REVIEW ARTICLE

Genetics Insights into Recurrent Pregnancy Loss: A Comprehensive Review

Shivani Mishra[1], Chetan Sahni[2], Sangeeta Rai[3], Ashish[4], Royana Singh[5]

Received on: 20 December 2023; *Accepted on:* 06 April 2024; *Published on:* 09 July 2024

Abstract

Recurrent pregnancy loss (RPL) mainly occurs due to the disorders that cause intrauterine fetal demise or damage, such as fetal, maternal, and paternal chromosomal structural and numerical abnormalities. Approximately, 15–20% of all clinically recognized pregnancies result in the first trimester (before 20 weeks of gestational age) in spontaneous recurrent abortion. Besides all internal factors like Anatomical, immunological, and coagulation factors, genetic factors appear to be most associated with reproductive organ damage and multiple pregnancy loss. Some factors are unexplored as mentioned in the previous research articles, and there is an enormous need to research for establishing the proper etiology and prognosis. This review is all about the various factors responsible for RPL and is mainly focused on the genetic factors involving many unexplored genes associated with recurrent miscarriages. In this review, searched the articles with keywords that were published recently from various journal searches such as Google Scholar, Science Direct, and the National Center for Biotechnology Information (NCBI) platform.

Keywords: Chromosomal abnormalities, Recurrent pregnancy loss, Uterine anatomical defects, Whole-exome sequencing.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2428

Introduction

According to the guidelines from the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), recurrent pregnancy loss (RPL) may be defined as two or more consecutive clinically recognized pregnancy loss before 20–22 weeks of gestational age.[1,2] According to recent epidemiological data released by the ASRM, approximately 15–20% of all pregnancies end in spontaneous abortion, of which nearly 2–5% result in RPL.[3] Recurrent pregnancy loss affects approximately 1% of couples trying to conceive worldwide. The pregnancy loss can be confirmed by clinical reporting like waning human chorionic gonadotrophin (hCG) levels, a transvaginal ultrasound, and biochemical profiling.[4] The pathogenesis of RPL may include some common factors such as uterine anatomical abnormalities (septate or bicornuate uterus), endocrine factors, pathogenic infections, immunologic factors such as lupus anticoagulant (LA) and antiphospholipid antibodies (APLA). Some environmental factors, metabolic or hormonal disorders, sperm quality (sperm DNA fragmentation and sperm aneuploidy), parental age (maternal and paternal) and single gene disorders (such as inherited thrombophilia) have been strongly associated to RPL.[5] Ectopic pregnancies, molar pregnancies, and implantation failures are excluded from the ESHRE guidelines for RPL.[6]

The current review is based on a detailed discussion of the different factors responsible for pregnancy loss and goals for setting the best investigation and treatment strategy for women facing RPL. This review is made by going through various research articles based on the genetic factors included in etiologies of RPL which were already explored with the help of some cytogenetic and molecular techniques such as conventional karyotyping, quantitative fluorescent polymerase chain reaction (QF-PCR), microarray-based comparative genomic hybridization (aCGH) single-nucleotide polymorphisms (SNPs) detection, whole-exome sequencing (WES)/next generation sequencing (NGS).

[1,2,5]Laboratory of Cytogenetics; Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[3]Department of Obstetrics and Gynaecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[4]Multidisciplinary Research Unit – ICMR–DHR, Department of Anatomy, Institute of Medical Sciences Banaras Hindu University, Varanasi, Uttar Pradesh, India

Corresponding Author: Royana Singh, Department of Anatomy, Institute of Medical Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India, Phone: +91 9450545650, e-mail: royanasingh@bhu.ac.in

How to cite this article: Mishra S, Sahni C, Rai S, *et al*. Genetics Insights into Recurrent Pregnancy Loss: A Comprehensive Review. J South Asian Feder Obst Gynae 2024;16(4):421–427.

Source of support: Nil

Conflict of interest: None

Methodology

To find out the recent updated research article regarding the concern topic, we comprehensively searched various peer reviewed published articles in databases like PubMed, Scopus, Web of Science. The keywords used to search literature is "spontaneous pregnancy loss," "miscarriages," "uterine anatomical defects." The inclusion criteria was considering only condition of two or more recurrent spontaneous pregnancy losses by excluding the induced abortions and any type of anatomical anomaly and other endocrinological factors responsible.

