 2004*). The impact of an arcuate uterus on pregnancy outcome remains unclear. A retrospective review of reproductive performance in women with untreated congenital uterine anomalies has suggested that these women experience high rates of pregnancy loss (*Grimbizis et al., 2001*).

Historical uncontrolled data have largely shown significant improvements in live birth rates after septum resection in patients with RPL (*Grimbizis et al., 2001*; *Homer et al., 2000*). However, a recently published retrospective cohort study of

patients with a uterine septum who were attempting pregnancy found no improvement in reproductive outcomes following septum resection compared with expectant management (*Rikken et al., 2020*). In a subset of patients with at least one prior pregnancy loss, 92 underwent septum resection while 50 were managed expectantly. There was no difference in the live birth rate after septum resection (51% versus 58%; hazard rate 0.61, 95% CI 0.36–1.02) but a higher rate of pregnancy loss (58% versus 40%; OR 2.65, 95% CI 1.05–6.67) (*Rikken et al., 2020*).

The only RCT to date evaluating septum resection versus expectant management (The Randomised Uterine Septum Transsection Trial, TRUST) (*Rikken et al., 2021*) analysed the reproductive outcome of 79 patients. The live birth rate with septum resection (31%) was not different from that seen with expectant management (35%; RR 0.88, 95% CI 0.47–1.65). Although most (50) trial participants had a history of pregnancy loss, outcomes were not reported separately for patients with REPL, nor was this trial sufficiently powered to generate conclusions in any subgroup.

A recent retrospective cohort study (*Fayek et al., 2023*) of a Canadian population with RPL reported on live birth rate in RPL in patients with a uterine septum with or without surgical management. In 377 patients with a septum, the odds of achieving a live birth were reduced by almost 50% (OR 0.51, 95% CI 0.30–0.86). Subgroup analysis of those undergoing surgery found that there was a higher likelihood of live birth in those who underwent septum resection (46/72, 63.9%) versus those who elected for expectant management (26/72, 36.1%); however, the difference did not achieve statistical significance, probably due to underpowering.

Intrauterine adhesions (IUA) or synechiae are thought to be caused by instrumentation or trauma to both the gravid and non-gravid uterus, as well as infection (*Schenker and Margalioth, 1982*). Pregnancy loss and other pregnancy complications have been attributed to IUA (*Yu 2008*). The reported prevalence of IUA in RPL patients varies considerably from 7% to 27% (*Guimaraes Filho et al., 2006*; *Seckin et al., 2012*). A systematic review of 10 studies and 912 women reported the prevalence of IUA detected by hysteroscopy within 1 year following a pregnancy loss of 19% (*Hooker et al., 2014*). Patients with two or more pregnancy losses were more likely to have IUA than those who had only one loss (OR 1.99, 95% CI 1.32–3.00) (*Hooker et al., 2014*). An uncontrolled study reported a 71% live birth rate in 24 participants with two or more prior losses, all of whom conceived following hysteroscopic lysis of adhesions (*Pabuccu et al., 1997*). However, there are no RCT comparing the treatment of IUA and expectant management in any patient population. In 292 patients with IUA from eight studies who were managed expectantly, the live birth rate was 53% and the pregnancy loss rate was 40% (*Schenker and Margalioth, 1982*).

The prevalence of endometrial polyps in RPL patients varies from 1% to 6% (*Seckin et al., 2012*; *Weiss 2005*). There is no clear association between uterine polyps and RPL (*Carbonnel et al., 2021*) and no high-quality evidence demonstrating reduction in pregnancy loss risk with polypectomy.

Submucous fibroids are reported in 1–8% of RPL patients (*Bohlmann et al., 2010*; *Seckin et al., 2012*). While uncontrolled data report a significant reduction in pregnancy loss rate following myomectomy (*Roy et al., 2010*), a systematic review demonstrated no benefit to pregnancy loss rates from the removal of submucous fibroids in infertile patients (*Pritts et al., 2009*).

While correction of acquired uterine factors may be of benefit, there are no RCT evaluating this in patients with REPL.

