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Recurrent Pregnancy Loss

Pregnancy loss is defined as the spontaneous miscarriage of a pregnancy before 24 weeks gestation. When the loss of pregnancies reaches two or more, it is considered recurrent pregnancy loss (RPL) (1). It affects approximately 1-2% of women of reproductive age (1). Recurrent pregnancy loss has a significant emotional impact on the couple; therefore, early specialist referral is warranted for appropriate investigations and ongoing supportive care.

Investigations:

1. Thorough history:

Lifestyle factors, including smoking, excessive alcohol intake, excessive exercise, and being overweight or underweight, have an impact on the risk of RPL (1). In addition, detailed medical, family, and reproductive history is warranted to tailor diagnostic investigations for women with RPL.

2. Genetic analysis

Genetic abnormalities of the fetus are a known cause of sporadic and recurrent pregnancy loss, and the incidence of aneuploid early pregnancy losses increases with maternal age (1). Genetic analysis of demised pregnancy tissue may provide the couple with an answer to the pregnancy loss and help further investigations or treatments required. The preferred method of genetic analysis is array-CGH (3).

Parental karyotyping is recommended for a couple with a strong genetic history, such as a previous child with known congenital abnormalities/unbalanced chromosome abnormalities or detection of translocation in the previous pregnancy tissue (1). For other couples with no apparent genetic history, the benefit of parental karyotyping is limited as the yield of finding any genetic abnormalities causing RPL is extremely low (1).

3. Anatomical assessment

Congenital uterine malformations and acquired uterine malformations can have an impact on the prevalence of RPL (1). Imaginings such as transvaginal 2D or 3D ultrasound, sonohysterography (SHG) or MRI could be considered to assess uterine anatomy. If a Mullerian uterine malformation is detected, kidney and urinary tract ultrasound should be considered.

4. Thrombophilia screening

Hereditary thrombophilia

There is a weak association between RPL and hereditary thrombophilia, including factor V Leiden, prothrombin gene mutation, protein C, protein S, antithrombin deficiency and MTHFR mutation (1). Therefore, routine screening for hereditary thrombophilia is not recommended. However, screening may be considered if additional risk factors for thrombophilia are identified, such as a family history of hereditary thrombophilia or previous venous thromboembolism (3).

Acquired thrombophilia

Acquired thrombophilia specifically refers to antiphospholipid syndrome (APS). It can lead to thrombosis in both arteries and veins and pregnancy complications. Screening for antiphospholipid antibodies such as lupus anticoagulant and anticardiolipin antibodies is recommended for women with RPL, as it can provide possible explanations for RPL and facilitate treatments to improve future pregnancy outcomes (1). Based on current evidence, B2 glycoprotein I antibodies were not statistically associated with RPL before 13 weeks gestation (1). However, it could be considered part of acquired thrombophilia screening to improve clinical knowledge.

5. Immunological screening

Routine screening for Human Leukocyte Antigen (HLA), anti-HY antibodies, cytokine testing, NK cell testing (peripheral blood or endometrial tissue) and anti-HLA antibodies is not recommended in women with RPL (1).

6. Metabolic and endocrine factors

Thyroid function, including TSH and TPO antibodies, should be screened in women with RPL (3). Overt hypothyroidism or hyperthyroidism should be treated to decrease the risk of miscarriage and improve pregnancy outcomes (3). Prolactin testing is not routinely recommended without clinical symptoms of hyperprolactinaemia. Screening for PCOS, ovarian reserve, fasting insulin, fasting glucose, luteal phase insufficiency, androgen level, LH and homocysteine is not recommended in women with RPL due to insufficient evidence (1).

7. Male factors:

Lifestyle factors in the male partner should also be routinely assessed, including age, smoking and alcohol consumption, exercise pattern and BMI, to improve the clinical outcomes of couples with RPL. DNA fragmentation could be tested for diagnostic purposes, and there is an association between unhealthy lifestyles and sperm DNA damage (1).

Treatment options:

Lifestyle modifications:

Lifestyle modifications for male and female partners experiencing RPL, such as smoking cessation, maintaining a healthy diet, exercising regularly, maintaining a healthy BMI, reducing caffeine intake, and avoiding excessive alcohol consumption, are recommended to improve future pregnancy outcomes.

Antithrombotic therapy

For women with a history of RPL and confirmed diagnosis of APS, low-dose aspirin (75-100mg/day) and unfractionated heparin may decrease the rate of miscarriage and improve the live birth rate, based on a recent Cochrane review (2). Aspirin and heparin are not recommended for women with a history of RPL and hereditary thrombophilia, as current evidence did not show any benefit to improve the live birth rate (1).

Treatment for thyroid dysfunction

Overt hypothyroidism should be treated either before conception or during the first trimester with Levothyroxine to decrease the risk of miscarriage, preterm birth or low birth weight (1). The treatment for women with subclinical hypothyroidism and RPL is controversial. Therefore, individual discussion is required to weigh potential benefits against the risks. Regular thyroid function check is required during the pregnancy to titrate dosing of Levothyroxine and decrease potential risks to the ongoing pregnancy (1). Levothyroxine is not indicated for euthyroid women with thyroid antibodies and RPL (1).

Genetic testing

Genetic counselling is warranted for couples with an abnormal fetal or parental karyotype to discuss prognosis and further diagnostic options (1). However, there is currently insufficient data to support the routine use of preimplantation genetic testing for women with unexplained RPL (3).

Surgeries

The evidence to evaluate the effect of surgeries on congenital uterine malformations is scant. Only one RCT showed no benefits of removing the septum via hysteroscopy to reduce the chance of pregnancy loss for women with RPL (1). There is insufficient evidence to support surgical removal of endometrial polyps, submucosal or intramural fibroids for women with RPL (1).

Women with a history of secondary trimester PL and cervical weakness should have serial cervical surveillance (1). The benefits of prophylactic cerclage are limited, but it can be considered for those women with recurrent secondary trimester PL due to cervical insufficiency (1).

Others:

Vaginal progesterone should be considered in women with recurrent miscarriage who presented with bleeding in early pregnancy until 16 weeks gestation (3). There is insufficient evidence to recommend using metformin, lymphocyte immunisation, glucocorticoids, intralipid therapy or endometrial scratching to improve life birth rates in women with RPL (1).

References:

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