Risk Factors for Recurrent Miscarriages

Anatomical Factors

Anatomical factors play a very significant role in etiologies of recurrent miscarriages by contributing about 19–20% of total

factors.[7,8] There are two types of anatomical factors—congenital and acquired abnormalities—which affect the normal pregnancy and leads to pregnancy loss. The congenital abnormality in women who have experienced pregnancy loss are arcuate, septate, unicornuate, bicornuate, and didelphis uterine which are more prevalent (13.3%) among them than in the general population (3.5%). The acquired anomalies like the presence of intrauterine adhesions, Asherman's syndrome which affect the normal pregnancy and leads to pregnancy loss and any defect in placentation, ultimately leading to early pregnancy loss. It has been demonstrated that intrauterine adhesions are sometimes associated with recurrent pregnancy loss.[8] Approximately 19% of the women who experience RPL suffer from uterine defects, which include both acquired and congenital defects.[6,8] The most common types of uterine anomalies are congenital and intrauterine adhesions as well as fibroids or polyps among women who endured RPL.[9]

Immunological Factors

Immune system is strongly responsible for the rejection of embryo implantation and here are some factors such as cytokines, human leukocyte antigen, antinuclear antibodies which had already been proven as immunological factors which are strongly associated with RPL. These are highly associated with the immune response generated during the development of the embryo and placentation.[10]

Human Leukocyte Antigen

There is a definite link between human leukocyte antigen-G (HLA-G) polymorphisms and natural killer (NK) cytotoxicity at fetal-maternal interfaces in RPLs. A significant increase in HLA-G frequency has been found in women who faced RPL.[11]

Cytokines

Cytokines-activated cytotoxic T lymphocytes produce cytokines such as tumor necrosis factor alpha (TNF-α), TNF-β, Interferon gamma, Interleukin (IL)1, and IL2 which activate other cells to initiate a Molecular cascade at cellular level.[12] The TNF-α levels in early pregnancy of secondary RPL women were higher than those of primary RPL women.[13,14] These factors can be used as biomarkers for the prognosis and diagnosis of RPL. It can be associated with increased TNF-*/IL-10 ratios in helper T-cells (Th) 1 cells from peripheral blood lymphocytes compared to controls and increased intracellular TNF-* production in Th1 cells from peripheral blood lymphocytes.[15]

Endocrine Factors

Pregnancy can be characterized by endocrine and metabolic changes caused by physiological alterations at the junction between mother and fetus and this results in proper growth and development of the fetus.[16] The functional abnormality of hormones like luteinizing hormone, follicle-stimulating hormone (FSH), prolactin, thyroid gland releasing hormones (T3, T4, and thyroid stimulating hormone), many complications may happen such as polycystic ovarian syndrome, luteal phase defects (LPD), all of these are associated with the RPL.[17,18]

Polycystic Ovarian Syndrome

Women with RPL may suffer from PCOS and other contributing factors such as obesity, hyperinsulinemia, insulin resistance, hyperhomocysteinemia, high levels of plasminogen activator inhibitor-1 factor, hyperandrogenism, and poor endometrial receptivity.[16] The most common is PCOS showing in many females having recurrent abortions.[19]

Luteal Phase Defects

The LPD is caused by the deficiency of endogenous progesterone or its action on the endometrium during luteal phase, thus the normal implantation become defected.[20] With the help of progesterone support, helps in maintaining early pregnancy, especially in case RPL.[21,22] When there is a raise in prolactin level, it inhibits the secretion of FSH and gonadotropin-releasing hormone (GnRH), and also directly inhibits the secretion of progesterone.[20,21]

Hyperthyroidism

Regular monitoring of the thyroid hormone levels and autoantibodies should be done in high-risk pregnancies and in those who have already thyroid levels on the higher or lower side.[22] The TSH levels should be determined in all pregnant women and those who are planning to become pregnant.[23]

Diminished Ovarian Reserve Association

Recurrent pregnancy losses could be caused by decline in ovarian reserve which involves several hormones such as the anti-müllerian hormone (AMH) and some other factors such as antral follicle count (AFC) and ovarian volume.[6,24]

Genetic Factors

The genetic factor plays a very important role in defining the pathogenesis of RPL loss or habitual abortions or women with bad obstetrics history. The 20–30% cases of recurrent miscarriages are found to be caused by genetic factors after excluding all the anatomical, immunological, thrombotic, endocrine, and pathological factors. Approximately 50–70% of specimens of miscarriage and maternal blood samples from spontaneous sporadic losses exhibit some type of cytogenetic abnormality, with the most common chromosomal abnormality including autosomal trisomy (60%), monosomy X (20%), and polyploidy (20%).[25] The cytogenetic analysis suggests that Balanced translocations reported in 2–5% of couples who are experiencing RPL.[26] The genetic factor includes the trio approach, that is, maternal, fetal, and paternal factors responsible for the identification of RPL. Following are the three major factors that cause RPL:

