http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i4.14

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Review Article

An Overview of Factors Responsible for Recurrent Pregnancy Loss

Authors
Dr Ranjana Rawat[1]*, Dr Pawan Kumar Sharma[1], Dr Sheela Sharma[2], Dr Pawan Arun Kulkarni[1], Dr Sukanta Bandyopadhyay[1]
[1]Department of Biochemistry Rama Medical College, Hospital & Research Centre Mandhana Kanpur, Uttar Pradesh, India
[2]Department of Obs. & Gyn. Rama Medical College, Hospital & Research Centre Mandhana Kanpur, Uttar Pradesh, India
*Corresponding Author
Ranjana Rawat
Department of Biochemistry Rama Medical College, Hospital & Research Centre Mandhana, Kanpur, Uttar Pradesh, India

Abstract
Many couples attempt to get pregnant but experience recurrent miscarriage, also referred to as recurrent pregnancy loss. It has become difficult to understand the reason even after numerous investigations and hence, it can be difficult for both patients and clinicians. It has been studied that the most frequent reason for spontaneous loss is spontaneous foetal aneuploidies, especially in the first stage of pregnancy. To prevent tests or treatments that are unnecessary or have not been proven to be beneficial, studies show that it is critical to use a methodical and evidence-based strategy to testing and management. A crucial component of the management of couples with recurrent miscarriage is the specialized clinic services and psychological assistance. Also, there are many case studies which show that losses caused by de novo foetal aneuploidies happen to women who experience sporadic and recurrent losses at about the same rates, some couples who experience recurrent pregnancy loss have additional genetic factors that are linked with them, while others have nongenetic causes. Genetic testing of the foetuses from couples who have experienced two or more miscarriages could help identify the root cause and inform patients about their chances of having a healthy baby in the future. The present review emphasizes on the various aspects of recurrent pregnancy loss. It also deals with the factors which aid in causing the same. In addition, it is an examination of the relation between pregnancy and immune factors.

Introduction

During pregnancy, many factors are responsible to cause problems and one such risk is recurrent pregnancy loss. When two or more pregnancies are lost at once then the condition is referred to as recurrent pregnancy loss (RPL). Although, it is impossible to pinpoint the actual prevalence of RPL, the majority of studies indicate that it affects 1-2% of women worldwide before 20 weeks of gestation.[1,2,3] It becomes extremely difficult for couples/ parents who have this disease to conceive effectively.[4] Also, it is reported that RSA/

recurrent spontaneous abortion is a typical pregnancy complication that causes 5% of abortions in most of women who are aged.[5]In addition, the first 20 weeks of pregnancy is marked by recurrent spontaneous abortion (RSA) which is defined as 3 or more clinically identifiable pregnancy losses.[6] A miscarriage is described by the World Health Organization (WHO) as the loss of a fetus or embryo weighing less than 500g, which would typically occur at 20–22 full weeks of gestation. (WHO 1977). The loss of three or more successive pregnancies before the 24th week of gestation is referred to as recurrent miscarriage, also known as RSA, habitual abortion, or habitual miscarriage.[7]

Generally speaking, there is a risk of having three or more abortions before week 20 of pregnancy. Various studies show that the cause of approximately 50% of cases is unknown. A number of risk factors have been linked to pregnancy loss that occurs repeatedly. So the causes of RM are many such as congenital or structural uterine defects, endocrine dysfunction, auto immunologic disorders, genetic abnormalities, maternal and paternal age, viral infections,thrombophilia as well as environmental pollutants.[8]Recurrent spontaneous abortion (RSA) is a worldwide issue that is getting worse. In fact, 1% to 5% of all women and specifically those with higher age are at the largest risk.[8]

The pathophysiology of repeatedly miscarrying pregnancies varies and it depends on the gestational age and maternal age. Chromosome mistakes are considered a common cause can lead to miscarriage, and discomfort.[9]

