Recurrent pregnancy loss

A GP's guide to evidence-based care

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With recurrent pregnancy loss now defined as two or more pregnancy losses, up to 5% of women are affected. Using an evidence-based approach, GPs are key in offering timely support, arranging investigations and initiating appropriate referral for ongoing management.

Recurrent pregnancy loss (RPL) is defined as two or more pregnancy losses before 20 weeks' gestation with the same partner, regardless of whether the losses are consecutive. Studies have shown a minimal difference in diagnostic yield when investigations are initiated after two losses versus three. This updated definition expands the eligibility for evaluation and recognises the significant psychological toll of repeated pregnancy loss. A sensitive, structured approach to management can make a meaningful difference in a couple's experience and support their path to parenthood.

This article is based on the *Australasian Recurrent Pregnancy Loss Clinical Management Guideline 2024* published by the Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence group.[1,2] GPs play a crucial role, often as a trusted first point of contact for couples. This article focuses on practical steps for GPs to initiate the investigation and management of RPL, and on helping to identify clear indications for referral to a fertility specialist.

KEY POINTS

- Recurrent pregnancy loss (RPL) is defined as two or more pregnancy losses before 20 weeks' gestation and affects up to 5% of women.
- The causes of RPL are diverse and include genetic, anatomical, endocrine, immunological, environmental and male factors.
- Aneuploidy is the most common cause of early miscarriage, whereas antiphospholipid syndrome is the strongest known acquired risk factor for RPL.
- Many couples with RPL will have no identifiable cause, but structured multidisciplinary care can improve outcomes and patient experience.
- Thorough evaluation of both partners, with attention to modifiable lifestyle and systemic factors, is essential in managing RPL.

What causes recurrent pregnancy loss?

RPL affects up to 5% of women.[3] There are several causes and associated factors with RPL, which can be broken down into the following groups.

Chromosomal factors

Aneuploidy (an abnormal number of chromosomes) in the embryo is the most common cause of first-trimester miscarriage and is strongly associated with increasing maternal age. Furthermore, chromosomal rearrangement in the parent, such as balanced translocations (i.e. where one segment of a chromosome breaks off and attaches to another with no overall gain or loss of genetic material), occurs in around one in 20 couples with RPL.[4] These couples have a greater likelihood of creating chromosomally unbalanced embryos, leading to pregnancy loss (Box 1).

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1. INVESTIGATIONS AND MANAGEMENT OF CHROMOSOMAL FACTORS IN RPL

- Parental (male and female) karyotyping should be performed to assess for chromosomal abnormalities
- If an abnormal karyotype is identified, refer to a fertility specialist to arrange and discuss:
  - genetic counselling
  - consideration of IVF with PGT-SR
- If karyotype is normal and maternal age >35 years, consider referral to a fertility specialist, as it may be appropriate to discuss IVF with PGT-A
- If products of conception are available following a recent loss, send for cytogenetic analysis (e.g. array-based testing), as this may confirm aneuploidy as the underlying cause

Abbreviations: IVF = in vitro fertilisation; PGT-A = preimplantation genetic testing for aneuploidy; PGT-SR = preimplantation genetic testing for structural rearrangements; RPL = recurrent pregnancy loss.

2. INVESTIGATIONS AND MANAGEMENT OF ANATOMICAL FACTORS IN RPL

- A combined pelvic two-dimensional or three-dimensional ultrasound (transvaginal approach) and sonohysterogram should be performed
- If the findings indicate fibroids, Müllerian anomalies or intrauterine adhesions, refer to a fertility specialist
- Management may involve a discussion of further investigations (e.g. laparoscopy, hysteroscopy as the gold standard) or MRI to further characterise the findings
- Counselling can involve discussing the risks and benefits of surgical correction, if appropriate

Abbreviation: RPL = recurrent pregnancy loss.