Recommendations:

17. In patients with REPL, investigation for uterine structural abnormalities should be considered (based on good clinical practice).

18. Patients should be counselled that there is no clear benefit to the routine surgical resection of a uterine septum for the prevention of pregnancy loss or increased live birth rate.

19. Patients should be counselled that there is no clear benefit to the routine surgical resection of uterine polyps, submucosal fibroids or IUA for the prevention of pregnancy loss or increased live birth rate.

Inherited thrombophilia and REPL

A recently published meta-analysis and systematic review of 88 case-control and one cohort study involving over 30,000 individuals with RPL demonstrated an association between thrombophilia and REPL (*Liu et al., 2021*). Factor V Leiden REPL (OR 2.44, 95% CI 1.96–3.03), prothrombin gene mutation (OR 2.08, 95% CI 1.61–2.68) and protein S deficiency (OR 3.45, 95% CI 1.15–10.35) were all associated with an increased risk of RPL while deficiencies in antithrombin III (OR 0.83; 95% CI 0.29-2.36) and protein C (OR 1.98, 95% CI 0.86-4.04) were not. However, there was significant heterogeneity among the included studies, and associations were confounded by other uncontrolled risk factors such as age and ethnicity (*Liu et al., 2021*). A separate systematic review reported that the overall prevalence of thrombophilia was 9% in women with three or more losses, similar to that of the general population (*Shehata et al, 2022*).

While cohort studies (*Brenner et al., 2005*; *Carp et al., 2003*; *Grandone and Piazza, 2021*; *Ogueh et al., 2001*) have suggested a benefit, two meta-analyses failed to demonstrate an improvement in live birth rate with low molecular weight heparin (LWMH) with or without low-dose aspirin (acetylsalicylic acid [ASA]) in patients with an inherited thrombophilia (*Intzes et al., 2021*; *Skeith et al., 2016*). However, both included studies with a significant number of patients who did not have RPL but rather mid-and late trimester losses or pregnancy complications. Skeith and colleagues reported that the relative risk of live birth was 0.97 (95% CI 0.86–1.19) with LMWH compared with no treatment when restricted to patients with at least two prior losses at less than 10 weeks (*Skeith et al., 2016*). However, only 66 pregnancies were included in this subgroup analysis.

Recommendations:

20. Routine testing for inherited thrombophilia should not be performed in patients with REPL.

21. Treatment of inherited thrombophilia with LMWH in patients with REPL should not be offered to improve live birth or reduce early pregnancy loss.

Antiphospholipid Syndrome (APS)

APS refers to the association between antiphospholipid antibodies (aPL) and adverse pregnancy outcome or vascular thrombosis (*Miyakis et al., 2006*; *Wilson et al., 1999*). The most commonly detected aPL are lupus anticoagulant, anticardiolipin IgG and IgM (aCL), and anti-β_2-

TABLE 1 DIAGNOSIS OF THE APS

Categories of criteria	Examples
Clinical criteria	One or more clinical episodes or arterial, venous or small vessel thrombosis One or more unexplained pregnancy losses of a morphologically normal fetus after the 10th week of gestation, identified by ultrasonography or direct examination of the fetus One or more premature births of a morphologically normal newborn at or before the 34th week of gestation because of severe pregnancy-induced hypertension or severe placental insufficiency Three or more unexplained consecutive pregnancy losses before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and maternal or parental structural genetic factors excluded
Laboratory criteria	The same antibody must be positive twice when drawn at least 12 weeks apart: Anticardiolipin IgG and/or IgM, present in medium or high titres (>40 IgG phospholipid units (GPL) or IgM phospholipid units (MPL)) Anti-β_2-glycoprotein-1 IgG or IgM, present in a titre >99th percentile Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Hemostasis

APS is present if a minimum of one clinical and one laboratory criterion is present (*Miyakis et al., 2006*).

APS, antiphospholipid antibody syndrome; GPL, IgG phospholipid units; MPL, IgM phospholipid units.

glycoprotein-1 IgG and IgM (*Opatrny et al., 2006*). APS is strictly defined based on both clinical and laboratory criteria as shown in TABLE 1 (*Miyakis et al., 2006*).

