JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1658279
J Contemp Med 2025;15(4):197-202

Review / Derleme

A Comprehensive Review of Paternal Causes of Recurrent Pregnancy Loss

Tekrarlayan Gebelik Kayıplarının Paternal Nedenlerine Kapsamlı Bir Bakış

Damica Clerveau[1], Sathees B Chandra[2]

[1]Biomedical Sciences Program, College of Health & Wellness, Barry University, Miami Shores, USA
[2]College of Health Sciences, Samuel Merritt University, Oakland, CA, USA

Abstract

Approximately 5% of couples attempting to reproduce face the challenge of recurrent pregnancy loss. Sadly, more than 50% of those couples will have their case remain unexplained. This can be problematic when families are trying to conceive. Past research mainly focused on maternal causes of recurrent pregnancy loss. A shift in research towards investigating paternal etiologies has revealed more causes of recurrent pregnancy loss. New research has shown how paternal age, physical health, lifestyle habits, sperm characteristics, metabolic disorders, inflammatory disorders, and clotting disorders all influence pregnancy outcomes. The purpose of this paper is to provide a review of the past twenty years of literature investigating the underexplored paternal causes of recurrent pregnancy loss.

Keywords: Pregnancy outcome, male fertility, reproductive medicine, spermatozoa, pregnancy complication

Öz

Çocuk sahibi olma çabası içindeki çiftlerin yaklaşık %5'i tekrarlayan gebelik kaybı (TGK) sorunu ile karşılaşmaktadır. Ne yazık ki bu çiftlerin %50'sinden fazlasında neden açıklanamamaktadır. Bu durum, çocuk sahibi olmaya çalışan aileler için ciddi bir sorun teşkil etmektedir. Geçmişte yapılan araştırmalar büyük ölçüde TGK'nın maternal (anneye ait) nedenlerine odaklanmıştır. Ancak son dönemde paternal (babaya ait) etiyolojilerin araştırılmasına yönelik yönelim, TGK'nın daha fazla nedenini ortaya çıkarmıştır. Güncel araştırmalar; baba yaşının, fiziksel sağlığın, yaşam tarzı alışkanlıklarının, sperm özelliklerinin, metabolik bozuklukların, inflamatuar hastalıkların ve pıhtılaşma bozukluklarının gebelik sonuçlarını etkilediğini göstermiştir. Bu derleme çalışmasının amacı, son yirmi yılda yapılan literatürün gözden geçirilmesiyle, yeterince araştırılmamış olan TGK'nın paternal nedenlerine dikkat çekmektir.

Anahtar Kelimeler: Gebelik sonucu, erkek doğurganlığı, üreme tıbbı, spermatozoa, gebelik komplikasyonu

INTRODUCTION

Spontaneous miscarriage is a worrisome yet common event for couples trying to conceive. Every year, there are more than 20 million occurrences of spontaneous miscarriage.[1] A portion of those couples who unexpectedly lose their fetus will try again to conceive. Those who experience a second spontaneous miscarriage make up 1-5% of annual miscarriages.[2] 75% of those couples who experience recurrent pregnancy loss (RPL) have their cases remain unexplained.[3] Concrete facts and research looking into unexplained recurrent pregnancy loss is tricky for researchers due to the varying definitions of RPL. Even guidelines addressing treatment for recurrent pregnancy loss provide different suggestions due to the varying definitions found in national guidelines such as the American Society for Reproductive Medicine (ASRM), the European Society of Human Reproduction and Embryology (ESHRE), and the Royal College of Obstetricians and Gynecologists (RCOG).[4] When defining recurrent pregnancy loss, the main definition must include a standard definition for pregnancy, how long the pregnancy has to last to be considered a loss, a standard definition for recurrence, and a standard definition for consecutive losses. Despite a lack of a standardized definition, past research into causes of recurrent pregnancy loss mainly focused on maternal causes.