Causes of Recurrent pregnancy loss/ factors affecting RPL

Aims for diagnostic and therapeutic recommendations are thwarted by the high baseline rate of spontaneous isolated and recurrent pregnancy losses in the general population, the lack of a clear definition for RPL, the difficulty in accessing tissues for the disorder's study, and the remarkably good prognosis for live birth among RPL patients. There are currently just a few recognised etiologies for RPL. These include specific uterine anatomic anomalies, uncontrolled diabetes mellitus, untreated hypothyroidism, parental chromosomal abnormalities, and antiphospholipid antibody syndrome (APS). Additional endocrine diseases, heritable and/or acquired thrombophilias, immunologic anomalies, infections, and environmental variables are some additional plausible or conceivable etiologies. About 50% of all cases will remain unsolved after being examined for this explanations.[10]

Genetic factors

A paternal balanced structural chromosomal rearrangement, such as a balanced reciprocal or Robertsonian translocation is responsible for about 2% to 4% of Recurrent pregnancy Losses in many regions. Chromosome insertions, inversions, and mosaicism are further structural anomalies connected to RPL.[10]

Rarely is RPL linked to single gene abnormalities, such as those linked to sickle cell anemia or cystic fibrosis. Parental karyotyping should be a part of a proper evaluation of RPL. In all instances of RPL linked to parental chromosomal disorders, genetic counselling is advised. In vitro fertilization with preimplantation genetic diagnosis may be used as part of differentiated therapy, depending on the specific diagnosis. In situations involving genetic abnormalities that always result in embryonic aneuploidy, the use of donor gametes may be advised (ie, Robertsonian translocations involving homologous chromosomes).[10]

Problems in sperms: It is debatable if sperm is defected it also a cause of repeated miscarriages. Studies have discovered higher DNA breakage and epigenetic alterations of sperm DNA, which may be linked to repeated miscarriages. Additionally, 1-5% of sperm contain aneuploidies, but there is no obvious age correlation.[9]

Anatomical factors

10% to 15% of RPL instances are assumed to be the result of anatomic anomalies, which are thought to result in improper and insufficient placentation by interrupting the endometrium's vasculature.

Arcuate, septate, unicornate, bicornate, and didelphis uteri are among the anatomical abnormalities that fall under the category of congenital uterine abnormalities. Compared to the general population, women who have lost a pregnancy are more likely to suffer these. In addition, compared to women who have primary recurrent pregnancy loss (9.0%), women with secondary recurrent pregnancy loss have a lower prevalence of congenital uterine anomalies, particularly septate uteri (4.6%).[10, 9] Intrauterine adhesions can greatly affect placentation and cause early miscarriage; they are sometimes linked to Asherman syndrome.[10]

Endocirne Factors

In addition to these disorders, other hormonal imbalances, such as abnormalities in the levels of progesterone, estrogens, and luteinizing hormone (LH), can also contribute to RPL. These imbalances can affect the development of the embryo, cause problems with implantation, and lead to early pregnancy loss. Luteal phase defect (LPD) occurs when the second half of a woman's menstrual cycle (the luteal phase) is shorter than normal or produces inadequate levels of progesterone. This can lead to an inability of the uterus to support a pregnancy, resulting in early pregnancy loss. PCOS is a hormonal disorder that affects how a woman's ovaries function. It can cause irregular menstrual cycles, high levels of male hormones (androgens), and multiple cysts on the ovaries. This condition can interfere with ovulation and lower the chances of successful pregnancy. Diabetes mellitus, particularly type 1 and type 2 diabetes, can negatively impact fertility and increase the risk of miscarriage. High levels of blood sugar can damage the developing embryo and impair its ability to implant in the uterine lining.

Thyroid disease, whether it is hypothyroidism or hyperthyroidism, can disrupt the balance of hormones in the body and affect ovulation and pregnancy. Thyroid hormones are essential for the proper functioning of the reproductive system. Hyperprolactinemia is a condition that results in high levels of prolactin, a hormone that stimulates milk production in women. This condition can interfere with ovulation and cause infertility, as well as increase the risk of miscarriage. To conclude, endocrinologic disorders are a significant contributing factor to RPL. Effective management and treatment of these conditions can improve the chances of successful pregnancy and reduce the risk of recurrent pregnancy loss.[9]