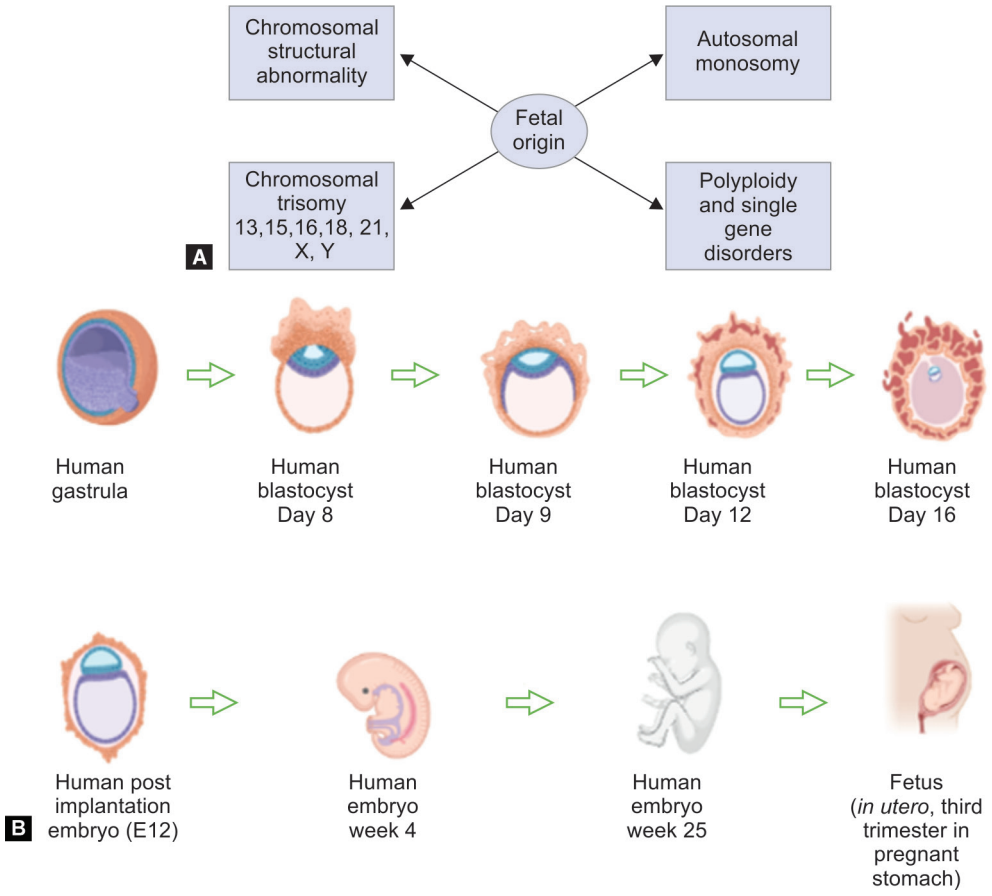
- Embryonic chromosomal errors.
- Maternal genetic abnormalities.
- Paternal genetic abnormalities.

Embryonic Chromosomal Errors

It is estimated that 50–70% of couples experience miscarriages as a result of fetal chromosomal errors during or before pregnancy, most of which occur before 10 weeks of pregnancy.[26]

In the first trimester of pregnancy, most of these abnormalities are detected by cytogenetic studies of miscarriage samples.[27] In RPL, fetal aneuploidy in sporadic is one of the important factors. Chromosomal trisomy at 13 (Patau's syndrome), 15, 16, and 18 (Edward's syndrome), 21 (Down's syndrome), Klinefelter's and Turner's syndrome (Fig. 1A).[28]

A number of genetic anomalies are known, including chromosomal aneuploidy, copy number variants (CNVs), and highly penetrant single-gene disorders, as well as constricted placental mosaicism, skewed X-inactivation, uniparental disomic, and genetic polymorphisms, among others.[29] According to various



Figs 1A and B: (A) Genetic causes associated with a fetal origin; (B) The developmental stage of a growing embryo

molecular and cytogenetic-related studies, the genetic factors are more commonly responsible for the recurrent abortions that are associated with some mutation in genes related to implantation, cell adhesion trophoblast endometrium interaction, coagulation, extracellular matrix remodeling, angiogenesis, and apoptosis, etc.[30]

In Figure 1B, it is shown here that the human gastrula, blastocyst days 8, 9, 12, and 16, human postimplantation embryo (E12), human embryo week 4, week 25, and fetus (*in utero*, third trimester in the pregnant stomach) lead to the complete formation of a human embryo. The different stages of complete embryo formation is found in embryo and fetal loss during RPL in and may be targeted to study the main genetic or other causes of RPL.

