SRIWIJAYA JOURNAL OF MEDICINE

Risk Factors of Spontaneous Abortion

Dinda Rizki Nawawi[1], Iman Ruansa [2*], Mariana[3]

[1]Medical Profession Study Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Obstetrics and Gynecology Department, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[3]Public Health Department, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
E-mail: imanruansa@gmail.com

Abstract

Spontaneous abortion is defined as a pregnancy loss at the gestational age of under 20 weeks or within the first trimester, which is usually marked by intravaginal bleeding and expulsion of conceptus through the cervix. In 20% of pregnancies, vaginal bleeding occurs prior to 20 weeks of gestational age, and 50% of these cases develop into spontaneous abortion. More than 80% of spontaneous abortion occurs before 12 weeks of gestational age. There are many factors contributing to the incidence of spontaneous abortion such as prior miscarriage and maternal age. Several chronic diseases are also known to trigger spontaneous abortion, such as diabetes and autoimmune diseases. Immediate postpartum conception and infections, such as cervicitis, vaginitis, HIV, syphilis and malaria are also common risk factors. In some cases, fetal chromosomal abnormalities may also cause spontaneous abortion. Environmental contaminants such as arsenic, lead, and organic solvents are thought to be factors that may induce spontaneous abortion.

Keywords: Miscarriage, Spontaneous Abortion, Risk Factors

1. Introduction

Spontaneous abortion is defined as fetal loss at the gestational age of less than 20 weeks or in the first trimester, which is usually characterized by intravaginal bleeding and expulsion of conceptus through the cervix.[1–3] Spontaneous abortion is divided into several types, including imminent, inevitable, complete, and missed abortion. Missed abortion happens when conceptus death is "missed," or asymptomatic, and there are no sufficient uterine contractions to push out the conceptus. Threatened abortion is characterized by vaginal bleeding in the early trimester of pregnancy and the discovery of a viable fetus on ultrasound and physical examination. In incomplete abortion, the conceptus has not fully been expelled through the cervical os, while in complete abortion, the conceptus has been fully expelled through the vagina.[1,2]

In 20% of pregnancies, vaginal bleeding occurs before 20 weeks of gestation, and 50% of these cases are spontaneous abortions. More than 80% of spontaneous abortions occur at less than 12 weeks of gestation.[3] The exact incidence of spontaneous abortion is estimated at 30% of cases, because most abortions occur before the mother realizes that she is pregnant, so the bleeding is usually only considered as late menstrual period.[2]

There are many factors that can lead to spontaneous abortion. History of previous miscarriages and maternal age are common risk factors. Some chronic diseases are known to trigger spontaneous abortion, such as diabetes and autoimmune diseases. Conception soon after delivery and infections, such as cervicitis, vaginitis, HIV infection, syphilis and malaria, are also common risk factors. In some cases, fetal chromosomal abnormalities may also be the cause of spontaneous abortion. Exposure to

environmental contaminants, such as arsenic, lead, and organic solvents are thought to be factors that can cause spontaneous abortion. [1,2]

2. Risk Factors for Spontaneous

2.1. *Age*

Age is known to have a considerable effect on the incidence of spontaneous abortion. As age increases, physiological changes will naturally occur in the body's organs, so that pregnancy at an older age increases the risk factor for spontaneous abortion.[4,5] A study in Norway reported that the highest risk of spontaneous abortion was found in mothers aged 45 years and older.[5] Attali and Yogev reported that miscarriage or abortion in mothers with advanced age (>48 years) as much as 80% were due to spontaneous abortion.[6]

Age alone is thought to be a fairly strong risk factor in the incidence of spontaneous abortion, independent of parity or previous history of abortion.[6] However, the underlying mechanism has yet to be definitively explained. Other studies suggest that the relationship between abortion and age may be based on chromosomal disorders (aneuploidy), where >90% of cases are caused by meiosis failure.[7]

2.2. *Previous history of abortion*

Individuals with a previous history of three consecutive abortions may be four times more at risk of spontaneous abortion. This risk is also thought to be strongly influenced by maternal age.[5] The incidence of recurrent abortion can be influenced by several factors, including abnormalities or anomalies in the uterus. Approximately 15% to 24% of women with uterine anatomical abnormalities were experiencing abortion. Meanwhile, an estimated 7-28% of women with congenital uterine abnormalities were experiencing abortion. About 6-15% of acquired uterine abnormalities are also thought to influence the incidence of recurrent abortion.[8]