Pregnancy and immunization

Because the foetus expresses the paternal MHC class I antigen (HLA-C), it is regarded as semi-allogeneic.[8]After being processed by maternal cells, the paternal antigen expressed in foetaltrophoblast cells is transmitted to particular CD4+ T helper cells along with its own MHC class II antigen. The initial CD4+ T cells undergo differentiation into distinct T cells under the stimulation of antigens, including Th1, Th2, Th17, and regulatory T (Treg) cells. Interleukin (IL-2), tumour necrosis factor (TNF), and interferon (IFN) are produced by CD4+ Th1 cells and are the primary phagocytes that initiate host defense and are extremely lethal to intracellular infection.[6]

CD4+ Th2 cells are primarily in charge of phagocytosing extracellular parasites, such as nematodes, and they also secrete IL-5 and IL-4, which can encourage eosinophil development and differentiation. By promoting IgE and IgG1 antibodies, IL-4 and IL-13 can also suppress macrophage activity[11]. Th1 and Th2 cell reactions exhibit a physiological imbalance in a healthy pregnancy, with Th2-type cells predominating at the maternal-fetal interface and contributing to the immune defense of the embryo.In addition to these disorders, other hormonal imbalances, such as abnormalities in the levels of progesterone, estrogens, and luteinizing hormone (LH), can also contribute to RPL. These imbalances can affect the development of the embryo, cause problems with implantation, and lead to early pregnancy loss. Luteal phase defect (LPD) occurs when the second half of a woman's menstrual cycle (the luteal phase) is shorter than normal or produces

inadequate levels of progesterone. This can lead to an inability of the uterus to support a pregnancy, resulting in early pregnancy loss.

PCOS is considered a hormonal disorder that aids in affectingthe functions of ovaries. It can cause irregular menstrual cycles, high levels of male hormones (androgens), and multiple cysts on the ovaries. This condition can interfere with ovulation and lower the chances of successful pregnancy. Diabetes mellitus, particularly type 1 and type 2 diabetes, can negatively impact fertility and increase the risk of miscarriage. High levels of blood sugar can damage the developing embryo and impair its ability to implant in the uterine lining.[7]

NK cells and pregnancy

One important element of innate defense is known as natural killer (NK) cells. Peripheral blood contains the majority of NK cells, but they can also be found in a number of lymphoid and non-lymphoid tissues, including the spleen, tonsils, lymph nodes, liver, lungs, and intestine. The most prevalent lymphocytes in uterine mucosa are NK cells. Uterine stromal cells undergo a decidualization process while being affected by different sex steroids and cytokines in the late luteal phase of the early pregnancy. Large granular decidual NK (dNK) cells are one of the most noticeable signs of decidualization.[11]The innate immune system's natural killer (NK) cells are a promising novel source of risk for RM. The presence of the surface marker CD56 identifies them. Peripheral NK and uterine NK cells (pNK and uNK cells) are two distinct groups. PNK cells differ from uNK cells phenotypically and functionally, exhibit strong cytotoxic activity, and have documented antiviral and anticancer effects. Human leukocyte antigen-C (HLA-C), killer cell immunoglobulin-like receptor (KIR), human leukocyte antigen-E (HLA-E), and HLA-G are just a few of the receptors and genes expressed differently by UNK cells, which are also less lethal. Both pNK and uNK cells have the ability to modulate the immune system.[12]

Genetic considerations for recurrent pregnancy loss

Spontaneous foetal aneuploidy is primarily to blame for human reproduction's astounding inefficiency. The majority of cases from sporadic spontaneous losses (50–70%) exhibit some form of cytogenetic abnormality, with autosomal trisomies (60%) and polyploidy (20%) being the most prevalent karyotypic defects. The majority are the result of irrational mistakes in germ cell development, which by necessity have an equal impact on pregnancies in couples with and without a history of RPL.[13]The prognosis for subsequent pregnancies in RPL couples is better after an aneuploid miscarriage than after a euploid miscarriage[13, 14, 15,16].

