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RECURRENT PREGNANCY LOSS

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Abstract

Miscarriage occurs when the fetus is unable to survive outside the womb and the results of conception are expelled. Although the issue of RPL is still controversial, current information about the suggested treatment offers effective treatment to improve reproductive quality and can provide appropriate therapy in a woman with RPL based on the etiology. The time restriction until the fetus is pronounced viable or capable of surviving outside the womb varies by country. According to the World Health Organization, over 21.6 million abortions occurred worldwide in 2008, with almost all of these cases occur in developing countries. The risk of miscarriage increases most significantly at the age of 35 years. Women aged 35 years have twice the risk of miscarriage compared to women aged < 35 years. Antiphospholipid syndrome is a risk factor for recurrent miscarriage, which occurs in about 15% of patients. The reason of recurrent miscarriage can be linked to both fetal and maternal factors. Diagnostic examinations are not recommended in patients with recurrent miscarriage unless certain criteria are met. However, screening can be used to identify risk factors. The management of recurrent miscarriage should be addressed toward the underlying cause with a treatable etiology or pathophysiology.

Keywords: Miscarriage, Fetus, Womb

1. INTRODUCTION

Almost every couple considers pregnancy to be a beautiful moment, makes the occurrence of miscarriage a pretty horrible one, especially if the incident happens repeatedly. Because of the unknown causes and a scarcity of evidence-based research, recurrent miscarriage is a challenging condition in the field of reproduction. Essentially, the term "miscarriage" refers to a type of pregnancy failure that is defined by fetal death and may be accompanied by the expulsion of the fetus or embryo before the products of conception have reached a viable stage of development (MMJ Van den Berg et al., 2014); (Rai & Regan, 2006))

Based on the statement of Indonesian experts, at any gestational age above 20 weeks, a fetus is recognized viable. As a result, in Indonesia the term "miscarriage" refers to a pregnancy that occurs between conception and 20 weeks of gestation. Ten to twenty percent of losses occur in the first trimester until twelve weeks' gestation, which is referred to as an early miscarriage. While about 1-2% of miscarriages occur at 13-20 weeks of gestation or late miscarriages. The Indonesian Association of Reproductive Endocrinology and Fertility (HIFERI) defines recurrent miscarriage as a miscarriage that occurs at least two or more times in a row at a gestational age of less than 20 weeks and/or a fetus weight less than 500 grams. Several professional organizations, such as ESHRE (ESHRE Early Pregnancy

Guideline Development Group 2017) and the American Society for Reproductive Medicine (ASRM) in the US (Practice Committee of the American Society for Reproductive Medicine 2012) now define recurrent miscarriage as the loss of two or more consecutive pregnancies for examination, however, the previous definition of three or more consecutive miscarriages is still used by others, such as the Royal College of Obstetricians and Gynecologists 2011, Health Service Executive (HSE) in Ireland (Health Service Executive 2016) and the French College of Gynecologists and Obstetricians (Laird et al., 2003; Baek et al., 2007;Jauniaux et al., 2006).

Recurrent Pregnancy Loss (RPL) is a serious reproductive health issue, affecting between 2% – 5% of couples. RPL prevalence varies significantly between reports, owing to discrepancies in definitions and criteria utilized, as well as population characteristics. Primary RPL is defined as multiple losses in women who have never had a viable baby, whereas secondary RPL is defined as multiple losses in women who have had a pregnancy lasting more than 20 weeks. While tertiary RPL is the term used to describe the loss of multiple pregnancies in between normal pregnancies. ((C.-S. et al., 2004); (Khalife et al., 2019)). Despite the fact that the topic of RPL is still highly controversial, current knowledge about the suggested treatment promises effective treatment to improve reproductive quality and can provide appropriate therapy in a woman with RPL based on the etiology in most cases.

2. THEORETICAL BASIS

2.1. Definition

Miscarriage is an expulsion of the products of conception before the fetus is able to survive outside the womb. In each country, there are different time limits until the fetus is declared viable or able to survive outside the womb. The European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynecologists (RCOG) recommend a time limit of 24 weeks' gestation. However, Indonesian experts stated that a fetus is viable after it has reached a gestational age of more than 20 weeks, hence the word "miscarriage" is used in that country to describe a pregnancy loss that occurs until 20 weeks of gestation ((El Hachem et al., 2017); (Baek et al., 2007)).