In women with APS, histological studies have found that placental infarction, impaired spiral artery remodelling, decidual inflammation and deposits of complement split products were common feature in the placenta. Together these antibodies manifest in pregnancy loss or placental insufficiency by disrupting trophoblast function, important in implantation and remodelling of the spiral arteries (Shaul et al. 2023). APS is found in approximately 15% of women with RPL (*van Dijk et al., 2020*). whereas the prevalence in the general low-risk obstetric population is below 1–5% for healthy reproductive-age women (*Ruiz-Irastrorza et al., 2004*). The untreated live birth rate in patients with RPL and APS has been reported to be as low as 10% (*Rai et al., 1995*).

A recent Cochrane review focused on the effect of ASA and heparin on improving outcome for women with persistent aPL and RPL (*Hamulyak et al., 2020*). ASA alone did not improve live birth rate (one trial, very low certainty of evidence). Combined heparin and ASA appeared to improve live birth rate (RR 1.27, 95% CI 1.09–1.49; five studies, 1295 patients); however, evidence was judged to be of low certainty due to heterogeneity and risk of bias. Excluding two trials with methodological limitations, the improvement was maintained for unfractionated heparin (RR 1.68, 95% CI 1.14–2.9) but not LWMH (RR 1.07, 95% CI 0.88–0.29) or all heparins combined (RR 1.20, 95% CI 0.91–1.59) (*Hamulyak et al., 2021*).

A 2005 Cochrane review found no benefit to other treatments including corticosteroids and intravenous immunoglobulin (IVIG) for RPL associated with APS (*Empson, 2005*).

There is controversy over the treatment of patients with persistent aPL who have not had 'three or more unexplained consecutive spontaneous abortions before the 10th week of gestation' (*Miyakis et al., 2006*). The current classification criteria for APS were originally developed for research purposes; however, the clinical management of individuals with RPL now starts after two, not necessarily consecutive losses (*ESHRE Guideline Group on RPL, 2023*; *Practice Committee of the American Society for Reproductive Medicine, 2012*). In a report of 1719 patients with recurrent losses, 18% had aPL. The number of prior losses (two versus three or more), the number of consecutive losses or the trimester of loss were not found to be different compared with individuals with unexplained RPL (*van den Boogaard et al., 2013*). Although some studies of heparin and ASA treatment specified two or more losses as inclusion criteria (*Bao et al., 2017*; *Laskin et al., 2009*), a subgroup analysis based on the number of prior losses was not possible in the meta-analysis (*Hamulyak et al., 2021*).

Recommendations:

22. Patients with REPL should be screened for aPL: lupus anticoagulant, anticardiolipin IgG and IgM, and anti-$\beta_2$glycoprotein IgG and IgM.

23. Individuals with APS should be treated with heparin and ASA in pregnancy to improve live birth rates.

24. Treatment with LMWH and ASA can be considered for patients with REPL who fulfil the laboratory criteria but not the clinical criteria for APS.

Chronic endometritis

There is no consensus on the diagnostic criteria for chronic endometritis. Therefore, the reported prevalence in REPL populations varies widely, from 9% to 56% (*Liu et al., 2018*). In a prospective cohort using traditional haematoxylin and eosin staining and immunohistochemistry for CD138 to identify plasma cells, and using the cell count per unit area, the prevalence of chronic endometritis did not differ between RPL patients with at least three losses (7.7%) and fertile controls (5%) (*Liu et al., 2018*).

