Review Article

Management and Counselling of Patients with Recurrent Pregnancy Loss Presenting to an Infertility Specialist–A Review Article

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Abstract:

Background: Recurrent pregnancy loss (RPL) is defined as the occurrence of two or more consecutive miscarriages before 20 weeks of gestation. It affects approximately 1-2 % of couples trying to conceive and be a devastating experience for those affected. The etiology of RPL is multifactorial, encompassing genetic, anatomical, hormonal, immunological and environmental factors. Genetic abnormalities, such as chromosomal rearrangement, are implicated in a significant proportion of cases. Uterine anomalies and hormonal imbalances also contribute to pregnancy loss, while autoimmune disorders and blood clotting abnormalities play a role in some cases. Diagnostic approaches involve a comprehensive evaluation including karyotyping, imaging studies and screening for autoimmune disorders. Management strategies are tailored to the underlying causes when identified and may include surgical interventions, medical therapies and lifestyle modifications. Despite advancements in understanding the causes and treatment of RPL, the condition remains a challenging area of reproductive medicine. This purpose of this review study is to address the etiology and pathology of RPL in women presenting with sub fertility and infertility in an infertility clinic which will encourage other researchers. Early detection and intervention of the factors responsible of RPL will help the patient suffering from RPL and will achieved a successful reproductive life.

Key words: RPL, Miscarriage, Infertility

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Introduction:

Recurrent miscarriages occur in women with subfertility and those that have no problems conceiving. Tamhankar et al (2015) estimated the risk of miscarriage in those with subfertility to range from 7-70 %. On the other hand, Ford and Schust (2009) state that about 50% of women with recurrent miscarriages have no identifiable reasons for the pregnancy losses.

Recurrent miscarriages, also known as recurrent pregnancy loss (RPL), is defined as having three or more miscarriages occurring one after the other, according to the United Kingdom's Royal College of Obstetricians and Gynecologists (RCOG) (2011). Across the Atlantic, the American College of Obstetricians and Gynecologists (ACOG) (2020), give a reduced threshold for the definition, declaring that recurrent miscarriages are two or more consecutive miscarriages.

It is estimated that about 1% of couples experience RPL (RCOG, 2011), which comes with a huge emotional burden. By recognising the existence of recurrence, we are at the same time acknowledging the likelihood of an elevation in the risk of a miscarriage in subsequent pregnancy. It is predicted that the risk of another miscarriage after two consecutive miscarriages is about 30% and this rises to 33% after three losses (Ford and Schust, 2009).

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This, in and of itself, puts pressure on health care providers to intervene and prevent further losses.

Aetiologies:

Maternal age and number of previous miscarriages are two dependable risk factors for a further miscarriage (Green-top Guideline, 2011). An abnormal foetal karyotype is found in about 60% of sporadic cases and in about 30% of RPL cases (Balen, 2014). Approximately 2-4% of RPL is associated with a parental balanced structural chromosome rearran gement, most commonly balanced reciprocal or Robertsonian translocations. Single gene defects, such as those associated with cystic fibrosis or sickle cell anaemia, are seldom associated with RPL (Ford and Schust, 2009). An abnormal Mullerian tract whether developmental or acquired is an uncommon cause of RPL, and there is debate as to whether there is any association between these conditions and RPL (Balen, 2014). Cervical insufficiency can occur in mid-second or early third trimester. Around 8% of women with previous midterm miscarriages will be diagnosed with cervical insufficiency (Thakur and Mahajan, 2022). Serial cervical sonographic surveillance during pregnancy in clinically suspected patients should be offered to diagnose cervical weakness (RCOG, 2011).

Luteal phase defect (LPD), polycystic ovarian syndrome (PCOS), uncontrolled diabetes mellitus, thyroid disease, and hyperprolactinaemia are among the endocrine disorders in approximately 17-20% of RPL. The most pertinent risk for RPL secondary to infection is a chronic infection in an immuno compromised patient (Balen, 2014). About 15% of women with RPL have the lupus anticoagulant (LA) or anticardiolipin (aCL) antibody both of which are antiphospholipid antibodies (aPLs). Primary antip hospholipid syndrome (APS) relates to recurrent miscarriage and a tendency to arterial and venous thrombosis or thrombocytopenia.