2.2. Epidemiology

According to the World Health Organization, over 21.6 million abortions occurred worldwide in 2008, with almost all of these cases occur in developing countries. The proportion of abortions in developing countries increased from 1995-2008, from 78% to 86%. Recurrent miscarriage is a different condition from infertility. Of all clinical pregnancies detected, 12 – 15% will end in miscarriage, but only less than 5% of women have two consecutive miscarriages, and less than 1% have three or more miscarriages in a row (Alfansury & Trisetiyono, 2018).

2.3. Risk Factors and Pathogenesis

a) Age factor
b) Psychological Factors
c) Environmental and Occupational Exposure Factors
d) Lifestyle Factor
e) Genetic Factors and Chromosomal Abnormalities
f) Uterine Anatomy Factors
g) Infection Factor
h) Hormonal and Metabolic Factors
i) Immunological Factors
j) Thrombophilia Factor
k) Apoptotic Factor

2.4. Diagnosis

a) Anamnesis

Recurrent miscarriage management mainly relies on anamnesis. Anamnesis questions pertaining to risk factors and prognosis are included in the questionnaire on recurrent miscarriage occurrence. The concept of the cause of recurrent miscarriage can be caused by factors related to the product of conception and maternal factors. The growth and development of the products of conception certainly do not only come from external factors, but also internal factors of the fetus, such as chromosomes and genes. Therefore, various cases of recurrent miscarriage have been widely studied and can generally be classified as the result of chromosomal abnormalities (paternal and conception), anatomic abnormalities, endocrine disorders (involving metabolic and reproductive hormones), immunological disorders, and coagulation disorders. (Hendarto et al., 2018).

b) Diagnostic Examination

According to ESHRE, several diagnostic tests can be performed on patients with recurrent miscarriage although it is not recommended for all couples, only relevant in certain recurrent miscarriage couples, for example: (a) Prolactin test in women with clinical symptoms of hyperprolactinemia (oligo-amenorrhea); (b) Determination of HLA II classification in women with secondary recurrent miscarriage after the birth of a boy; and (c) Assessment of sperm DNA fragmentation, which may be more relevant in men with an unhealthy lifestyle (smoking, alcohol, excessive exercise, and unhealthy weight) (Khalife et al., 2019).

2.4.1. Genetic Factor Screening

There are two types of abnormalities that are common in early pregnancy loss, namely developmental and genetic. On embryoscopic examination, direct visualization of the embryo or early fetus in utero shows that this abnormality occurs in 86 – 91% of miscarriages. Genetic analysis of pregnancy tissue is not routinely recommended, but it can be done to provide counseling to the patient regarding the causes of miscarriage and to assist in determining whether or not further testing or therapy is necessary. The Array-CGH technique is recommended for genetic analysis of gestational tissue, based on the reduced effect of maternal contamination (Merel MJ van den Berg et al., 2012).

Parental karyotyping is not routinely recommended in couples with recurrent miscarriage. Parental karyotyping may be recommended in couples with recurrent

miscarriage only after an individual risk assessment has been carried out. A parental karyotype may be recommended based on the genetic history (e.g., in cases of previous birth of a child with a congenital anomaly, a chromosomal abnormality in the family, or the detection of a translocation in the gestational tissue). Meanwhile, for other couples, the benefits obtained from this examination are limited because the possibility of finding abnormalities is very low, such as in couples with women over 39 years of age, having less than 3 miscarriages and not being found in a family history, where in this couple the possibility of becoming a career translocation is very low (Franssen et al., 2011).

2.4.2. Metabolic and Endocrine Factor Screening

Hormonal and metabolic factors are important risk factors for recurrent miscarriage. Thyroid hormone is very important for fetal development. A recent review of thyroid function and reproduction concluded that impaired thyroid hormone and elevated levels of thyroid peroxidase (TPO) antibodies (TPOAb) are associated with impaired folliculogenesis, spermatogenesis, fertilization and embryogenesis. Hence, thyroid tests (TSH and TPOAb) are recommended in women with recurrent miscarriage (Alexander et al., 2017).