Three studies have examined the impact of antibiotic treatment of chronic endometritis in individuals with REPL. In 31 patients with chronic endometritis, the live birth rate improved from 7% to 56% after antibiotics successfully eliminated the chronic endometritis. This improvement was similar to a contemporary cohort of RPL patients without chronic endometritis (from 15% to 59%) (*McQueen et al.,2014*). A second retrospective cohort found a higher live birth rate in 13 REPL patients treated for chronic endometritis compared with nine who were not treated (85% versus 44%) (*Gay et al., 2020*). A single RCT involving 114 patients showed a significant cure rate of chronic endometritis with oral antibiotics compared with no treatment (90% versus

13%), but there was no difference in subsequent pregnancy loss rates (5.4% versus 14.3%; RR 0.38, 95% CI 0.08–1.83) (*Song et al., 2021*). Only 20 participants had RPL, and a subgroup analysis was not reported.

A recent paper demonstrated that the prevalence of plasma cells on biopsy at the time of embryo transfer had no impact on pregnancy outcome (*Herlihy et al, 2022*).

Recommendation:

25. Routine screening for chronic endometritis in REPL should not be performed.

Male factor

While sporadic or recurrent early pregnancy loss is often associated with maternal factors, the impact of male factors has largely remained uninvestigated. The contribution of male characteristics and lifestyle factors to RPL is yet to be fully elucidated and requires further investigation (*du Fossé et al., 2022*).

The association of traditional semen parameters with pregnancy loss has been inconsistent. Although a recent meta-analysis of 19 studies including 2413 participants found a reduced total and progressive motility of spermatozoa in patients with unexplained RPL, significant heterogeneity was present among the included studies, calling into question the strength of the association (*Dai et al., 2022*). Also, due to a lack of predictive thresholds for diagnosis or prognosis, the utility of traditional semen parameters in the investigation of RPL have not been well established.

Another meta-analysis of 901 patients in 13 studies demonstrated higher degrees of sperm DNA fragmentation among the partners of patients with otherwise unexplained RPL compared with fertile controls, with a mean difference of 11.91 (95% CI 4.97–18.86) (*McQueen et al., 2019*). Again, significant heterogeneity was noted among the included studies.

A single study reported on subsequent pregnancy outcomes in 211 participants with RPL who underwent sperm DNA fragmentation testing using the sperm chromatin dispersion test (*Peuranpaa et al., 2022*). A high DNA fragmentation index (DFI; >30%) was found in 16 patients, an intermediate DFI (15–30%) in 60 and a normal DFI (<15%) in the remaining 135. Lifestyle advice was the only intervention provided for a high DFI. There was no difference in the proportion of patients who had a live birth in their next pregnancy in each DFI group (71.1% versus 63.3% versus 68.85%; $P = 1.0$), nor was there a difference in median DFI in those with (11%) or without (13%) a live birth. Further prospective studies are required to correlate sperm DNA fragmentation with clinical outcome and to define predictive thresholds for use in diagnosis.

Recommendations:

26. A complete assessment of paternal health and lifestyle factors, with appropriate counselling, should be part of the evaluation and management of REPL (based on good clinical practice).

27. Routine testing for sperm DNA fragmentation should not be performed in individuals with REPL.

Management in subsequent pregnancies

REPL has a significant impact on the mental health of those who are affected. Studies have reported elevated risks of anxiety, depression and post-traumatic stress disorder in individuals with RPL (*Kolte et al., 2015*; *Kolte et al., 2019*; Sheilds et al. 2022; *Toffol et al., 2013*).

Most couples have significant anxiety regarding future pregnancies and desire a plan for care during early pregnancy. Older retrospective cohort studies and case series described a dramatic improvement in live birth rates in patients with unexplained RPL who received supportive care (*Brigham et al, 1999*; *Clifford et al., 1997*; *Stray-Pedersen et al., 1984*). In one study, supportive care included optimal psychological support and weekly medical examinations, as well as some questionable interventions such as avoidance of heavy work and travel, abstinence from intercourse and bedrest around the time of prior losses (Stray-Pedersen et al., 1997).

Patient preferences for supportive care identified by survey in 174 women with RPL include having a follow-up plan with a provider who is knowledgeable about RPL and the patient's obstetric history, is supportive, empathetic and informative, takes them seriously and enquires about their emotional needs (*Musters et al., 2013*). Ultrasound reassurance of viability was desired with symptoms and every 2 weeks.