Corresponding *(İletişim)*: Sathees Chandra, College of Health Sciences (COHS), Samuel Merritt University, 450 30th Street, Suite 2877, Oakland, CA 94609, USA
E-mail *(E-posta)*: schandra@samuelmerritt.edu
Received *(Geliş Tarihi)*: 15.03.2025 **Accepted *(Kabul Tarihi)*:** 27.06.2025

The history of research with recurrent pregnancy loss has mostly been focused on maternal factors until recently. The research conducted in the past has found numerous maternal etiologies for recurrent pregnancy loss. Despite that, there are still 50 to 75% of the cases worldwide that remain unexplained.[3] Research looking into maternal etiologies of recurrent pregnancy loss has found increased maternal age, autoimmune disorders, uterine abnormalities, endocrine abnormalities, maternal microbiome, genetic anomalies, vitamin deficiencies, and maternal lifestyle factors as all contributors to recurrent pregnancy loss.[5] A widely known fact is as a mother increases in age, the riskier the outcome of her pregnancy will be. Outcomes can include spontaneous miscarriage or health defects in the newborn baby. Certain mothers have autoimmune disorders that prevent them from carrying their baby to full term. Research into mothers with Antiphospholipid Syndrome (acquired thrombophilia) or inherited thrombophilia has shown how common it is for mothers with this disorder to experience RPL.[6] Thrombophilia, a blood disorder that can be inherited or acquired (antiphospholipid syndrome) is seen to cause blood to abnormally clot. Uterine abnormalities such as congenital anatomic structural defects, acquired anatomical abnormalities and endometriosis are maternal etiologies proven to lead to RPL. A mother's endocrine system can also play a role in experiencing recurrent pregnancy loss. Research has shown endocrine disorders such as Polycystic Ovary Syndrome (PCOS), thyroid disorders, and prolactin disorders have continuously led to miscarriages.[7] Chromosomal abnormalities of the parents make up 50% - 60% of early pregnancy loss.[8] Research on Vitamin D deficiency and how it could possibly be a risk factor for RPL remains inconclusive.[9] Fairly new research for maternal etiologies of recurrent pregnancy loss have been looking into the mother's microbiome. The environment of the endometrial, gut, and vaginal biome has all shown results in how they could contribute to couples experiencing RPL.[10] While past research focused primarily on maternal risk factors, recent research has started to investigate paternal causes of recurrent pregnancy loss.

Past research heavily focused on maternal causes as sole contributors to recurrent pregnancy loss. This perspective overlooked the significant role paternal factors may have played. Research focused on paternal causes increased after recommendations from the ESHRE.[2] Past research has referenced sperm DNA fragmentation and chromosomal abnormalities as paternal causes for RPL.[11] New research has found evidence that other paternal factors such as lifestyle, metabolic syndromes, and genetic markers may play a significant role in recurrent pregnancy loss. Research into etiologies of recurrent miscarriage has always been very nuanced and multifaceted with an interconnectedness of genetic, environmental, and biological factors. The purpose of this review is to explore the underrecognized male causes of unexplained recurrent pregnancy loss based on literature from the past two decades.

Age and Unhealthy Lifestyle

It is a long-proven fact, that the older a woman is when pregnant, the higher the chances her pregnancy will result in miscarriage. The increased age leads to a decline in egg quality, changes in uterine conditions, along with a higher risk of other health complications.[12] Recent research has now shown an older father could also impact the success of a pregnancy. A meta-analysis study that evaluated the effect of paternal age on pregnancy outcomes, showed fathers between 40-44 years of age had a 23% greater chance of spontaneous miscarriage before 20 weeks compared to younger counterparts.[13] If the father was older than 45 the risk of spontaneous miscarriage increased by 43% for before 20 weeks and 74% for 13 weeks gestation. A study with over 1,900 male participants clearly indicated the association between increased paternal age and RPL with those paternal ages averaging to 35 vs 32 years old.[14] The relationship between increased paternal age and pregnancy success may be due to sperm DNA integrity. As numerous research articles emphasize the effect of paternal age on pregnancy outcomes, there is also abundant research that shows the effect of older paternal age on sperm DNA quality.[11,15,16] It's important that clinicians understand the research shows higher paternal age has significant risks when families are trying to conceive successfully and experience unexplained recurrent pregnancy loss. As research shows, paternal age greatly impacts RPL, it is also important to notice how paternal lifestyle habits further contribute to pregnancy outcomes.