Genetic Causes of Recurrent Pregnancy Loss: Maternal Origin

In addition to uterine myomas (fibroids), endometrial polyps, intrauterine adhesions, or Asherman's syndrome, there are a number of acquired abnormalities in the uterus. The most common candidate genes studied in RPL are those that affect mainly immune tolerance, inflammation, maternal metabolism, and blood coagulation.[31]

In some studies, associated with the techniques like aCGH, fluorescent *in situ* hybridization (FISH), WES/NGS, the data analysis shows that there are many genes that are found to be more relevant to maternal factors responsible for the RPL and spontaneous abortions.

Figure 2 is showing the most common causes associated with RPL, besides the genetic causes, there are many factors present in the uterus, ovaries, endometrium, fallopian tube, etc. These involves some uterine factors, thrombotic anomalies, autoimmune disorders, endocrinological factors, genetic factors, chromosomal aneuploidies, other stress conditions, and basal metabolic index.

Genetic Causes of Recurrent Pregnancy Loss: Paternal Origin

Male factors that largely overlook and contribute to RPL, despite some evidence that sperm affects embryogenesis and placental function. Researchers have begun to investigate how spermatozoa contribute beyond genetic factors to early embryogenesis.[32]

Sperm DNA Fragmentation

The integrity of sperm is very essential for sperm–ovum fertilization and embryonic development, as well as early embryonic development.[33] Moreover, the expression of paternally expressed genes affects the proliferation of trophoblast cells as well as placental development.[34]

Sperm Aneuploidy

According to Neusser et al.[34] which states that RPL involves some chromosomes that are found most associated and relevant targets to sperm aneuploidy such as chromosomes 15, 16, and 21, testing with chromosome 16 being the most commonly

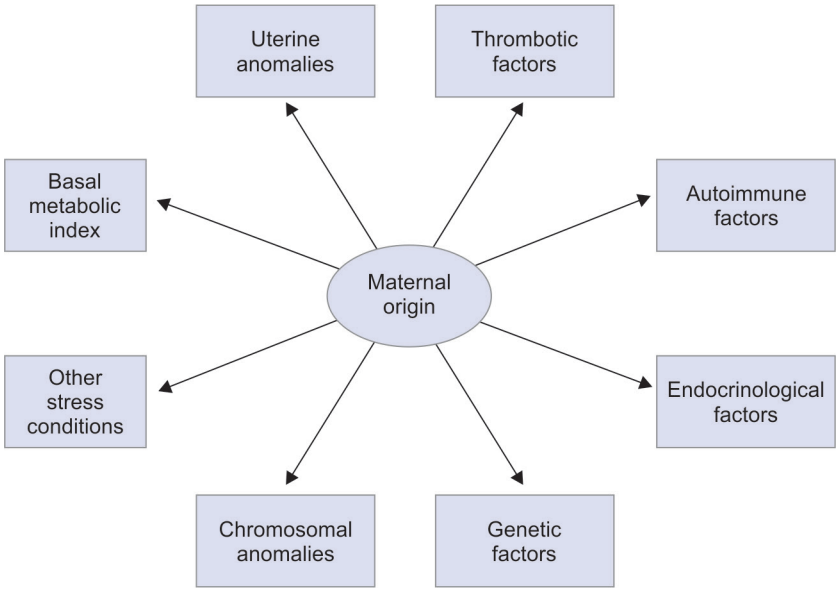


Fig. 2: Genetic causes associated with maternal origin

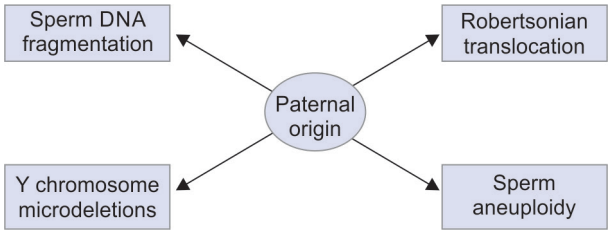


Fig. 3: Genetic causes associated with paternal origin

expressing target in any sperm defects.[35] Figure 3 shows paternally originated factors that are commonly expressed during RPL and spontaneous miscarriages. It includes sperm DNA fragmentation, Robertsonian translocation, sperm aneuploidy, and Y chromosome microdeletions.[36]