An increased risk of miscarriage is associated with abnormal glucose levels. Therefore, it is important to correct abnormal fasting blood glucose and/or hemoglobin A1C (HgbA1c) levels in the preconception period to reduce risk as recommended by ASRM. Patients with polycystic ovary syndrome (PCOS) are also at higher risk for miscarriage (Toth et al., 2010). Insulin resistance has been shown to be more common in women with a history of recurrent miscarriage than in women without a history of recurrent miscarriage. However, no studies have been found regarding the potential prognosis in subsequent pregnancies through insulin resistance testing. In addition, the mechanism by which insulin resistance can lead to miscarriage is still unknown. Therefore, assessment of insulin and fasting glucose is not recommended to determine the prognosis of subsequent pregnancies in women with recurrent miscarriage (Wang et al., 2011).

2.4.3. Anatomical Abnormalities Screening

Imaging methods to detect uterine abnormalities have been carried out using various techniques, with different potentials and limitations for diagnosing various types of abnormalities. A study by Saravelos in 2008 said that the combination of hysteroscopy and laparoscopy is the gold standard examination in diagnosing uterine abnormalities because it gets direct visualization of the internal and external contours of the uterus. Sonohysterography or Hysterosonography (SHG) is a safe procedure that can provide a more detailed image of uterine abnormalities than hysterosalpingography (HSG) or ultrasound (US). In addition, SHG is more accurate in diagnosing and classifying congenital uterine abnormalities ((Makris et al., 2007); Hendarto et al., 2018).

Three-dimensional ultrasound allows visualization of the internal and external contours of the uterus, has high sensitivity and specificity, and is non-invasive. Two-dimensional ultrasound and HSG are non-invasive, in 2D ultrasound has low sensitivity, but has high specificity for diagnosing abnormalities, whereas HSG has good sensitivity to diagnose uterine abnormalities more clearly, but is limited in distinguishing between types of abnormalities. Magnetic resonance imaging (MRI) has been recommended as an examination to assess the uterine cavity and fundus, although there is controversy as to whether MRI can replace the combination of hysteroscopy and laparoscopy. Sono-

embryoscopy and Uterine Doppler ultrasound have been recommended as studies of uterine abnormalities in women with recurrent miscarriage,

Uterine abnormalities (submucosal myomas, endometrial polyps, and uterine adhesions) are found in women who have had miscarriages, but their clinical relevance is unclear. Although the relevance of acquired uterine abnormalities in recurrent miscarriage is unclear, they can be diagnosed by the tests used to detect congenital abnormalities. Therefore, 2D ultrasound is not a sensitive method for detecting uterine adhesions. Submucosal fibroids and endometrial polyps can be detected using 3D ultrasound, SHG, 2D ultrasound, or HSG. However, there is no strong evidence regarding the preferred examination, but hysteroscopy is considered the gold-standard examination (Makris et al., 2007).

2.4.4. Immunology Screening

Existing tests to investigate immunological disorders include antiphospholipid, antithyroid, antinuclear and antisperm antibodies, natural killer cells, antipaternal cytotoxicity and embryotoxic factors. Several of these autoimmune disorders have been linked to possible causes of miscarriage. A meta-analysis study by Beydoun et al. in 2005 showed that the distribution of alleles at the HLA-A, -B and -C loci was not found to be different in frequency between the recurrent miscarriage couple group and the control group where the allele distribution in the HLA-DR locus was found to increase significantly. Meanwhile, in a 2011 study by Aruna et al that used DNA-based HLA assays, no increase in HLA-DR was found in couples with recurrent miscarriage. There is insufficient evidence to show an association between subsequent pregnancy outcomes and HLA polymorphisms in women or couples with recurrent miscarriages. In the compatibility of HLA and HLA-C alleles in couples, inconsistent associations with recurrent miscarriage were found, while weak associations with specific HLA-G alleles were found in women with recurrent miscarriages. Therefore, examination of the HLA-DR (or other classic HLA gene) in women with recurrent miscarriage is not recommended in clinical practice (Aruna et al., 2011; Toth et al., 2010).

2.4.5. Thrombophilia Screening

Acquired thrombophilia refers to Antiphospholipid Syndrome (APS). APS is diagnosed based on the presence of persistent antiphospholipid antibodies and vascular thrombosis and/or pregnancy complications. There are three clinically relevant antiphospholipid antibodies (thrombosis-associated antibodies), namely Lupus Anticoagulant (LA), anticardiolipin antibody (ACA, IgG and IgM), and antibodies ß2 glycoprotein I (aß2GPI, IgG and IgM). In clinical criteria, three or more idiopathic recurrent miscarriages before 10 weeks of gestation, in the absence of maternal or hormonal anatomic abnormalities and paternal and maternal chromosomal abnormalities is one of the clinical criteria that can lead to the diagnosis of APS (Miyakis et al., 2006)

Screening for aß2GPI antibody may be considered in women with recurrent miscarriage. Results of a recent prospective study showed that decreased a2GPI (IgM) antibodies with anticoagulant therapy correlated with better pregnancy outcome. Although the time interval for LA, ACA and aß2GPI antibody tests after miscarriage is unknown, it is generally considered appropriate at 6-week intervals. Based on the Miyakis criteria for APS diagnosis requires confirmation of examination results at least after 12 weeks (Miyakis et al., 2006).