A parent's healthy lifestyle habits are important for preventing the risk of spontaneous miscarriage. Research has shown how a mother's lifestyle habits such as obesity, excessive alcohol, caffeine, and tobacco intake increase the risk of the pregnancy ending spontaneously.[9] New research literature is still controversial on the lifestyle habits of the father and how it might impact RPL. There are research articles that state there has been no association between a father's alcohol intake, tobacco intake, and BMI on pregnancy outcomes.[17] There has also been recent research that states how a father's obesity has a negative association with recurrent spontaneous miscarriage.[18] Paternal obesity, alcohol consumption, and tobacco intake all have research supporting a negative association with RPL.[19,20] New research discusses how these habits in a father's life can negatively impact pregnancy outcomes through DNA fragmentation and Reactive Oxygen Species (ROS) generation.[21] As the research has shown, a father's age and lifestyle habits may be a topic discussed or reviewed when clinicians are determining the cause of a patient's RPL. In addition to paternal age and lifestyle habits, research has shown paternal health and specific diseases are associated with spontaneous miscarriage.

Metabolic Syndromes

Paternal etiologies of recurrent pregnancy loss are as multifaceted as maternal etiologies. As mentioned previously, research shows how an older paternal age during efforts to conceive can lead to compromised sperm DNA quality.

This shows that there is an interconnected nature between paternal etiologies of RPL. A father's lifestyle habits are major influences on his physical health which can lead to poor pregnancy outcomes. Physical health syndromes such as obesity, diabetes, hypertension, and hyperlipidemia are all metabolic syndromes negatively associated with RPL. A case-control study analyzed over a million pregnancy cases in the United States of America to see if there was any correlation between paternal metabolic syndromes and pregnancy outcomes. The data showed a higher chance of pregnancy loss with the more metabolic disorders a father had. For example, the risk of pregnancy loss progressively increased by 10%, 15%, and 19% in cases where fathers exhibited one, two, or three metabolic conditions, respectively, compared to pregnancies involving healthy fathers.[22] While research has shown compounded metabolic disorders, such as obesity, hypertension, and diabetes collectively influence pregnancy outcomes their individual effects appear to be specific to the syndrome.

A comprehensive review that analyzed over 115,000 fathers found that men with obesity were more likely to be infertile and had a 10% chance overall of their pregnancy being non-viable.[23] While there is research that states compounded metabolic syndromes of the father negatively impact pregnancy outcomes, recent research suggests that individual syndromes are not significant enough to negatively impact pregnancy outcomes. A cohort study that investigated the chance of successful pregnancy in fathers with diabetes mellitus found that of the 990 male participants with diabetes mellitus, there was no statistical significance seen of a negative impact on pregnancy outcomes.[24] Similarly, there is minimal research examining how paternal hypertension alone can negatively influence pregnancy outcomes. These research findings emphasize the interplay of paternal etiologies with how a father's age and lifestyle habits influence his health which then influences his sperm quality and ultimately his pregnancy outcomes. The changes in sperm cell quality could influence placental function and leading to a greater risk of pregnancy loss.[11] Advancing research on paternal health and its impact on pregnancy outcomes is important to consider and will be further discussed with inflammatory and clotting disorders.