Epigenetic Factors

Epigenetic factors play a very important role in spontaneous recurrent miscarriages as it performs DNA methylation (CpG methylation), Histone modification in chromatin and noncoding RNA, X chromosomal inactivation, and histone methylation (H3-K9).[37] Some epigenetic factors are also related to kidney and urinary tract malfunctions, and hyperhomocysteinemia, which indirectly affects DNA methylation, and causes many birth deformities. Early pregnancy losses associated with DNMT 1 expression and also epigenetically associated with DNA methylation were found to diminish in chorionic villi.[38]

Pathological Factors

The infectious factors that sometimes play a major role in recurrent miscarriages may be caused by some pathogens such as *Listeria monocytogenes, Toxoplasma gondii*, Rubella, Herpes simplex virus (HSV), measles, cytomegalovirus (CMV). The probability of infectious causes occurring during or after pregnancy loss may be uterus infections, fetus malformations, placental insufficiency, chronic endometritis or endocervicitis, amnionitis, or infected intrauterine reproductive tract.[39]

Psychological Factors

According to a study, depression/stress/anxiety after stillbirth is a posttraumatic disorder, a group of symptoms coming from depression by the attachment and emotions of the fetus that was lost.[40]

Vascular Remodeling and Tissue Formation

At the maternofetal intersection point, a competent decidual response is exceptive to inhibit cell demise, necrosis, and bleeding exclusively when there is oxidative stress present during the first trimester of pregnancy.[41]

Multiple genes involved in the immune surveillance of senescent cells, including *CXCL14*, *IL-15*, and *TIMP-3*, are hardwired to be activated prior to the emergence of senescent decidual cells.[42]

Artificial Intelligence and Machine Learning in Predicting Future High-risk Pregnancies: Complications and Interventions

The digital assessment of the future risk of miscarriage in the case of recurrent spontaneous miscarriages would be a better option in future diagnosis and prognosis. In accordance with the diagnosis and prognosis in recurrent spontaneous miscarriages, there is a kernel learning method supporting vector machine framework joint self-adaptive slime mould algorithm (JASMA–SVM) with the common kernel learning support vector machine is prospective from the vitamin D, thyroid hormone (T3, T4, and TSH), and thyroid antiantibodies.[43,44]

Conclusion

Recurrent pregnancy loss have been associated with many risk factors, which are involved in multiple pregnancy failure as mentioned in this study. It is suggested genetic counselling usually for couples having a history of known genetic defects in any family member or history of miscarriages in previous pregnancy to improve the fate of future pregnancies in this scenario. The flow chart of factors associated with recurrent miscarriages, we need to correlate the genetic factors with RPL. The majorly correlated

Table 1: Genomic data found most common in recurrent miscarriages and couples with a history of RPL

S.No.	*Gene symbol*	*Gene position*	*Common name*	*Biological function*	*Gene expression*
1.	*MMP2*	16q12.2	Matrix metallopeptidase	Extracellular matrix remodeling and trophoblast invasion	Uterus, ovary, and placenta
2.	*MMP9*	20q13.12			
3.	*MMP10*	11q22.2			
4.	*DYNC2H1*	11q22.3	Dynein cytoplasmic 2 heavy chain 1	Cilia biogenesis	Ciliated cells and cell projections
5.	*CDH11*	16p22.1	Cadherin 11	Establishment and maintenance of epithelial cell morphology during embryogenesis and adulthood	Small intestine during colorectal cancer
6.	*CREB*	2q33.3	CAMP responsive element binding protein 1	Transcription factor regulates diverse cellular responses, including proliferation, survival, and differentiation	T cell, DNA-binding proteins
7.	*MTHFR*	1p36.22	Methylene tetrahydro folate reductase	The enzyme plays a role in processing amino acids, the building blocks of proteins.	Methylenetetrahydrofolate reductase is important for a chemical reaction involving the vitamin folate
8.	*PLAC1*	Xq26.3	Placenta enriched 1	May play a role in placental development	Involved in placenta development; predicted to be located in the extracellular region
9.	*DNMT*	19p13.2	DNA methyltransferase	An important component of mammalian epigenetic gene regulation, methylates CpG residues associate with DNA replication sites in the S phase maintaining the methylation pattern in the newly synthesized strand	Gene encodes an enzyme that transfers methyl groups to cytosine nucleotides of genomic DNA
10.	*FOXF1*	16q24.1	Forkhead Box F1	It is a developmental gene plays role in lungs and gastrointestinal tract organogenesis and also acts as transcription activator for a number of lung-specific genes	Lungs, bladder, and colon