Anatomical factors

Structural uterine abnormalities, such as congenital Müllerian anomalies (e.g. unicornuate, bicornuate, septate uterus or uterus didelphys), certain types of fibroids (intramural and submucosal) and intrauterine adhesions (i.e. Asherman's syndrome), may increase the risk of pregnancy loss. In contrast, endometrial polyps do not appear to increase the risk of RPL, although they may have a negative impact on implantation and reduce the likelihood of conception (Box 2).[5]

TABLE 1. INVESTIGATIONS AND MANAGEMENT OF ENDOCRINE FACTORS IN RPL

Endocrine factors	Investigations	Management
Thyroid function	• Testing for TSH, free T4, anti-TPO and anti-Tg levels • If TSH levels are low or suppressed, order tests to measure free T3 and TRAb levels	• Overt hypothyroidism or hyperthyroidism should be treated as per standard Australian guidelines • In the absence of a population standard, TSH ≥4.0 mIU/L should be considered abnormal • If the findings indicate subclinical hypothyroidism (TSH ≥4.0 mIU/L, normal free T3/4 levels) regardless of antibody status, commence levothyroxine aiming for euthyroid levels (TSH <4.0 mIU/L) • If the findings indicate antibody positivity and a euthyroid state, consider either: – monitoring TFTs every 4 weeks during pregnancy until 20 weeks' gestation, and treat with levothyroxine if TSH ≥4.0 mIU/L – commencing on low-dose levothyroxine (25–50 mcg PO in the morning) with the aim of maintaining TSH <4.0 mIU/L
Prolactin	• Order a test of prolactin levels if clinical symptoms of hyperprolactinaemia (e.g. headache with visual disturbance, galactorrhoea) are present	• Refer to an endocrinologist if prolactin levels are elevated
Polycystic ovary syndrome		• Implement individualised management of diet and lifestyle to support achieving a healthy body mass index • Consider metformin as an insulin sensitiser
Obesity	• Measure body mass index	• Aim for a body mass index 18.5–24.9 kg/m^2 through diet and exercise, as weight loss can improve live birth rates
Glucose intolerance	• Screen with fBSL and HbA_{1c} • If the findings of either are abnormal, consider 75 g OGTT	• Refer to an endocrinologist if OGTT results are abnormal
Progesterone		• Provide micronised progesterone (400 mg PV twice daily) in women with ≥2 pregnancy losses in the setting of a threatened pregnancy loss

Abbreviations: anti-Tg = antithyroglobulin; anti-TPO = antithyroid peroxidase; fBSL = fasting blood sugar level; HbA_{1c} = glycated haemoglobin; OGTT = oral glucose tolerance test; PO = per oral; PV = per vaginal; RPL = recurrent pregnancy loss; T3 = triiodothyronine; T4 = thyroxine; TFT = thyroid function test; TRAb = thyroid receptor antibody; TSH = thyroid-stimulating hormone.

Endocrine factors

The key endocrine factors associated with RPL, along with their investigations and management approaches, are summarised in Table 1 and described below.

- **Thyroid function:** Overt hypothyroidism and hyperthyroidism

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3. UPDATED INTERNATIONAL CONSENSUS SYDNEY CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME[3]

Clinical criteria

- Either previous thrombosis (venous or arterial) OR pregnancy morbidity:
  - multiple unexplained pregnancy losses (≥3 losses, <10 weeks' gestation)
  - ≥1 unexplained fetal death (≥20 weeks' gestation)
  - ≥1 preterm birth (34 weeks' gestation) due to eclampsia, pre-eclampsia or recognised features of placental insufficiency

Biochemical criteria

- AND persistent presence of the following on two occasions, at least 12 weeks apart:
  - anticardiolipin antibody
  - lupus anticoagulant
  - beta-2 glycoprotein 1 antibody

4. INVESTIGATIONS AND MANAGEMENT OF THROMBOPHILIA IN RPL

- Test for lupus anticoagulant, anticardiolipin antibody and beta-2 glycoprotein 1 antibody to screen for antiphospholipid syndrome (as per diagnostic criteria listed in Box 3)
- If diagnosed with antiphospholipid syndrome, consider referral to a fertility specialist, haematologist or obstetrician (if pregnancy test result is positive)
- Consider commencing on low-dose aspirin (100 mg daily) and a heparin (either unfractionated 5000 IU twice a day, or enoxaparin 20–40 mg/day) if pregnancy test result is positive

Abbreviation: RPL = recurrent pregnancy loss.