Clotting and Inflammatory Disorders

Autoimmune diseases are conditions where the body's immune system is overly active and starts attacking itself. New research is diving into paternal factors of pregnancy loss and has started investigating the effects of fathers with Inflammatory Bowel Diseases such as Ulcerative Colitis or Crohn's Disease and pregnancy outcomes. A study using information from the Danish Assisted Reproduction Registry found that for fathers with ulcerative colitis, the likelihood of a successful pregnancy was significantly similar to fathers without the disorder. In fathers with Crohn's disease compared to fathers without, the chances of a successful pregnancy were 20% less.[25] The study also showed fathers with ulcerative colitis have a slightly better chance of a successful pregnancy, but fathers diagnosed with Crohn's disease have lower chances meaning they may be at a higher risk of losing the baby early. Due to research finding an association between inflammatory bowel disorders having a negative impact on RPL, there's been emerging research that has investigated the effects of inflammatory bowel disorder medications and their potential impact on semen parameters and pregnancy outcomes. A study that included over 25,000 fathers with inflammatory bowel disorders found that there were no significant associations between a father's intake of inflammatory bowel disorder medications and sperm quality or adverse pregnancy outcomes.[26] Emerging research in this field highlights the significance of considering paternal factors in etiologies of RPL. The increased risk of early pregnancy loss associated with fathers diagnosed with Crohn's disease could be attributed to past cases of unexplained RPL or cases previously attributed solely to maternal etiologies. In addition to inflammatory bowel disorders, recent research has uncovered the effect a father's blood disorder can have on successful pregnancy outcomes.

Thrombophilia is a blood disorder that causes blood in the circulatory system to be more likely to clot. This disorder can be inherited from the mother or father due to mutations in the genes Factor V Leiden and Prothrombin G20210A. Mutations in these two specific genes lead to higher risks of recurrent pregnancy loss because they directly lead to increased thrombosis.[3] Research into pregnant women with inherited thrombophilia has shown they have higher risks of experiencing RPL.[27] Past research was controversial on whether inherited thrombophilia would impact a pregnancy so screenings and treatments for mothers with this disorder were not recommended.[8] Updated research now also focuses on the inherited disorder through the father. A study that did a comparative analysis of inherited paternal thrombophilia in Argentinian males, found couples with the father having the Factor V Leiden mutation had a risk of RPL that was six times higher when compared to a control group.[28] Research looking into acquired parental thrombophilia (antiphospholipid syndrome) rather than inherited found that more than 5% of those couples experienced RPL.[9] In addition to Factor v Leiden and prothrombin genetic mutations, the ANXA5 gene also impacts normal blood clotting. Numerous research studies into paternal and maternal carriage of the haplotype have shown the negative contribution of the ANXA5 gene mutation to increasing thrombophilia and RPL.[29,30] Research has shown how mutations in the MTHFR gene impacts blood clotting and leads to hyperhomocysteinemia. Evidence shows when fathers have this condition the risk of miscarriage increases more than 6-fold.[31.32] In addition to blood clotting disorders and inflammatory disorders of the father impacting successful pregnancy outcomes, physical and functional characteristics of sperm have vast amounts of research showing similar pregnancy outcomes.

Characteristics of Sperm

In the past, research conclusions conflicted on the impact of sperm and semen characteristics on successful pregnancy outcomes.[13,33] However, more recent research has solidified the critical role these characteristics have. Sperm quality, decrease in sperm motility, and abnormal sperm head research have all displayed a negative association with successful pregnancies.[34] These results showcase the importance of assessing sperm and semen parameters before couples try to conceive. Numerous studies have shown that semen volume, sperm movement, shape, and concentration negatively impact RPL.[17] Past research that looked into sperm parameters found that pregnancies with abnormal sperm morphology, and sperm motility were all factors that impacted recurrent pregnancy losses.[35] These findings help shed light on the multifaceted interplay of paternal etiologies and how they can impact unexplained recurrent pregnancy loss cases. In addition to sperm morphology and motility, ROS in sperm have shown influence on successful pregnancies.

