International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

IJAMSCR |Volume 2 | Issue 2 | April-June-2014
www.ijamscr.com

Review article

Overview on Recurrent Pregnancy Loss etiology and risk factors

Rasha A Mohamed[1], *Asmaa Darwish[2], Amal Ghouraba[1], Rehab Elbanhawy[1], Samah Shehata[1], Al-shaymaa Darwish[1].

[1]Biochemistry, Faculty of Pharmacy for Girls, Al-Azhar University , Egypt.
[2]Desert Research Center Matrouh, Egypt.

ABSTRACT

Recurrent pregnancy loss (RPL) can be defined as two or three consecutive miscarriages before 20 weeks' gestation; it affects approximately 1% to 2% of women. RPL is a multifactorial disease. It is very important to study the etiology and risk factors of RPL to find the best diagnostic tests and suitable therapeutic intervention. This article will discuss the current understanding etiologies and risk factors of RPL.

Key words: Recurrent Pregnancy Loss, Etiology, Risk Factors.

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as two or more consecutive spontaneous abortions before week 20 of pregnancy.[1] The World Health Organization recommends that in developing countries, where gestation is often uncertain, a birth weight of 500 g should be used to define viability.[2] There are 10% to 20% of women have experience a miscarriage throughout their reproductive period. 2% of those women have 2 consecutive abortions and 0.5-1% of them have 3 consecutive abortions.[3] It is very important to study the etiology and risk factors of RPL to find the best diagnostic tests and suitable therapeutic intervention.[4] Epidemiological studies have suggested that the disease might be multifactorial, with a possible genetic predisposition and involvement of environmental factors in its pathogenesis.[1]

Etiology of recurrent miscarriage

Genetic Factors

Approximately 2% to 4% of RPL is associated with a parental balanced structural chromosome rearrangement.[4] They have no chromosomal material loss or duplication in their own somatic cells and are phenotypically normal but they have meiotic segregation in haploid gonadal cells results in duplication or lack of genetic. 60% of balanced translocations are reciprocal translocations that are formed by exchange of segments between two non-homologous chromosomes, and 40% are Robertsonian translocations that are formed by the fusion of two acrocentric chromosomes at centromere with the loss of short arms.[2,3] Additional structural abnormalities associated with RPL include chromosomal inversions, insertions, and mosaicism. Single gene defects, such as those associated with cystic fibrosis or sickle cell anemia, are seldom associated with RPL.[4]

Anatomic Abnormalities

Anatomic abnormalities are 10% to 15% of cases of RPL.[4] The most common congenital anomaly of the uterus in RPL cases is the subseptate uterus. The proposed mechanisms of the abortion are poor decidualization and placental development due to the avascular uterine septum as well as uncoordinated myometrial contractions caused by increased muscle tissue in the septum.[3]

Other anatomic abnormalities like congenital uterine anomalies, intrauterine adhesions, and uterine fibroids or polyps.[4] Although, the uterine malformation more readily associated with second trimester losses or preterm labor, congenital uterine

*** Corresponding author: Asmaa Darwish**
E-mail address: **nan_ph135@yahoo.com**

anomalies also play a part in RPL. In addition, Müllerian anomalies, including unicornuate, didelphic, and bicornuate uteri have been associated with smaller increases in the risk for RPL.[2, 5]

Endocrine fators

Luteal phase defect (LPD), polycystic ovarian syndrome (PCOS), diabetes mellitus, thyroid disease, and hyperprolactinemia are the most common endocrinologic disorders implicated in approximately 17% to 20% of RPL.[4,5]

The rate of early pregnancy loss is increased with increasing interval between ovulation and implantation. This may occur due to delay in endometrial growth and maturation as result of insufficient secretion of progesterone in the corpus luteum which can lead to LPD.[3,5]

The diabetic women who had a risk of spontaneous abortions had higher fasting and postprandial glucose levels in the first trimester than those whose pregnancies continued to delivery.[2,4]

Some studies assume that patients with PCOS have an increased risk of pregnancy loss however; its mechanism is not fully elucidated. This risk is thought due to higher levels of LH, testosterone, and insulin resistance.[5] However, other studies have shown that reproductive outcome did not differ between patients diagnosed with PCOS and healthy controls. The two groups had similar live birth and miscarriage rates.[6]

Hyperprolactinemia may be associated with RPL through alternations in the hypothalamic- pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation, and/ or a short luteal phase.[7]

Infectious Etiologies

Certain infections, including Toxoplasma gondii, rubella, herpes simplex virus (HSV), measles and cytomegalovirus, are suspected to play a role in sporadic spontaneous pregnancy loss. However, the role of infectious agents in recurrent loss is less clear, with a proposed incidence of 0.5% to 5% as the most infections are isolated events.[8, 4]

Thrombotic Etiologies

The physiology of normal pregnancy involves major changes in the coagulation system such as decreased protein-c levels, the formation of resistance against the activated protein-c, increased clotting factors, and deteriorated fibrinolysis, those can cause Hypercoagulability. These changes appear to be related to the development of the uteroplacental circulation and provide a protective mechanism during delivery.[1, 3]