Recommendation:

28. Early access to care and monitoring should be offered as an important supportive measure in this patient population (based on good clinical practice).

Empirical treatment of REPL

Aspirin (ASA)

The prophylactic or empirical use of anticoagulants in unexplained RPL is based on the proposed immunological and thrombotic activity of decidualization and ongoing placental function (*Matthieson et al., 2012*). Aspirin alone (50–80 mg per day) compared with placebo has not been shown to improve the live birth rate among women with unexplained RPL in three RCT (*Blomqvist et al., 2018*; *Kaandorp et al., 2010*; *Tulppala et al., 1997*).

A large randomized trial, EAGeR (Effects of Aspirin in Gestation and Reproduction) (*Schisterman et al, 2014*), reported on the association of live birth and early pregnancy loss when low-dose aspirin (LDA) was initiated pre-conceptually. Pregnancy loss was recorded in 68 out of 535 of the women in the LDA group in comparison to 65 out of 543 in the placebo group ($P = 0.7812$). LDA was associated with increased vaginal bleeding, but not associated with pregnancy loss.

Further analysis examined the association between LDA initiated before conception and very early losses or euploid losses among a recurrent loss group of women (one or two prior losses) (*Mumford et al, 2016*). In the final intention-to-treat analysis that included all women who completed the study, the proportion of pregnancy losses in the LDA group was 17.9% (96/537) compared with 16.7% (92/551) in the placebo group (RR 1.07, 95% CI 0.83–1.39). Importantly, the results were examined according to the number of prior losses and there was still no significant association found.

A subsequent per protocol analysis took into account a biological effect from LDA with adherence for at least 5 of 7 days. In the previous analysis, non-adherence was defined as less than 7 days per week of treatment (*Naimi et al. 2021*).

This subgroup analysis found that, relative to the placebo group, taking LDA on at least 4 days per week starting the week prior to conception led to 15 more live

births (RR 0.58, CI 7.65–21.15) and six fewer losses (RR 0.14, 95% CI −12 to −0.20) per 100 women in the trial.

LMWH

LMWH is considered to have benefit on trophoblast implantation and placentation in addition to anti-thrombotic effects with a very minimal side effect profile. It has therefore been considered in the medical management of unexplained RPL. Several meta-analyses have been published examining the effect of LMWH treatment on patients with RPL. Compared with no treatment, LMWH did not improve the live birth rate (RR 1.19, 95% CI 0.99–1.43) or pregnancy loss rate (RR 0.67, 95% CI 0.41–1.11) in five trials of participants with unexplained RPL (*Wang et al., 2022*). However, a subgroup analysis of three trials in patients with three of more losses showed an improvement in pregnancy loss rate with LMWH (RR 0.46, 95% CI 0.35–0.61). Interestingly, a previous meta-analysis of the same three trials showed no improvement in live birth rate compared with control participants (RR 1.47, 95% CI 0.83–2.61) (*Rasmark Roepke et al., 2018*).

Jiang and colleagues published another meta-analysis of eight trials showing an improvement in live birth rate (RR 1.19, 95% CI 1.03–1.38) and pregnancy loss risk (RR 0.62, 95% CI 0.43–0.91) with LMWH compared with no treatment in unexplained RPL (*Jiang et al., 2021*). However, the findings can be questioned given the inclusion of one trial focused on patients with recurrent implantation failure and another that was a prospective cohort study. Both these trials showed a benefit of LMWH.

Several other meta-analyses have also recently been published. Owing to differences in inclusion criteria, treatments, controls and co-interventions, there was significant variance in the individual studies included for analysis. While two showed no difference with LMWH (*Intzes et al., 2021*; *Yan et al., 2022*), one meta-analysis of four studies of LMWH and ASA compared with ASA alone showed an improvement in live birth (OR 2.09, 95% CI 1.29–3.40) in individuals with unexplained RPL (*Li et al., 2000*).