An important functional sperm characteristic that can negatively impact a pregnancy is the production of ROS in sperm and semen. ROS in semen are unstable oxygen-carrying molecules with different roles such as aiding in sperm motility, activation, and egg fertilization.[36] Research has shown how the secondary effect of ROS leads to DNA damage thus negatively affecting pregnancy outcomes.[34] The generation of ROS is influenced by external factors including lifestyle habits and a father's environment. Specific lifestyle habits including environmental toxins exposure, alcohol consumption, and smoking have been shown to be associated with an increase in the generation of ROS which leads to complications in sperm quality and function.[21] With research investigating the associations between abnormal sperm parameters and oxidative stress, these studies emphasize the importance of addressing paternal health in cases of unexplained recurrent pregnancy loss. They also stress the need for lifestyle interventions and environmental modifications in fathers to reduce oxidative stress and improve sperm quality. The interplay between paternal etiologies in RPL is further supported by an abundance of research displaying how a father's lifestyle habits influence sperm genetic markers which in turn affects pregnancy outcomes.

Genetic Markers

Outside of maternal factors, genetic and molecular markers in sperm have a significant influence on pregnancy outcomes. DNA fragmentation, chromosome abnormalities, chromosome deletions, and proteins all have been shown to play a role in RPL. DNA fragmentation, the breaking of DNA strands, is an extensively studied marker that has shown a negative association with RPL. A study has investigated sperm elemental composition in young fathers versus older fathers and its association with sperm quality. The findings revealed older men showed that older men had increased concentrations of calcium, copper, and zinc in sperm with elevated levels of zinc and calcium contributing to DNA fragmentation.[37] As seen throughout all paternal factors of recurrent pregnancy loss there is a connection they all have with one another. Research has shown that a father's lifestyle habits such as smoking, alcohol, and environmental toxins all have been found to contribute to sperm DNA fragmentation.[21] Research over time and across various races (Asians, Africans, Europeans) has consistently found that DNA fragmentation is linked to RPL.[17,38] In addition to DNA fragmentation, genetic mutations of specific genes have shown to negatively impact pregnancy outcomes. A study that used bioinformatic tools to investigate the HPA2 gene and its effects on recurrent pregnancy loss found numerous harmful mutations linked to recurrent pregnancy loss.[39] Sperm DNA fragmentation, specific genetic mutations, and other epigenetic factors have all shown to influence RPL.

Paternal epigenetic factors have also been shown to influence recurrent pregnancy loss. Recent research investigated paternal epigenetic factors such as DNA methylation through pyrosequencing to see any effects of RPL.[40] The results of the study found a decrease in sperm methylation associated with RPL. DNA fragmentation, DNA methylation patterns, and mutations in genes have all shown how sperm quality can contribute to recurrent miscarriage. Genetic abnormalities, such as balanced translocations, are an established cause of pregnancy loss but account only for 3% of couples who experience RPL.[11] Existing research is controversial about the negative effects of Y chromosome microdeletions on RPL.[41] Proteins found in sperm have a vital role in fertilization. Research into proteomics has found deviations in these sperm proteins have a negative impact on recurrent pregnancy loss. Specifically, in research conducted that compared the protein in sperm of those who experience RPL to a comparison group, the sperm had notable differences in 36 proteins.[42] New research is diving into sperm transcriptomics - which looks at coding and non-coding regions of RNA.[34] Alterations in coding RNA and non-coding RNA can serve as molecular markers for recurrent pregnancy loss. It is important to emphasize the influence each paternal factor has on each other because research has shown a father's age and lifestyle habits affect sperm quality which then affects important biological processes. Paternal age has been shown to impact various cellular mechanisms, such as ROS production, genetic alterations, chromosomal anomalies, deletions on the Y chromosome, elongation of telomeres, centromeric disruptions, shifts in epigenetic modifications, and irregularities in microRNA activity.[16] Given the importance of these genetic markers, this is a signifier for clinicians to evaluate and discuss with patients who might be predisposed to RPL or experiencing unexplained pregnancy loss. Genetic markers, sperm characteristics, and paternal health all contribute to pregnancy outcomes. This emphasizes the importance of including paternal evaluations in the discussion when clinicians are reviewing diagnoses and treatment plans.