5. INVESTIGATION AND MANAGEMENT OF AUTOIMMUNE CONDITIONS IN RPL

- Investigations are not recommended outside of research settings
- Ensure autoimmune conditions (e.g. coeliac disease) are well controlled

Abbreviation: RPL = recurrent pregnancy loss.

6. INVESTIGATION AND MANAGEMENT OF CHRONIC ENDOMETRITIS IN RPL

- Endometrial biopsy should be performed by a gynaecologist or fertility specialist
- If chronic endometritis is suspected, refer to a fertility specialist for consideration of endometrial biopsy

Abbreviation: RPL = recurrent pregnancy loss.

are both associated with an increased risk of RPL and spontaneous pregnancy loss.[6,7] The presence of thyroid antibodies, in the context of either normal or subclinical thyroid function, appears to be associated with RPL.[8] However, management in this group remains contentious.

- **Prolactin:** It is unclear if high prolactin levels are associated with RPL. Nevertheless, if there is clinical suspicion of hyperprolactinaemia, levels should be checked, as treating this condition may improve the live birth rate.
- **Polycystic ovary syndrome:** Polycystic ovary syndrome is the most common endocrine disorder in women. It is difficult to study due to its heterogeneity and may be associated with an increased risk of spontaneous pregnancy loss.
- **Obesity:** Obesity is associated with an increased risk of RPL, as well as poor obstetric outcomes (e.g. increased risk of gestational diabetes, hypertensive disorders of pregnancy, preterm birth, delivery via Caesarean section, neonatal morbidity).[9,10]
- **Glucose intolerance:** Glucose intolerance is comprised of overt diabetes mellitus, impaired fasting glucose levels and impaired glucose tolerance. Evidence on its association with RPL is currently mixed and inconclusive.
- **Progesterone:** Progesterone supplementation may help reduce the rate of pregnancy loss in RPL. Evidence favours progesterone supplementation in women who have had three or more previous losses, and a threatened pregnancy loss (i.e. bleeding in early pregnancy).[11]

Thrombophilia

It is unclear whether inherited thrombophilias (such as Factor V Leiden, prothrombin gene mutation, protein C and S deficiency and antithrombin deficiency) are associated with RPL. As such, routine testing for these conditions is not recommended (Box 3).[12]

Conversely, acquired thrombophilia, namely antiphospholipid syndrome, and its associated antibodies are strongly associated with RPL and should be considered in the workup (Box 4).[13] Although the methylenetetrahydrofolate reductase mutation is often grouped with thrombophilias, it is not classified as one and has no established link with RPL.

Autoimmune conditions

It is acknowledged that immune factors are associated with RPL. Currently, strong evidence is lacking, although research in this area continues to evolve. Therefore, it is recommended that autoimmune-related investigations occur only within a research setting (Box 5). Poorly controlled coeliac disease has been associated with RPL.[14]

Endometrial factors

Infective

Chronic endometritis may be more prevalent in women with RPL. If diagnosed, it can be easily treated with antibiotics, and some evidence suggests this may improve live birth rates.[15] However, as diagnosis requires an endometrial biopsy, patients should be referred to a fertility specialist for further evaluation in suspected cases (Box 6).

Endometriosis

Endometriosis is an inflammatory condition that can affect egg quality and early pregnancy outcomes. Nationwide historical cohort study data from Danish national health registers have revealed a link to RPL, strengthened by the number of pregnancy losses.[16] Currently, there are no identified treatments that have proven to be effective in reducing RPL within this population.