genes involved in the pathways of some necessary metabolic compounds like *MTHFR* with fetal growth like *CREB5* and fetal development, angiogenesis, organogenesis, the extracellular matrix in the female reproductive tract. The maternal reproductive organ-related gene expressions in the uterus, ovaries, and endometrium lining should be monitored for further correlation. The matrix metallopeptidase (*MMP9,10*) and epigenetic genes (*DNMT*) involved in the maintenance of a healthy pregnancy are paramount to investigating, whether the fetus's development is taking place in a healthy and proper manner or not. For the confirmation of commonly expressed genes, we can easily predict the correlated metabolic pathway, upregulation, and down-regulation of genes, with the help of WES, which can be further applied in prognosis and diagnosis of risk factors and the possibility of a healthy pregnancy in case of RPL and early pregnancy loss.

Table 1 is showing majorly expressed genes studied among various articles. It contain some genes that show SNPs and some deletion/addition/gain/loss mutation commonly found expressed during abnormal fetal growth like *MTHFR, CREB5 (1), DNMT, MMP9 (52)*. The genomic details were taken from gene cards (the human gene database) and National Center for Biotechnology Information (NCBI).

Discussion

The overall genetic and other thorough evaluation of women having two or more spontaneous pregnancy losses would be undergone the wholesome approach of treatment according to the results of these cytogenetic and molecular analysis.

As it is discussed previously, there are several associated genes which may be together with causing spontaneous pregnancy loss mainly in first trimester must be deeply explored in future research. The genetic analysis can be done starting from conventional karyotyping to whole genome sequencing. The prenatal genetic monitoring can be done by rapid detection of fetal aneuploidies by QF-PCR could be a choice of investigation in RPL patients. The genetic biomarker can be made based on the following trend of a particular gene that is expressed commonly in each case; it can be revalidated after the results of aCGH and whole genome sequencing. On behalf of array based CGH and NGS analysis of recent studies, a gene may be standardized for the diagnosis of the maternal and fetal development stage wise. So, it is been suggested that in case of high-risk pregnancies with recurrent miscarriages, the complete genetic analysis for prognosis and diagnosis of maternal, paternal, and fetus may be preferable in case of RPL. It is necessary

to validate the risk in the next future high-risk pregnancies and also to council the affected couples.

Acknowledgment

This research was sponsored by multidisciplinary research units (MRUs), a grant by Indian Council of Medical Research (ICMR)–Department of Health Research (DHR).

Authors' Contributions

Authors RS, CS, and SR contributed to the conception, design, and writing of the study protocol and the design of search strategies; A and SM located and obtained reports, helped to select and assess cases, conducted the data analysis, and drafted and approved the final paper. All authors contributed to the conception, design, and writing of the study protocol, conducted data analysis, and revised and approved the final paper.

Orcid

Chetan Sahni https://orcid.org/0000-0002-4301-4643
Ashish https://orcid.org/0000-0002-6844-1289