Treatment and Diagnosis

Past diagnosis guidelines for RPL focused primarily on maternal etiology. With emerging research diving into how paternal factors can contribute to pregnancy loss, clinicians should follow the data and evaluate the father's all-around health when planning to conceive. Diagnosing RPL will require a comprehensive approach due to the multifaceted nature of the problem. As seen, paternal genetics and environment all influence pregnancy outcomes. With the significant influence sperm has on successful pregnancies, the first diagnostic tool would be sperm analysis. With a sperm analysis, all sperm characteristics such as sperm concentration, structure, and DNA integrity can be analyzed. Research has shown how abnormal characteristics in these features are linked to pregnancy loss.[34,35] Additionally, paternal genetic testing would reveal abnormalities in DNA, chromosomes, or specific genes known to contribute to RPL. Epigenetic testing could be a potential diagnostic tool as it would examine DNA methylation patterns that could potentially impact pregnancy outcomes.[40] It is important for a father to do a thorough review of his lifestyle habits, including alcohol consumption, smoking, and lack of exercise because research has shown their influence on sperm quality and pregnancy success. With all these diagnostic tools combined, in addition to diagnostic measures for maternal health, clinicians and patients can better understand the role of paternal factors in recurrent pregnancy outcomes and coordinate treatment plans accordingly.

Treatment for paternal etiologies of RPL would focus on targeting issues in sperm quality and overall paternal health. For cases of DNA fragmentation in sperm, antioxidants such as vitamin C have been suggested to reduce oxidative stress.[43] And for men with identified chromosomal abnormalities and chromosome microdeletions, assisted reproductive technologies can be considered. Lifestyle modifications are crucial in treatment plans. This includes smoking cessation, reducing alcohol consumption, and avoiding environmental toxins all in an effort to improve sperm health. In specific cases, where paternal age is a factor, the most likely option is to use sperm from a younger age as an option. Overall, treatment strategies should be personalized towards the patient and incorporate medical treatments in addition to paternal lifestyle changes to optimize chances of fertility and successful pregnancy outcomes.

Future Directions

A significant 75% of recurrent pregnancy loss cases remain unexplained despite extensive past research.[3] Future studies should continue to look into paternal etiologies contributing to recurrent pregnancy loss. Researchers can continue to investigate paternal etiologies such as paternally inherited and acquired thrombophilia, the role of sperm proteomics, and sperm transcriptomics. This research can solidify or challenge the current literature. More research should be conducted on paternal lifestyle factors such as obesity, alcohol intake, and smoking, as these can influence reproductive health. Lastly, examining the impact of other paternal autoimmune and metabolic disorders on recurrent pregnancy loss could add to the existing literature on paternal causes of recurrent pregnancy loss. By following these future research recommendations, treatment therapies for recurrent pregnancy loss can be improved and better predictive models of recurrent pregnancy loss can be created. As seen with the 2022 ESHRE guidelines, current research on paternal lifestyle factors and sperm DNA quality provides results that update treatment guidelines.[44]

CONCLUSION

The issue of recurrent pregnancy loss is multifaceted and complex. A majority of cases remain unexplained. A shift in focus from maternal etiologies to paternal etiologies have revealed new causes of recurrent pregnancy loss. New research has focused on paternal factors such as age, thrombophilic disorders, metabolic disorders, lifestyle, and sperm characteristics. This review's purpose was to gain knowledge from the findings of the last twenty years of research focusing on male risk factors associated with unexplained recurrent pregnancy loss. Although there is still a need for additional research, the current literature provides guidelines to improve pregnancy success in couples experiencing unexplained recurrent pregnancy loss.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.
Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors have no conflicts of interest to declare.
Financial Disclosure: This study was supported by Barry University Biomedical Sciences Program, Miami Shores, FL 33161 USA
Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. 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):1658–67.
2. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018(2):hoy004.
3. Turesheva A, Aimagambetova G, Ukybassova T, et al. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. J Clin Med. 2023;12(12):4074.
4. Youssef A, Vermeulen N, Lashley EELO, Goddijn M, van der Hoorn MLP. Comparison and appraisal of (inter)national recurrent pregnancy loss guidelines. Reprod Biomed Online. 2019;39(3):497-503.
5. Yu N, Kwak-Kim J, Bao S. Unexplained recurrent pregnancy loss: Novel causes and advanced treatment. J Reprod Immunol. 2023;155:103785.
6. de Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric Antiphospholipid Syndrome. Autoimmunity Reviews. 2014;13(8):795–813.