Women with thrombophilia may be at increased risk of RPL. Thrombophilic conditions include deficiencies of anti-thrombin III, protein C and protein S, and activated protein C resistance which is secondary to a mutation in the factor V Leiden gene (Balen, 2014). There is no evidence that environmental factors are implicated in RPL. Three exposures-smoking, alcohol, and caffeine-have gained particular attention and merit special consideration given their widespread use and modifiable nature (Ford and Schust, 2009).

Investigations for RPL:

A thorough history should be taken, including details of previous pregnancy losses. The gestational age of prior pregnancy loss is critical, as RPL typically occurs at a similar gestational age in successive pregnancies. Physical examination should include a detailed general, speculum (e.g. for cervical dilatation and effacement) and pelvic examination (Thakur and Mahajan, 2022).

First-trimester miscarriages (Balen, 2014):

- Chromosomal analysis of both partners
- Early and mid-follicular phase LH measurement
- Early follicular phase FSH measurement
- Endocervical swabs for bacterial vaginosis
- Measurement of LA and aCL antibodies (IgG and IgM)
- Factor V Leiden and prothrombin gene mutations
- Possible assessment of haemostatic-activated protein C resistance and thermoelasticity.

Second-trimester miscarriages (Balen, 2014):

- Chromosomal analysis of both partners
- Measurement of LA and aCL antibodies (IgG and IgM)
- Uterus ultrasound followed by hysteroscopy and/or HSG if an abnormality is detected (e.g. short cervical length)
- Genetic evaluation of miscarriage tissue obtained at the time of the second and subsequent pregnancy losses should be offered to all couples with two or more consecutive pregnancy losses (Pilliarisetty and Mahdy, 2022).

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The combination of a genetic evaluation of miscarriage tissue with an evidence-based assessment for RPL will identify a probable or definitive cause in over 90% of miscarriages. Even in cases of unexplained recurrent pregnancy losses, future successful pregnancy can be achieved in 50-60% of cases depending on maternal age and parity (ASRM, 2012).

Treatment:

The management of people with RPL is multi-factorial and, in general, depends upon the cause. When specific cause is not identified empirical therapy may be considered. General measures for the management include:

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- Lifestyle modification

Even in cases of RPL due to male factor infertility, such as increased (>15%) sperm DNA fragmentation index, life style modification is advised (ASRM, 2012). It in general includes:

  - o Smoking cessation
  - o Optimising alcohol intake
  - o Optimising caffeine consumption
  - o Avoiding use of illicit drugs like cocaine
  - o Optimising BMI

- Providing constant psychological support
- Prophylactic Vitamin D supplementation
- Empirical use of progesterone (ESHRE, 2018 and Haas, 2019)

Progesterone use (with or without additional treatment) plays an important role in reducing the rate of RPL (Haas, 2019). Treatment options include pre-i mplantation genetic diagnosis (PGD) for specific translocations with transfer of unaffected embryos (via IVF), reducing significantly a miscarriage chance (Agenor and Bhattacharya, 2015), or the use of donor gametes. Cervical cerclage may be of benefit in cases due to cervical insufficiency and of bicornuate uterus for the prevention of preterm deliveries (Romero et al., 2006 and Yassaee and Mostafaee, 2011) and ultrasound-indicated cerclage should be offered if a cervical length of 25mm or less is detected before 24 weeks of gestation (RCOG, 2011). But cervical incompetence is thought to be over diagnosed. A Cochrane review has failed to find evidence of the benefit of cervical cerclage in reducing recurrent miscarriage (Balen, 2014).