2.5. Management

Management of recurrent pregnancy loss (RPL) should be directed on treatable causes. Patients and their families should be informed about the risks, alternatives, and success rates of each available treatment option. Treatment success can be increased by providing emotional support for the couple. There should be collaborative teamwork and clear communication between reproductive endocrinologists and obstetricians, whenever it possible to be done (Pillarisetty & Bragg, 2020).

Management of Recurrent Miscarriage Based on Etiology

2.5.1. Genetic Factors

a. Genetic Counseling

All couples with a history of recurrent miscarriage and known parental karyotype abnormalities should be offered any necessary prenatal diagnostic procedures. This information is critical for parents concerned about the chromosomal abnormality's inheritance pattern. If the karyotype analysis reveals an abnormality, counseling regarding chromosomal disorders and genetics must be provided. Additionally, couples are informed about the available therapy alternatives, including their benefits and drawbacks, in order to select their preferred therapy (Baek et al., 2002).

b. Prenatal Screening

In cases of severe recurrent miscarriage, assisted reproductive technology services with prenatal screening facilities may be required. Preimplantation Genetic Testing for Monogenic / Single Gene Defects (PGT-M) or Chromosomal Structural Rearrangements (PGT-SR), previously PGD (Preimplantation Genetic Diagnosis), is an alternative examination in invasive prenatal diagnosis which can avoid termination of pregnancy in high-risk couples in transmitting genetic disorders such as various monogenic diseases and chromosomal structural abnormalities, which are later found in the recurrent miscarriage population (Franssen et al., 2011).

In a study by Ikuma et al reported a live birth rate of 37.8% in the first pregnancy after PGD (PGT-SR) and 53.8% in the first natural pregnancy (non-PGD) after the determination of carrier status (OR 0.52; 95%CI 0.22-1.23). PGD (PGT-SR) reduced the rate of miscarriage, but the cumulative live birth rate (OR 1.10; 95%CI 0.45–2.70) and time for pregnancy (12.4 months vs. 11.4 months) did not differ between the two groups (Ikuma et al., 2015). Apart from that, Franssen et al in a systematic review of PGD (PGT-SR) for couples with carrier status of chromosomal structural abnormalities and recurrent miscarriage concluded that there was no improvement in the live birth rate with PGD (PGT-SR) (Franssen et al., 2011).

2.5.2. Thrombophilia

In women with thrombophilia and recurrent miscarriage, therapy given to prevent placental thrombosis (antithrombotic agents including aspirin and anticoagulants) and/or suppress the immune system is recommended to increase the chances of a successful pregnancy (Pilarisetty and Gupta, 2020).

a. Hereditary thrombophilia
b. Antiphospholipid Syndrome (APS)

- Anticoagulants
- Steroids

- Intravenous Immunoglobulin (IVIg)

2.5.3. Factors of Metabolic Disorders/ Endocrinology

a. Thyroid disorders
b. Luteal Phase Insufficiency
c. Insulin Resistance
d. Hyperprolactinemia
e. Vitamin D consumption

2.5.4. Infection

An observational cohort study by McQueen et al (2014) in women with recurrent miscarriage and chronic endometritis who received antibiotic therapy, found a cure rate of 100% after treatment with antibiotics. The cumulative live birth rate was 88% (21/24) for the treated chronic endometritis group compared with the group without chronic endometritis of 74% (180/244). The live birth rate per pregnancy for the treated chronic endometritis group was 7% (7/98) before treatment, while after treatment it was 56% (28/50) (McQueen et al., 2014).