On the other hand, losses that occur early in pregnancy seem to reveal a wide range of rather odd aneuploidies, whereas deaths that happen later in gestation show those aneuploidies more typically discovered in live newborns, such as trisomies 21, 18, and 13.Also, Endometrial studies in women who have experienced recurrent miscarriages have provided biological proof in favor of the absence of embryo selection. RPL is linked to decreased epithelial secretory function, altered uterine fluid composition, and lower expression levels of mucin 1, an anti-adhesion molecule that supports the luminal epithelium's barrier function, according to a comparative analysis of timed mid-secretory endometrial biopsies.[17]A set of deceptively straightforward experiments measuring the expression of two marker genes provided evidence that the capacity of endometrial stromal cells to produce a decidual phenotype is impaired in RPL.[6] The first marker gene was PROK1, which produces PROK1, a newly identified cytokine that stimulates leukaemia inhibitory factor in endometrial epithelial cells, promoting endometrial receptivity and embryo-uterine interaction.[17] Prolactin (PRL), the prototypical marker of decidualizing uterine stromal cells, served as the second marker.[18,19,20,21]

Conclusion

Recurrent pregnancy loss is a common and upsetting condition. It can be claimed that the psychological and physical toll on women increases with each loss they endure. The psychological and physical toll on women is frequently intolerable. According to some studies, it has been known that live birth rates among women who experience recurrent miscarriages were comparable, demonstrating that the situation has not changed since the mid-1990s. Even though receiving the RPL diagnosis can be extremely upsetting, it can be beneficial for both the doctor and the patient to remember how likely it is that the following baby will be a success.

Couples who experience pregnancy loss have a significantly higher proportion of chromosomally abnormal embryos than couples who do not experience this reproductive issue, which is primarily caused by non-disjunction. Parental karyotype is crucial once an unbalanced translocation in the fetus or kid has been discovered. In chorionic villi from RPL cases, molecular analysis techniques like PCR-based subtractive hybridization revealed a small number of genes. Since not all differentially expressed genes may be represented by the PCR-based cDNA subtractive hybridization analysis, it is predicted that there will be more genes engaged in the process of establishing and maintaining pregnancy.

Therefore, additional study is required to validate the clinical relevance of these genes that were found to express abnormally in RPL patients. A better understanding of the physiological significance of these genes may therefore help in controlling the management of future pregnancies. Finding any aberrant expression of these genes may thus delineate general health during pregnancy. The underlying reason of RPL directs the therapeutic intervention. In every situation, providing emotional support is crucial to caring for these frequently anxious partners and may even increase therapeutic success.

References

1. Eshre Guideline Group on RPL, Bender Atik, R., Christiansen, O. B., Elson, J., Kolte, A. M., Lewis, S., ... &Goddijn, M. (2018). ESHRE guideline: recurrent pregnancy loss. *Human reproduction open*, *2018*(2), hoy004.
2. Wang, X. H., Xu, S., Zhou, X. Y., Zhao, R., Lin, Y., Cao, J., & Zhao, J. Y. (2021). Low chorionic villous succinate accumulation associates with recurrent spontaneous abortion risk. *Nature Communications*, *12*(1), 3428.
3. Chaithra, P. T., Malini, S. S., & Kumar, C. S. (2011). An overview of genetic and molecular factors responsible for recurrent pregnancy loss. *International journal of human genetics*, *11*(4), 217-225.
4. Toth, B., Vomstein, K., Togawa, R., Böttcher, B., Hudalla, H., Strowitzki, T., ... & Kuon, R. J. (2019). The impact of previous live births on peripheral and uterine natural killer cells in patients with recurrent miscarriage. *Reproductive Biology and Endocrinology*, *17*, 1-8.
5. Hyde, K. J., & Schust, D. J. (2015). Genetic considerations in recurrent pregnancy loss. *Cold Spring Harbor perspectives in medicine*, *5*(3), a023119.
6. Zhao, X., Jiang, Y., Wang, L., Li, Z., Li, Q., & Feng, X. (2018). Advances in understanding the immune imbalance between T-lymphocyte subsets and NK cells in recurrent spontaneous abortion. *Geburtshilfe und Frauenheilkunde*, *78*(07), 677-683.
7. Meka, A., & Reddy, B. M. (2006). Recurrent spontaneous abortions: an overview of genetic and non-genetic backgrounds. *International Journal of Human Genetics*, *6*(2), 109-117.
8. Muyayalo, K. P., Li, Z. H., Mor, G., & Liao, A. H. (2018). Modulatory effect of intravenous immunoglobulin on Th17/Treg cell balance in women with

unexplained recurrent spontaneous abortion. *American Journal of Reproductive Immunology*, *80*(4), e13018.