Thrombophilia is thought to have a role in RPL. Thrombophilia is a group of gentic conditions in which the risk of venous thrombosis is increased, and can be classified as hereditary and acquired thrombophilia.[2,3] The heritable thrombophilias most often linked to RPL include: hyper homocysteinemia resulting from MTHFR mutations, activated protein-c resistance associated with factor V Leiden mutations, protein-c and protein-c deficiencies, prothrombin promoter mutations, and antithrombin mutations. Acquired thrombophilias associated with RPL include hyperhomocysteinemia and activated protein-c resistance.[2,9] The potential association between RPL and heritable thrombophilias is based on the theory that thrombophilia lead to impaired placental development and function secondary to venous and/or arterial thrombosis.[4] The placental perfusion impairment may lead to RPL, fetal death, pre-eclampsia, intra-uterine growth retardation and abruptio placentae.[2]

Antiphospholipid syndrome (APS), is a typical example of acquired thrombophilia, causes RPL.[2] Antiphospholipid antibodies increase the aggregation of platelets and the interaction of platelets with endothelium. The expression of Annexin V that creates a protective antithrombotic shield on trophoblasts was decreased in patients with APS.[3]

Immunological factors

Because the fetus is not genetically identical to its mother, it is reasonable to infer that there are immunological events that must occur to allow the mother to carry the fetus throughout gestation without rejection.[4] The rejection of the embryo as a result of a defect in the maternal immune tolerance against semi-allogenic fetus is thought to be another mechanism that can play a role in the etiology of RPL.[3] However, This hypothesis has never been proven.[2]

Unexplained Etiologies

No apparent causative factor is identified in 50 % to 70% of couples with RPL.[5] The optimal management of these patients is often as unclear as the etiology of their RPL.[10] They have the chance for future successful pregnancy can exceed 50% - 60% depending on maternal age and parity.[5] Progesterone has been shown to be beneficial in decreasing the miscarriage rate among women who have experienced at least 3 losses.[10]

Risk Factors

Age and timing of pregnancy loss

When women with RPL are categorized by their ages, the probability of the next pregnancy ending in miscarriage is similar between the 30-34 years and the 35-39 years groups, and the risk rises dramatically to 70 % for the 40-44 years group.[3] The increase in the risk of miscarriage in this group is due to an increase in chromosomally abnormal conceptuses, probably as a result of poor oocyte quality, and a decline in uterine and ovarian function. Advanced paternal age is also a risk factor for miscarriage. The risk of miscarriage is highest in couples where the woman is older than 35 years and the man older than 40 years.[2, 11]

A woman's obstetric history predicts her future risk of miscarriage. Some studies have shown that the risk of another miscarriage increases after each subsequent pregnancy loss.[2]

It has been reported that women with recurrent pregnancy loss during pre-embryonic or embryonic period have a better prognosis than women with recurrent fetal losses.[3]

Lifestyle and environmental factors:

Cigarette smoking has been suggested to have an adverse effect on trophoblastic function and is linked to an increased risk of sporadic pregnancy loss. Obesity has also been shown to be associated with an increased risk of RPL in women whom conceive naturally. Other life style such as cocaine use, alcohol consumption and increased caffeine consumption have been associated with misscarrage.[5]

The relation between sporadic and/or RPL and occupational and environmental exposures to organic solvents, medications, ionizing radiation, and toxins have been suggested, although the studies performed are difficult to draw strong conclusions from because they tend to be retrospective and confounded by alternative or additional environmental exposures.[8]

CONCLUSION

RPL is a multifactorial disorder, need to more researches to indentify the etiology and risk factors to be easily to make standard guidelines for early diagnosis and treatment of this disorder.

REFERENCES

[1] Jeddi-Tehrani M, Torabi R, Mohammadzadeh A et al. Investigating Association of Three Poly-morphisms of Coagulation Factor XIII and Recurrent Pregnancy Loss. Am J Reprod Immunol 2010; 64: 212–217 doi:10.1111/j.1600-0897.2010.00838.x

[2] Van Niekerk EC, Siebert I, Kruger TF. An evidence-based approach to recurrent pregnancy loss. SAJOG 2013; 19(3): 61-6.

[3] Ayse seyhan1, Baris ATA, Bulent urman. Evidence based approach to recurrent miscarnage. Journal of Turkish Society of Obstetrics and Gynecology2011; 8 (1): 5- 20

[4] Ford BH and Schust DJ. Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy. Rev Obstet Gynecol (2009); 2(2): 76-88.

[5] The Practice Committee of the American Society for Reproductive Medicine. Evaluation and Treatment of Recurrent pregnancy Loss: A committee opinion. ASRM (2012); 98 (5): 1103-1110.

[6] Hudecova M, Holte J, Olovsson M, Sundstr◌m Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: Reproductive outcome and ovarian reserve. Hum Reprod 2009; 24(5):1176- 1183. [http://dx.doi.org/10.1093/humrep/den482]

[7] Arredondo F and Noble LS. Endocrinology of recurrent pregnancy loss. Semin Reprod Med 2006; 24: 33- 9.

[8] Fox-Lee L, Schust DJ. Recurrent pregnancy loss. In: Berek JS, ed. Berek and Novak's Gynecology. Philadelphia: Lippincott Williams & Wilkins; 2007:1277-1322.

[9] Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol. 2006;132:171-196.

[10] Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2008;(2):CD003511.

[11] De la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage: Results of a multicentre European study. Hum Reprod 2002;17(6):1649-1656. [http://dx.doi.org/ 10.1093/humrep/17.6.1649]