7. Tomkiewicz J, Darmochwał-Kolarz D. The Diagnostics and Treatment of Recurrent Pregnancy Loss. J Clin Med. 2023;12(14):4768.
8. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet PE. Recurrent pregnancy loss: current perspectives. Int J Womens Health. 2017;9:331-45.
9. de Assis V, Giugni CS, Ros ST. Evaluation of Recurrent Pregnancy Loss. Obstet Gynecol. 2024;143(5):645-59.
10. Vomstein K, Krog MC, Wrønding T, Nielsen HS. The microbiome in recurrent pregnancy loss - A scoping review. J Reprod Immunol. 2024;163:104251.
11. Muncey W, Scott M, Lathi RB, Eisenberg ML. The paternal role in pregnancy loss. Andrology. 2025;13(1):146–50.
12. Owen A, Carlson K, Sparzak PB. Age-Related Fertility Decline. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
13. du Fossé NA, van der Hoorn MP, van Lith JMM, le Cessie S, Lashley EELO. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Hum Reprod Update. 2020;26(5):650-69.
14. Lindman J, Vomstein K, Egerup P, Krog MC, Nielsen HS. Is lifestyle different in male partners experiencing recurrent pregnancy loss compared to men fathering a live birth? Andrology. 2025;13(1):151–8.
15. Crafa A, Leanza C, Condorelli RA, La Vignera S, Calogero AE, Cannarella R. Relationship between degree of methylation of sperm long interspersed nuclear element-1 (LINE-1) gene and alteration of sperm parameters and age: a meta-regression analysis. J Assist Reprod Genet. 2024;41(1):87–97.
16. Kaltsas A, Moustakli E, Zikopoulos A, et al. Impact of Advanced Paternal Age on Fertility and Risks of Genetic Disorders in Offspring. Genes. 2023;14(2):486.
17. Inversetti A, Bossi A, Cristodoro M, et al. Recurrent pregnancy loss: a male crucial factor-A systematic review and meta-analysis. Andrology. 2023;13(1):130–45.
18. Peuranpää PL, Gissler M, Peltopuro P, Tiitinen A, Hautamäki H. The effect of paternal and maternal factors on the prognosis of live birth in couples with recurrent pregnancy loss. Acta Obstet Gynecol Scand. 2022;101(12):1374-85.
19. Brandt NB, Kristensen MLS, Catalini L, Fedder J. Effect of paternal health on pregnancy loss - A review of current evidence. Andrologia. 2022;54(1):e14259.
20. du Fossé NA, van der Hoorn MLP, de Koning R, et al. Toward more accurate prediction of future pregnancy outcome in couples with unexplained recurrent pregnancy loss: taking both partners into account. Fertil Steril. 2022;117(1):144–52.
21. Ibrahim Y, Johnstone E. The male contribution to recurrent pregnancy loss. Transl Androl Urol. 2018;7(Suppl 3):S317–27.
22. Kasman AM, Zhang CA, Li S, et al. Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data. Hum Reprod. 2021;36(3):785–93.
23. Campbell JM, Lane M, Owens JA, Bakos HW. Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis. Reprod Biomed Online. 2015;31(5):593-604.
24. Sønnichsen-Dreehsen A-S, Fedder J, Wod M, Thorarinsson CT, Nørgård BM. The association between paternal diabetes mellitus and successful pregnancy-Examined in a nationwide population undergoing reproductive treatment. Andrology. 2024;13(3):485–93.
25. Friedman S, Thorarinsson CT, Wod M, Fedder J, Nørgård BM. Paternal Inflammatory Bowel Disease and the Risk of Pregnancy Loss. Inflamm Bowel Dis. 2025;31(4):995-1002.
26. Gubatan J, Barber GE, Nielsen OH, et al. Paternal Medications in Inflammatory Bowel Disease and Male Fertility and Reproductive Outcomes: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2023;21(9):2222-38.