9. Dimitriadis, E., Menkhorst, E., Saito, S., Kutteh, W. H., &Brosens, J. J. (2020). Recurrent pregnancy loss. *Nature reviews disease primers*, *6*(1), 98.
10. Hennessy, M., Dennehy, R., Meaney, S., Linehan, L., Devane, D., Rice, R., & O'Donoghue, K. (2021). Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review. *Reproductive Bio Medicine Online*, *42*(6), 1146-1171.
11. Park, D. W., Lee, H. J., Park, C. W., Hong, S. R., Kwak- Kim, J., & Yang, K. M. (2010). Peripheral blood NK cells reflect changes in decidual NK cells in women with recurrent miscarriages. *American Journal of Reproductive Immunology*, *63*(2), 173-180.
12. Toth, B., Vomstein, K., Togawa, R., Böttcher, B., Hudalla, H., Strowitzki, T., & Kuon, R. J. (2019). The impact of previous live births on peripheral and uterine natural killer cells in patients with recurrent miscarriage. *Reproductive Biology and Endocrinology*, *17*, 1-8.
13. Warburton, D. O. R. O. T. H. Y., Kline, J., Stein, Z., Hutzler, M., Chin, A., &Hassold, T. (1987). Does the karyotype of a spontaneous abortion predict the karyotype of a subsequent abortion? Evidence from 273 women with two karyotyped spontaneous abortions. *American journal of human genetics*, *41*(3), 465.
14. Ogasawara, M., Aoki, K., Okada, S., & Suzumori, K. (2000). Embryonic karyotype of abortuses in relation to the number of previous miscarriages. *Fertility and sterility*, *73*(2), 300-304.
15. Carp, H., Toder, V., Aviram, A., Daniely, M., Mashiach, S., &Barkai, G. (2001). Karyotype of the abortus in recurrent miscarriage. *Fertility and sterility*, *75*(4), 678-682.
16. Teklenburg, G., Salker, M., Heijnen, C., Macklon, N. S., &Brosens, J. J. (2010). The molecular basis of recurrent pregnancy loss: impaired natural embryo selection. *Molecular human reproduction*, *16*(12), 886-895.
17. Evans, J., Catalano, R. D., Brown, P., Sherwin, R., Critchley, H. O., Fazleabas, A. T., & Jabbour, H. N. (2009). Prokineticin 1 mediates fetal-maternal dialogue regulating endometrial leukemia inhibitory factor. *The FASEB Journal*, *23*(7), 2165.
18. Hochner-Celnikier, D., Ron, M., Eldor, A., Segal, S., Palti, Z., Fuks, Z., &Vlodavsky, I. (1984). Growth characteristics of human first trimester decidual cells cultured in serum-free medium: production of prolactin, prostaglandins and fibronectin. *Biology of reproduction*, *31*(4), 827-836.
19. Brosens, J. J., Hayashi, N., & White, J. O. (1999). Progesterone receptor regulates decidual prolactin expression in differentiating human endometrial stromal cells. *Endocrinology*, *140*(10), 4809-4820.
20. Cloke, B., Huhtinen, K., Fusi, L., Kajihara, T., Yliheikkilä, M., Ho, K. K.,&Brosens, J. J. (2008). The androgen and progesterone receptors regulate distinct gene networks and cellular functions in decidualizing endometrium. *Endocrinology*,*149*(9), 4462-4474.
21. Lynch, V. J., Tanzer, A., Wang, Y., Leung, F. C., Gellersen, B., Emera, D., & Wagner, G. P. (2008). Adaptive changes in the transcription factor HoxA-11 are essential for the evolution of pregnancy in mammals. *Proceedings of the National Academy of Sciences*, *105*(39), 14928-14933.