Uterine anomalies like septate uterus can be managed by hysteroscopic septal resection (ASRM, 2012). The role of Asherman syndrome/intrauterine synechiae, fibroids and polyps are controversial but ones causing significant uterine cavity defects should be managed surgically. In cases of irreparable uterine abnormalities, the role of surrogacy comes into play. Maternal endocrine disorders can be managed medically. For example, elevated prolactin levels can be optimised with dopamine agonists, resulting in live births in about 86% of cases (in contrast to 54% in untreated cohort). In overt hypothyroidism levothyroxine is used (ESHRE, 2018), but there is an emerging consensus that even a TSH level above 2.5 mIU/L is enough to need treatment (ASRM, 2012). Uncontrolled diabetes is associated with increased pregnancy loss so needs optimisation before conception (ASRM, 2012). Studies report folic acid, vitamin B6 and B12 supplementation and low-molecular weight heparin (LMWH) are improving pregnancy outcomes in women with hyperhomocysteinaemia. Another study also suggests that metformin significantly reduces the rates of pregnancy loss in women with PCOS and RPL (Glueck, et al., 2004). Finally, there is no reliable test to confirm a LPD so empirical progestogen admin istration is offered in patients with three or more consecutive miscarriages.

For antiphospholipid syndrome the standard treatment comprises of low-dose aspirin (starting before conception at 75-100 mg per day) and LMWH or unfractionated heparin given once or twice daily respectively starting from the day of positive pregnancy test (ESHRE, 2012). However, not all sources support the use of LMWH as they report its comparable efficacy has not been established (ASRM, 2012). The role of IVF in cases of RPL is debatable as there is no problem conceiving but with maintenance of pregnancy (Kirshenbaum and Orvieto, 2019). Proponents of IVF as an empirical treatment for RPL state that IVF helps to shorten the time to conceive, optimise the timing of conception, improve gamete and embryo quality and increase endometrial receptivity with the use of adjuvant treatments or ‘add-ons’ like assisted hatching, biological glue, immunologic therapy, etc. to improve implantation and live rates but their role is controversial and cannot be recommended currently (Kirshenbaum and Orvieto, 2019). Moreover, cases undergoing prenatal genetic screening with IVF have not resulted in increased live birth rate as compared to natural pregnancy so this recommendation cannot be provided with current evidence (RCOG, 2011).

Counselling:

Couples face significant concerns while undergoing fertility treatment as they cope with complex decision-making, rigid medication schedules and the ongoing process of dealing with the diagnosis of infertility. The basic aim of counselling is to ensure that patients understand the implications of their treatment choice, receive sufficient emotional support and can cope in a healthy way with the consequences of the infertility experience. Infertility commonly activates feelings of "shame, guilt, sadness, and loss of control" (Koser, 2019).

Referrals often are made for counselling with pregnancy losses in the late second or third trimester but it is important for healthcare providers to understand that even an early loss can be very difficult and indicate need for referral for counselling as well (Alqassim et al., 2022).

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"Women are more likely to want to discuss what's happening, and men typically want more distance and emotional control," says Dr Karen Hall (Weir, 2018). "In couples therapy, it's helpful to open women's eyes to the fact that the loss is affecting their partners, just in a different way. That alone can decrease the conflicts significantly."

Couples expect to be treated with empathy with an attitude of: every pregnancy loss counts and must not be trivialized (Koert et al, 2019). According to Bennet, a genetic counsellor at UW Medical Center (Sowers, 2005), following screening of the patient, partner and their first and second degree relatives, a team approach should be utilised, involving other medical and psychosocial disciplines so that patients with RPL will receive good care.

Conclusion:

There is no one size fits all with the management of a couple with RPL. But awareness of the common causes can enable the clinician to form an individualized plan, educate their patients and target treatment. The best approach to a couple facing RPL not only involves good clinical knowledge but also appropriate and realistic counselling, addressing their feelings, concerns and misconceptions. Some causes are difficult to diagnose and even more difficult to treat or counteract. While some patients (such as those with genetic disorders) may be offered PGD and subsequent replacement of an embryo free from disease, in many cases of RPL conception is not the issue so IVF will offer little to no benefit. A multi-disciplinary team which, alongside a structured and transparent approach to medical management, will offer the best route to good quality patient care of the RPL group of patients.

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