References

1. Yu M, Du G, Xu Q, et al. Integrated analysis of DNA methylome and transcriptome identified CREB5 as a novel risk gene contributing to recurrent pregnancy loss. EBioMedicine 2018;35:334–344. DOI: 10.1016/j.ebiom.2018.07.042.
2. Atik RB, Christiansen OB, Elson J, et al. ESHRE guideline: Recurrent pregnancy loss. Hum Reprod Open 2018;2018(2):hoy004. DOI: 10.1093/hropen/hoy004.
3. Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harb Perspect Med 2015;5(3):a023119. DOI: 10.1101/cshperspect.a023119.
4. Sultana S, Nallari P, Ananthapur V. Recurrent pregnancy loss (RPL): An overview. J Womens Heal Dev 2020;3(3):302–315. DOI: 10.26502/fjwhd.2644-28840038.
5. Pinar MH, Gibbins K, He M, et al. Early pregnancy losses: Review of nomenclature, histopathology, and possible etiologies. Fetal Pediatr Pathol 2018;37(3):191–209. DOI: 10.1080/15513815.2018.1455775.
6. Bashiri A, Halper KI, Orvieto R. Recurrent implantation failure: Update overview on etiology, diagnosis, treatment and future directions. Reprod Biol Endocrinol 2018;16(1):1–18. DOI: 10.1186/s12958-018-0414-2.
7. Turocy JM, Rackow BW. Uterine factor in recurrent pregnancy loss. In: Seminars in Perinatology. Elsevier; 2019, pp. 74–79.
8. Ahmad W, Bilal S, Azhar S, et al. Puzzle Out the Reason behind Habitual Miscarriage. Journal of Pharmaceutical Research International 2020;32(32). pp. 92–98. DOI: 10.9734/jpri/2020/v32i3230938.
9. Maddirevula S, Awartani K, Coskun S, et al. A genomics approach to females with infertility and recurrent pregnancy loss. Hum Genet 2020;139(5):605–613. DOI: 10.1007/s00439-020-02143-5.
10. Sung N, Khan SA, Yiu ME, et al. Reproductive outcomes of women with recurrent pregnancy losses and repeated implantation failures are significantly improved with immunomodulatory treatment. J Reprod Immunol 2021;148:103369. DOI: 10.1016/j.jri.2021.103369.
11. Kim JA, Bang CH, Song GG, et al. Tumour necrosis factor alpha gene polymorphisms in women with recurrent pregnancy loss: A meta-analysis. Hum Fertil (Camb) 2020;23(3):159–169. DOI: 10.1080/14647273.2018.1543899.
12. Ticconi C, Pietropolli A, Di Simone N, et al. Endometrial immune dysfunction in recurrent pregnancy loss. Int J Mol Sci 2019;20(21):5332. DOI: 10.3390/ijms20215332.
13. Coomarasamy A, Dhillon–Smith RK, Papadopoulou A, et al. Recurrent miscarriage: Evidence to accelerate action. Lancetw 2021;397(10285):1675–1682. DOI: 10.1016/S0140-6736(21)00681-4.
14. Liu X, Qiu Y, Yu ED, et al. Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: A systematic review and network meta-analysis. Am J Reprod Immunol 2020;83(4):e13219. DOI: 10.1111/aji.13219.
15. Sfakianoudis K, Rapani A, Grigoriadis S, et al. The role of uterine natural killer cells on recurrent miscarriage and recurrent implantation failure: From pathophysiology to treatment. Biomedicines 2021;9(10):1425. DOI: 10.3390/biomedicines9101425.
16. Quenby S, Gallos ID, Dhillon–Smith RK, et al. Miscarriage matters: The epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 2021;397(10285):1658–1667. DOI: 10.1016/S0140-6736(21)00682-6.
17. Naeem A, Jan S, Shah BG. Association of the thyroid function disorder with recurrent pregnancy loss in women: Thyroid function disorder with recurrent pregnancy loss in women. Pakistan Biomed J 2022;5(7):274–277. DOI: 10.54393/pbmj.v5i7.687.
18. Kodogo V, Azibani F, Sliwa K. Role of pregnancy hormones and hormonal interaction on the maternal cardiovascular system: A literature review. Clin Res Cardiol 2019;108(8):831–846. DOI: 10.1007/s00392-019-01441-x.
19. Sokhadze K, Kvaliashvili S, Kristesashvili J. Reproductive function and pregnancy outcomes in women treated for idiopathic hyperprolactinemia: A non-randomized controlled study. Int J Reprod Biomed 2020;18(12):1039–1048. DOI: 10.18502/ijrm.v18i12.8025.
20. Amrane S, McConnell R. Endocrine causes of recurrent pregnancy loss. In: Seminars in perinatology. Elsevier; 2019, pp. 80–83.
21. Finley J, Hay S, Oldzej J, et al. The genomic basis of sporadic and recurrent pregnancy loss: A comprehensive in-depth analysis of 24,900 miscarriages. Reprod Biomed Online 2022;45(1):125–134. DOI: 10.1016/j.rbmo.2022.03.014.
22. Dimitriadis E, Menkhorst E, Saito S, et al. Recurrent pregnancy loss. Nat Rev Dis Prim 2020;6(1):1–19. DOI: 10.1038/s41572-020-00228-z.
23. Lucas ES, Vrljicak P, Muter J, et al. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window. Commun Biol 2020;3(1):1–14. DOI: 10.1038/s42003-020-0763-1.
24. Moghbeli M. Genetics of recurrent pregnancy loss among Iranian population. Mol Genet Genomic Med 2019;7(9):e891. DOI: 10.1002/mgg3.891.
25. van Dijk MM, Kolte AM, Limpens J, et al. Recurrent pregnancy loss: Diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update 2020;26(3):356–367. DOI: 10.1093/humupd/dmz048.
26. Yalçın S, Öztürk KH, Özbaş H, et al. Cytogenetic analysis in couples with recurrent pregnancy loss. J Surg Med 2021;5(5):449–452. DOI: 10.28982/josam.912521.
27. Bahia W, Soltani I, Abidi A, et al. Identification of genes and miRNA associated with idiopathic recurrent pregnancy loss: An exploratory data mining study. BMC Med Genomics 2020;13(1):75. DOI: 10.1186/s12920-020-00730-z.
28. Arias–Sosa LA, Acosta ID, Lucena–Quevedo E, et al. Genetic and epigenetic variations associated with idiopathic recurrent pregnancy loss. J Assist Reprod Genet 2018;35(3):355–366. DOI: 10.1007/s10815-017-1108-y.
29. Wyatt MA, Baumgarten SC, Weaver AL, et al. Evaluating markers of immune tolerance and angiogenesis in maternal blood for an association with risk of pregnancy loss. J Clin Med 2021;10(16):3579. DOI: 10.3390/jcm10163579.
30. Ewington LJ, Tewary S, Brosens JJ. New insights into the mechanisms underlying recurrent pregnancy loss. J Obstet Gynaecol Res 2019;45(2):258–265. DOI: 10.1111/jog.13837.
31. Nanassy L, Carrell DT. Paternal effects on early embryogenesis. J Exp Clin Assist Reprod 2008;5(1):2. DOI: 10.1186/1743-1050-5-2.