An RCT study by Ugwumadu et al (2003) regarding the effectiveness of oral clindamycin in 485 pregnant women with bacterial vaginosis or asymptomatic abnormal vaginal flora, found that women receiving clindamycin experienced fewer miscarriages (13/244) than those in the placebo group (38/241; percentage difference 10.4%, 95% CI 5.0–15.8, P = 0.0003). Thus, it was concluded that treatment of asymptomatic abnormal vaginal flora infection and bacterial vaginosis with oral clindamycin administration in the early second trimester significantly reduces the rates of miscarriage and preterm delivery in the general obstetric population (Ugwumadu et al., 2003)

2.5.5. Factors Anatomical Abnormalities

a) Congenital Uterine Abnormalities
b) Acquired intrauterine abnormalities

Endometrial Polyps

Despite the fact that there are no valid research demonstrating the benefits of polypectomy for recurrent miscarriage, however, in (Jaslow, 2014) said that if polyps were found on examination of women with recurrent miscarriages and no other known cause, polypectomy could be considered if the polyp size was > 1 cm. This size limit is based on observations from the study of Lieng et al (2009) who found a significant proportion (27%) of endometrial polyps that regressed spontaneously within one year, and were specifically seen in smaller polyps (<1cm) (Lieng et al., 2009)

Fibroids

In a Cochrane systematic review by Metwally et al (2012) who said that there was no significant effect of myomectomy therapy on the rate of miscarriage in each type of fibroid (intramural fibroids OR 0.89 (95%CI 0.14-5.48), submucosal fibroids OR 0.63 (95%CI 0.09-4.40), the combination of intramural and subserous fibroids OR 0.25 (95%CI 0.01-4.73) and the combination of intramural and submucosal fibroids OR 0.50 (95%CI 0.03-7.99). In two studies comparing laparotomy with laparoscopic myomectomy also did not find significant effect on live birth rate (OR 0.80, 95%CI 0.42-1.50), miscarriage rate (OR 1.31, 95%CI 0.40-4.27), and preterm birth rate (OR 0.68, 95%CI 0.11-4.43) (Metwally et al., 2020).

Intrauterine adhesions (Asherman's syndrome)

Surgery is the treatment for intrauterine adhesions. However, there are no robust enough RCT studies, so this conclusion is based on only a few small observational studies comparing miscarriage rates before and after adhesiolysis. which found a miscarriage rate of about 15-16% after adhesiolysis. Another study reported that the postoperative miscarriage rate in women with a history of previous miscarriages was 10% (10/103), compared with infertile women, which was 30% (24/79) suggesting that adhesiolysis may be a more effective treatment for women with recurrent miscarriage compared to women with reproductive problems (Jashlow, 2014).

2.5.6. Management for Idiopathic Recurrent Miscarriages

a. Lymphocyte Immunization Therapy (LIT)

A Cochrane (2014) systematic review that evaluated the effectiveness of LIT on live birth rates found OR 1.23 (95% CI 0.89-1.70) in 12 RCTs using paternal lymphocytes and OR 1.39 (95% CI 0.68-2.82) in 3 RCTs using donor lymphocytes (excluding paternal) compared with placebo. There is no significant benefit on live birth rates in LIT therapy with paternal lymphocytes or donor lymphocytes in women with recurrent miscarriage (Wong et al., 2014).

Studies by Christiansen et al regarding the serious side effects of using LIT suggest that there is a substantial risk of neonatal alloimmune thrombocytopenia and red cell antibody production that can lead to erythroblastosis fetalis, and some risk of transferring infectious agents such as hepatitis and HIV and increasing the long-term risk of hematology malignancy (Hendarto et al., 2018)

b. Intravenous Immunoglobulin (IVIg)

A systematic review and meta-analysis by Egerup et al (2015) on 11 RCTs (531 patients) showed no significant difference in miscarriage rates in the IVIg group compared with the placebo group (RR 0.92, 95%CI 0.75-1.12, p=0.42). In addition, the administration of IVIg showed an increased risk of side effects compared to placebo.