IVIG

In keeping with the theory of alloimmune dysfunction in REPL, IVIG has been studied for its suppressive effects. Mechanisms of benefit have been proposed in the role of IVIG including suppression of natural killer cell populations, inhibition of complement binding, modification of cytokine binding and T lymphocyte activity, especially in the case of secondary recurrent early loss. A meta-analysis of 528 participants in 11 studies examining IVIG treatment compared with no treatment, placebo or albumin in unexplained RPL found no improvement in live birth rate (RR 1.25, 95% CI 1.00–1.56) (*Wang et al., 2016*). A subgroup analysis of four trials found a possible benefit when IVIG was started pre-conceptually (RR 1.67, 95% CI 1.30–2.14).

Two trials have been conducted assessing IVIG as a treatment for secondary idiopathic pregnancy loss. The first, in 2010, was a multicentred, double-blind RCT of 82 participants and 47 index pregnancies (*Stephenson et al., 2010*). Clinical pregnancy and live birth rates were similar in both the treatment and control groups. The second, in 2015 (*Christiansen et al., 2015*), was a single-centre, double-blind, placebo-control RCT of 82 women with unexplained secondary pregnancy loss and at least four losses. IVIG was administered at time of pregnancy test to 15 weeks or the time of the loss. Intention-to-treat analysis did not show any improvement in live birth rates in the treatment groups (23/42, 54.8% versus 20/40, 50%; RR 1.11, 95% CI 0.70–1.74).

Paternal leukocyte immunization

Another controversial treatment in unexplained recurrent early loss has been paternal leukocyte immunization (LIT). LIT was suggested to benefit women who lacked anti-paternal antibodies or blocking antibodies necessary to prevent fetal rejection, but meta-analyses for paternal LIT have reported mixed findings of benefit. A Cochrane review of 12 trials including unpublished data found no improvement in live birth with LIT compared with placebo (OR 1.23, 95% CI 0.89–1.7) (*Wong et al., 2014*). In a more recent analysis of four trials including one that was not analysed in the Cochrane review, LIT was found to improve live birth rate over autologous immunization (RR 1.8, 95% CI 1.34–2.41) (*Rasmark Roepke et al., 2018*). In 2016, another meta-analysis of 18 trials showed a significant benefit of LIT over placebo for improving live birth rates (OR 3.75, 95% CI 3.07–4.57). Of the included trials showing a benefit of LIT, 7 out of 8 have been conducted in Asian patients within the past two decades while all the trials conducted in Europe and North America were published at least 25 years ago and showed no difference (*Liu et al., 2016*).

There is considerable heterogeneity among RCT of treatments for unexplained RPL, resulting in difficulty identifying true treatment effects. Discerning treatment effects is challenging owing to differing definitions of RPL, different treatment doses and agents within the interventions themselves, varying control groups and co-interventions, issues with the methodological quality of trials, particularly of older studies, and a lack of reporting on important safety outcomes.

Recommendations:

29. The empirical use of LDA-ASA should not be offered to all individuals with unexplained REPL.

30. Given the low level of evidence, the empirical use of LMWH should not be used in patients with REPL other than in research settings.

31. IVIG and LIT should not be offered for the management of REPL outside of a research setting.

CONCLUSIONS

Recurrent early pregnancy loss (REPL) affects a small but significant minority – fewer than 5% of the reproductive population. For those impacted, the burden can be profound, encompassing both physical and emotional challenges. This includes the fear of further loss and the perceived pressure of losing valuable time, especially in the context of advance maternal age.

Despite the absence of universally acceptable standards of care, there are several practices that are of benefit. Patients desire consultation, close pregnancy surveillance and a clear plan of management (*Musters, 2013*). The initial visit provides an important opportunity for pre-pregnancy consultation and reassurance in these vulnerable patients.

It is essential to acknowledge that the prognosis for a live birth in most patients with REPL is optimistic. Therefore, each case should be viewed as unique, requiring a careful consideration of the individual's experience, risk factors and desired outcome. The use of expensive, unproven, invasive and potentially harmful

therapeutics should be avoided. A patient-centred case by case approach is recommended.

DATA AVAILABILITY

No data was used for the research described in the article.

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