32. Ibrahim Y, Johnstone E. The male contribution to recurrent pregnancy loss. Transl Androl Urol 2018;7(Suppl. 3):S317–S327. DOI: 10.21037/tau.2018.05.14.
33. Liu Y, Tang Y, Ye D, et al. Impact of abnormal DNA methylation of imprinted loci on human spontaneous abortion. Reprod Sci 2018;25(1):131–139. DOI: 10.1177/1933719117704906.
34. Neusser M, Rogenhofer N, Dürl S, et al. Increased chromosome 16 disomy rates in human spermatozoa and recurrent spontaneous abortions. Fertil Steril 2015;104(5):1130–1137. DOI: 10.1016/j.fertnstert.2015.07.1160.
35. McQueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: A systematic review and meta-analysis. Fertil Steril 2019;112(1):54–60. DOI: 10.1016/j.fertnstert.2019.03.003.
36. Yin L-J, Zhang Y, Lv P-P, et al. Insufficient maintenance DNA methylation is associated with abnormal embryonic development. BMC Med 2012;10:26. DOI: 10.1186/1741-7015-10-26.
37. Lubinsky M. An epigenetic association of malformations, adverse reproductive outcomes, and fetal origins hypothesis related effects. J Assist Reprod Genet 2018;35(6):953–964. DOI: 10.1007/s10815-018-1197-2.
38. Iacobazzi V, Infantino V, Castegna A, et al. Hyperhomocysteinemia: Related genetic diseases and congenital defects, abnormal DNA methylation and newborn screening issues. Mol Genet Metab 2014;113(1–2):27–33. DOI: 10.1016/j.ymgme.2014.07.016.
39. Khambata K, Raut S, Deshpande S, et al. DNA methylation defects in spermatozoa of male partners from couples experiencing recurrent pregnancy loss. Hum Reprod 2021;36(1):48–60. DOI: 10.1093/humrep/deaa278.
40. Hedegaard S, Landersoe SK, Olsen LR, et al. Stress and depression among women and men who have experienced recurrent pregnancy loss: Focusing on both sexes. Reprod Biomed Online 2021;42(6):1172–1180. DOI: 10.1016/j.rbmo.2021.03.012.
41. Valero–Pacheco N, Tang EK, Massri N, et al. Maternal IL-33 critically regulates tissue remodeling and type 2 immune responses in the uterus during early pregnancy in mice. Proc Natl Acad Sci U S A 2022;119(35):e2123267119. DOI: 10.1073/pnas.2123267119.
42. Huppertz B. Traditional and new routes of trophoblast invasion and their implications for pregnancy diseases. Int J Mol Sci 2019;21(1):289. DOI: 10.3390/ijms21010289.
43. Yi Y, Lu G, Ouyang Y, et al. A logistic model to predict early pregnancy loss following in vitro fertilization based on 2601 infertility patients. Reprod Biol Endocrinol 2016;14(1):1–7. DOI: 10.1186/s12958-016-0147-z.
44. Wang Y, Zhang Q, Yin C, et al. Automated prediction of early spontaneous miscarriage based on the analyzing ultrasonographic gestational sac imaging by the convolutional neural network: A case–control and cohort study. BMC Pregnancy Childbirth 2022;22(1):621. DOI: 10.1186/s12884-022-04936-0.