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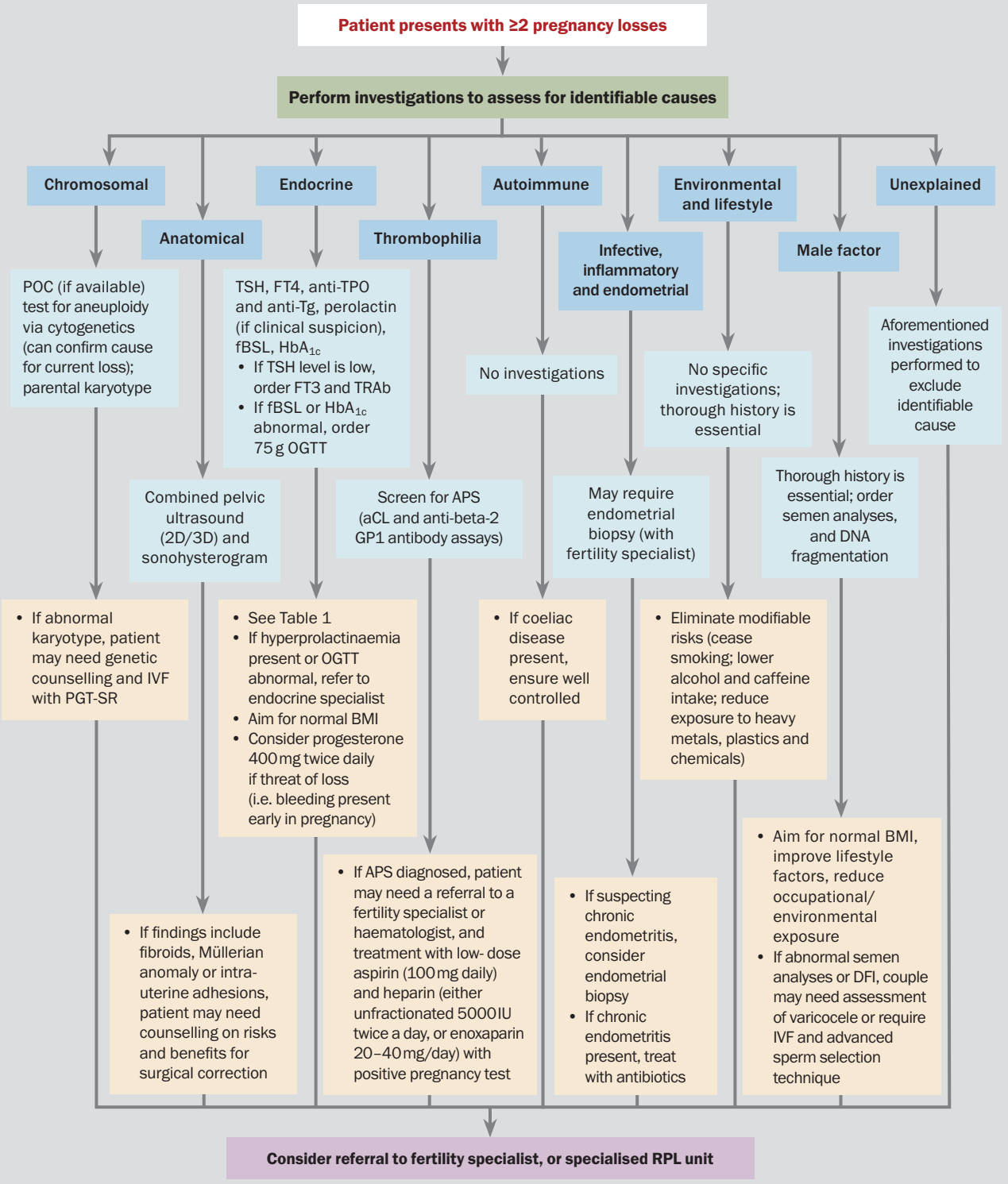
SUMMARY OF A GP'S APPROACH TO RECURRENT PREGNANCY LOSS



Abbreviations: 2D = two-dimensional; 3D = three-dimensional; aCL = anticardiolipin; anti-Tg = antithyroglobulin; anti-TPO = antithyroid peroxidase; APS = antiphospholipid syndrome; BMI = body mass index; DFI = DNA fragmentation index; fBSL = fasting blood sugar level; FT3 = free triiodothyronine; FT4 = free thyroxine; GP1 = glycoprotein 1; HbA_{1c} = glycated haemoglobin; IVF = in vitro fertilisation; OGTT = oral glucose tolerance test; PGT-SR = preimplantation genetic testing for structural rearrangements; POC = products of conception; RPL = recurrent pregnancy loss; TRAb = thyroid receptor antibody; TSH = thyroid-stimulating hormone.