27. Liu X, Chen Y, Ye C, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. Hum Reprod. 2021;36(5):1213–29.
28. Udry S, Aranda FM, Latino JO, de Larrañaga GF. Paternal factor V Leiden and recurrent pregnancy loss: a new concept behind fetal genetics?. J Thromb Haemost. 2014;12(5):666-9.
29. Ang KC, Bogdanova N, Markoff A, Ch'ng ES, Tang TH. Association between M2/ANXA5 haplotype and repeated pregnancy loss: a meta-analysis. Fertil Steril. 2019;111(5):971-981.e2.
30. Rogenhofer N, Engels L, Bogdanova N, Tüttelmann F, Markoff A, Thaler C. Paternal and maternal carriage of the annexin A5 M2 haplotype are equal risk factors for recurrent pregnancy loss: a pilot study. Fertil Steril. 2012;98(2):383–8.
31. Giannubilo SR, Marzioni D, Tossetta G, Montironi R, Meccariello ML, Ciavattini A. The "Bad Father": Paternal Role in Biology of Pregnancy and in Birth Outcome. Biology (Basel). 2024;13(3):165.
32. Sah AK, Shrestha N, Joshi P, et al. Association of parental methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism in couples with unexplained recurrent pregnancy loss. BMC Res Notes. 2018;11(1):233.
33. Eisenberg ML, Sapra KJ, Kim SD, Chen Z, Buck Louis GM. Semen quality and pregnancy loss in a contemporary cohort of couples recruited before conception: data from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Fertil Steril. 2017;108(4):613–9.
34. Naglot S, Thapliyal A, Tomar AK, Yadav S. Male Contributory Factors in Recurrent Pregnancy Loss. Reprod Sci. 2023;30(7):2107–21.
35. Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. J Assist Reprod Genet. 2013;30(11):1513-8.
36. Davies R, Minhas S, Jayasena CN. The role of seminal reactive oxygen species assessment in the setting of infertility and early pregnancy loss. World J Urol. 2023;41(11):3257.
37. Schmid TE, Grant PG, Marchetti F, Weldon RH, Eskenazi B, Wyrobek AJ. Elemental composition of human semen is associated with motility and genomic sperm defects among older men. Hum Reprod. 2013;28(1):274–82.
38. Zhu XB, Chen Q, Fan WM, Niu ZH, Xu BF, Zhang AJ. Sperm DNA fragmentation in Chinese couples with unexplained recurrent pregnancy loss. Asian J Androl. 2020;22(3):296-301.
39. Mohanty G, Jena SR, Kar S, Samanta L. Paternal factors in recurrent pregnancy loss: an insight through analysis of non-synonymous single-nucleotide polymorphism in human testis-specific chaperone HSPA2 gene. Environ Sci Pollut Res Int. 2022;29(41):62219-34.
40. Khambata K, Raut S, Deshpande S, et al. DNA methylation defects in spermatozoa of male partners from couples experiencing recurrent pregnancy loss. Hum Reprod. 2020;36(1):48–60.
41. Golin AP, Yuen W, Flannigan R. The effects of Y chromosome microdeletions on in vitro fertilization outcomes, health abnormalities in offspring and recurrent pregnancy loss. Transl Androl Urol. 2021;10(3):1457-66.
42. Mohanty G, Jena SR, Nayak J, Kar S, Samanta L. Proteomic Signatures in Spermatozoa Reveal the Role of Paternal Factors in Recurrent Pregnancy Loss. World J Mens Health. 2020;38(1):103-14.
43. Hamidian S, Talebi AR, Fesahat F, et al. The effect of vitamin C on the gene expression profile of sperm protamines in the male partners of couples with recurrent pregnancy loss: A randomized clinical trial. Clin Exp Reprod Med. 2020;47(1):68–76.
44. The ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023;2023(1):hoad002.