Side effects such as headache and skin rash were significantly more common in patients treated with IVIg than in patients treated with placebo. However, there was no difference in the incidence of serious side effects (Christiansen et al., 2005).

c. Prednisone

Laskin et al conducted an RCT study to examine the effectiveness of the combination of prednisone and aspirin compared with placebo in women with idiopathic recurrent miscarriage and positive for immunological biomarkers (antiphospholipid, antinuclear, anti-DNA or anti-lymphocyte antibodies). The dose of prednisone given is very high (40-50 mg/day) for the entire duration of pregnancy. In the intervention group, the live birth rate was 9% higher, which was not significantly different from the control (OR 1.5; 95%CI 0.8-2.6). However, the intervention group had a significantly higher risk of preterm birth (62% vs 12%, $p < 0.001$), diabetes and hypertension were associated with high-dose and long-term use of prednisone. So, it can be concluded that the combination therapy of prednisone and aspirin is not effective in increasing live births but rather increases the risk of prematurity (Hendarto et al., 2018).

d. Anti coagulant

A Cochrane review by de Jong et al (2014) of 9 RCT studies of anticoagulant therapy in women with idiopathic recurrent miscarriage with or without hereditary thrombophilia,

found that there was no significant benefit on live birth rates from any of the anticoagulant therapies (aspirin, LMWH, and LMWH + aspirin) compared with placebo or no therapy.

A multicenter RCT study by Pasquier et al (2015) to determine the effect of heparin (enoxaparin 40 mg IM) compared with placebo in 258 pregnant women with a history of idiopathic recurrent miscarriage ("2 consecutive miscarriages before 15 weeks of gestation) and negative thrombophilia test results was found that live births were 66.6% in the group receiving heparin and 72.9% in the placebo group (MD ($6%), 95%CI ($17.1) – (5.1). So, it can be concluded that heparin administration did not increase live births in non-thrombophilic women with idiopathic recurrent miscarriage (Pasquier et al., 2015).

2.6. Complications

Women who suffer from recurrent miscarriages may face emotional and mental distress as a result of this diagnosis, which has a severe influence on the woman and her family as a whole. When a couple experiences recurrent miscarriages, they may experience psychological distress and the fear that the situation may never be resolved (Pillarisetty and Gupta, 2020).

Based on a study conducted by Ticconi et al (2020) when women with RPL were grouped according to two main diagnostic categories namely with explained and unexplained RPL, the overall rates of pregnancy complications were similar. However, analyzes performed for specific complications revealed that the risk of preeclampsia and placental abruption was higher in women with unexplained RPL. A possible and plausible explanation for this finding considering that the condition is related because preeclampsia is a major known risk factor for placental abruption, is that some women with unexplained RPL have impaired placentation (Ticconi et al., 2020)

When women with RPL were divided according to the other two main diagnostic categories of primary and secondary RPL, the overall rates of pregnancy complications were similar. However, analyzes performed with specific complications revealed that the risk of gestational diabetes mellitus (GDM) was higher in women with secondary RPL than in women with primary RPL. A possible explanation for these findings is that women with secondary RPL are more exposed than women with primary RPL to the well-known diabetogenic effects of pregnancy given primarily in the second half of pregnancy, making them more susceptible to GDM in successive pregnancies. This possibility is also supported by recent observations showing a link between high pregnancy counts and an increased prevalence of GDM (Ticconi et al., 2020).

Ultimately, there is evidence to suggest that women with RPL are at increased risk of long-term cardiovascular issues; as a result, the International Federation of Gynaecology and Obstetrics (FIGO) has recently published guidance on long-term follow-up of all these women in an effort to mitigate this risk. However, this necessitates additional investigation (Ticconi et al., 2020).

2.7. Prognosis

Couples who experience recurrent miscarriage (RPL) suffer greatly in terms of their emotional and psychological well-being. It has been linked to depression, anxiety, and low self-esteem in the past. A woman's increased maternal age, together with the number of previous losses, appears to be the most powerful independent risk factors for a subsequent miscarriage (Pillarisetty and Gupta, 2020).

Constant frustration and anxiety of a repeat miscarriage are the result of RPL, and couples will continue to hope for and fear a successful pregnancy at the same time. In addition to the women and families affected by RPL, doctors who treat them suffer as well. Anger, sadness, frustration, and confusion are just a few of the negative emotions a partner may experience as a result. It can also have a negative impact on the relationship and lead to a decrease in harmony (Pillarisetty and Gupta, 2020).