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7. MANAGEMENT OF LIFESTYLE AND ENVIRONMENTAL FACTORS IN RPL

Lifestyle exposures (e.g. endocrine-disrupting chemicals and heavy metals, high caffeine intake, cigarette smoking, alcohol consumption)

- No specific investigations are performed for these factors (as there are no high-quality supportive data)
- Recommendations for management are in line with general health recommendations. These include smoking cessation, alcohol avoidance, decreasing caffeine intake and reducing unnecessary exposure to heavy metals, chemicals and plastics

Psychological stress

- Consider referral for psychological support (counsellor or psychologist) or referral to RPL clinic if available

Abbreviation: RPL = recurrent pregnancy loss.

TABLE 2. INVESTIGATIONS AND MANAGEMENT OF MALE FACTORS IN RPL

Factor	Investigations	Management
Lifestyle factors (overweight or obesity, smoking, alcohol consumption, environmental and occupational exposure)	• No specific investigations are recommended (as there are no high-quality supportive data)	• Maintain healthy weight through diet and exercise, cease smoking, reduce alcohol intake, cease recreational drug use and limit occupational exposure (e.g. reduce high heat exposure)
Sperm or semen factors	• Semen analyses and DNA fragmentation	• If DNA fragmentation is elevated, refer to a fertility specialist • Management includes examination and discussion on testicular ultrasound (assessment of varicocele), lifestyle changes and consideration of antioxidant supplementation (such as vitamin C, vitamin E, coenzyme Q10 and zinc), with re-evaluation of DNA fragmentation • If no improvement on re-evaluation, consider IVF with advanced sperm selection technique • If varicocele are present on ultrasound, referral to urology is warranted

Abbreviations: IVF = in vitro fertilisation; RPL = recurrent pregnancy loss.

Lifestyle and environmental factors

Exposure to endocrine-disrupting chemicals (e.g. bisphenol A and phthalates) and heavy metals, high caffeine intake, cigarette smoking and alcohol consumption may be associated with an increased risk of spontaneous pregnancy loss (Box 7). There is no evidence to support routine serum or urine testing for heavy metal exposure.

It is acknowledged that a high level of psychological stress is associated with RPL. Positive outcomes (i.e. higher live birth rates) have been observed when couples have received formal clinical support for the first 12 weeks of pregnancy within multidisciplinary care settings.[17,18]

Male factors

Excessive weight (overweight and obesity), smoking, alcohol consumption, and environmental and occupational exposures in men have all been associated with RPL (Table 2). It is important to take a thorough history of the male partner to identify and address these modifiable risk factors.

Damage to sperm DNA, which can occur during spermatogenesis or during transit through the reproductive tract, has been implicated in RPL. Elevated levels of sperm DNA fragmentation have been observed in affected couples, suggesting a potential contributing role.

Unexplained recurrent pregnancy loss

In up to 50 to 70% of couples with RPL, no specific underlying cause is identified.[19] These couples may benefit from specialist referral for further evaluation, support and management.

Conclusion

RPL can be multifactorial, complex and emotionally distressing for couples. As the first point of contact, GPs are uniquely positioned to offer early clinical assessment and emotional support. With a structured history and appropriate investigations, a potential cause can be identified in up to half of all cases, many of which are treatable. Referral to a fertility specialist is appropriate when no clear causes are found, or if specialist management is needed. Patient-friendly resources are now also available to help guide and support couples through this challenging time.[20] A summary of a GP's approach to RPL is presented in the Flowchart. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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