3. RESULT AND DISCUSSION

Miscarriage occurs when the fetus is unable to survive outside the womb and the results of conception are expelled. Although the issue of RPL is still controversial, current information about the suggested treatment offers effective treatment to improve reproductive quality and can provide appropriate therapy in a woman with RPL based on the etiology. The time restriction until the fetus is pronounced viable or capable of surviving outside the womb varies by country. According to the World Health Organization, over 21.6 million abortions occurred worldwide in 2008, with almost all of these cases occur in developing countries. The risk of miscarriage increases most significantly at the age of 35 years. Women aged 35 years have twice the risk of miscarriage compared to women aged < 35 years. Several studies have shown that stress during pregnancy is associated with an increased risk of pregnancy outcomes. Furthermore, exposure to heavy metals (cadmium and lead) and micronutrient deficiencies (zinc, copper, and vitamin E) can cause miscarriage in women with a history of recurrent miscarriages. While unhealthy lifestyle is also a risk factor for miscarriage.

Smoking, alcohol consumption (>4 drinks/week) and caffeine consumption (>3 cups/>300mg/day) are associated with an increased risk of recurrent miscarriage through their effect on the tropoblast invasion process. Ethnicity is associated with risks to health posed by obesity, BMI less than 27 kg/m2 is more recommended than a BMI of 30 kg/m2 for Asian populations. Uterine malformations can be one of risk factors for recurrent miscarriage. One of the most common malformations is a septate, bicornuate, and didelphic uterus. In patients with recurrent miscarriage with a septate uterus, hysteroscopic metroplasty can be performed. Infection is also a risk factor for recurrent miscarriage.

Hormonal and metabolic factors are important risk factors for recurrent miscarriage. For successful implantation, progesterone induces secretory changes in the endometrial lining, resulting in insufficient progesterone levels which can lead to miscarriage. Uncontrolled diabetes, thyroid disorders, and hyperprolactinemia are strongly associated with an increased risk of miscarriage, and according to ASRM guidelines should be assessed and treated in the clinical setting of recurrent miscarriage. Abortion can occur as a result of impaired humoral or cellular responses to the embryo. Antiphospholipid syndrome (APS) is one of the risk factors for recurrent miscarriage which is reported to occur in about 15% of patients.

Recurrent miscarriage can be caused by elements connected to the product of conception and maternal factors, according to the concept. External and internal components, such as chromosomes and genes, play a role in the growth and development of conception products. Developmental and genetic abnormalities are the two categories of abnormalities that typically occur in early pregnancy loss. Recurrent miscarriage is associated with hormonal and metabolic factors. Thyroid hormone is essential for fetal development. An increased risk

of miscarriage is associated with abnormal glucose levels. Therefore, it is important to correct abnormal fasting blood glucose and/or hemoglobin A1C (HgbA1c) levels in the preconception period to reduce risk as recommended by ASRM. The prevalence of uterine abnormalities is higher in women who have a history of recurrent miscarriage than in the general population.

Treatment for recurrent miscarriage can be guided by anamnesis, which can be used to confirm the diagnosis. Anamnesis questions pertaining to risk factors and prognosis are included in the questionnaire on recurrent miscarriage occurrence. Patients with a history of recurrent miscarriages should not undergo examination unless certain conditions are met. In addition, risk factors can be identified by screening. Recurrent miscarriage best managed by addressing the underlying pathophysiology or etiology, which can usually be addressed. The risks, alternatives, and success rates of each treatment choice should be explained to patients and their families. Emotional support for the couple can improve treatment outcomes.

Pre-eclampsia, placental abruption, and the development of cardiovascular abnormalities are all risks that can arise during the pregnancy. The emotional and mental impact of recurrent miscarriages can also be significant. When it comes to having children, patients and their families may endure depression, anxiety, and a loss of self-esteem. Increased maternal age, as well as a history of past losses, are two additional risk factors that can contribute to further miscarriages in women.

4. CONCLUSION

Miscarriage occurs when the fetus is unable to survive outside the womb and the results of conception are expelled. The time restriction until the fetus is pronounced viable or capable of surviving outside the womb varies by country. According to the World Health Organization, over 21.6 million abortions occurred worldwide in 2008, with almost all of these cases occur in developing countries. The risk of miscarriage increases most significantly at the age of 35 years. Women aged 35 years have twice the risk of miscarriage compared to women aged < 35 years. Antiphospholipid syndrome is one of the risk factors for recurrent miscarriage which is reported to occur in about 15% of patients. The concept of the cause of recurrent miscarriage can be caused by factors related to the product of conception and maternal factors. In the diagnostic examination in patients with recurrent miscarriage is not recommended outside of certain criteria. In addition, screening can be carried out to detect risk factors. Management of recurrent miscarriage should be directed according to the cause with the underlying etiology or pathogenesis that can be treated.

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