Vomstein *et al.* reported that immunological conditions play a role in the incidence of recurrent abortion. The role of anti-nuclear antibodies (ANA) in recurrent abortion is thought to have several mechanisms. First, ANA can reduce oocyte quality and interfere with embryo development. ANA is thought to activate the intraplacental complement cascade and cause immune complex deposits in placental tissue. Activation of plasmacytoid dendritic cells by ANA also leads to increased production of inflammatory cytokines. In patients with anti-phospholipid syndrome, the risk of recurrent abortion is thought to occur due to an increased risk of placental microthrombosis in line with the effect of auto-antibodies on trophoblasts directly. In the placenta of mothers with antiphospholipid antibodies, histopathological changes were found indicating a greater likelihood of placental tissue infarction and inflammation of the decidua with fewer thrombotic signs, such as arthrosis or intraluminal thrombosis.[9]

2.3. *Family History*

Genetic factors are one of the many risk factors contributing to the incidence of spontaneous abortion (50-60%).[10] Parental chromosomal rearrangements, or abnormal genotyping and karyotyping of embryos, are thought to affect the incidence of spontaneous abortion.[5] Andrea et al. reported that family history was found to be associated with the incidence of spontaneous abortion.[11] However, further research is still needed on this matter, since it is necessary to make sure whether the genetic abnormalities already exist in parents or occur during fetal formation.[10–12]

2.4. *Psychological Factors*

Magnus et al. reported that spontaneous abortion is common in patients with bipolar disorder, attention deficit hyperactivity disorder (ADHD), behavioral disorders, anxiety disorders, personality disorders, depression, and somatoform disorders. The risk increases if the patient has multiple psychiatric disorders, the most common combination being anxiety and depression. Women suffering from psychiatric disorders have a higher risk of spontaneous abortion, ranging from 2-5%.[13]

Some pregnant women with psychiatric disorders, especially if not treated, may have an increased incidence of spontaneous abortion. However, some antidepressants used either before or during pregnancy may also harbor a negative impact on the fetus.[14]

2.5. *Comorbidities*

Some viruses, bacteria and parasites that commonly affect humans can infect the fetoplacental system through blood transmission. Other microorganisms may infect or colonize the genitourinary tract.[3] *Toxoplasma gondii* is one of the intracellular pathogens that can cause abortion in infected mothers. *Toxoplasma* infection begins with the consumption of food or drink contaminated by oocytes released by the definitive host. The pathogen is then transmitted vertically through the mother to the fetus.[15–17] *Toxoplasma* can pass through the placental wall and infect the fetus before immunity is established, so the risk of infection is very high.[16] *Toxoplasma gondii* can cause spontaneous abortion especially in the first 3 months of gestation.[18] The prevalence of infection by *Toxoplasma* gondii in pregnant women globally range between 7 and 51.3%. The risk of abortion will also increase if the *Toxoplasma*-infected mother has had a previous abortion.[16] Nayeri et al. reported several risk factors were found and thought to play a role in cases of *Toxoplasma* infection resulting in abortions, including socioeconomic status, history of contact or keeping cats, consumption of raw meat, maternal immunological status, and smoking. However, these risk factors were not specifically studied further.[16] Ignacio et al. mentioned that if the infection occurs during the second or third trimester of pregnancy, the risk of abortion will decrease but the possibility of a child with congenital abnormalities increases. A possible preventive measure is to check the prevalence of anti-*Toxoplasma gondii* antibody, or perform serology tests. These measures can also reduce the rate of reinfection in the individual.[18,19]

Several studies have been conducted to see the relationship between diabetes mellitus and spontaneous abortion. A study by Wei et al. found an association between diabetes mellitus and an increased risk of spontaneous abortion. The increase in risk is also influenced by the duration, severity, and other complications of the disease.[20] Another study states that the risk of spontaneous abortion in mothers with HbA1c levels above 11% increases by 40%. The risk of spontaneous abortion is also higher in patients with type 1 diabetes compared to type 2 and gestational diabetes, but the difference is not statistically significant. Factors increasing the occurrence of spontaneous abortion in patients with diabetes mellitus are lack of glycemic control and the presence of vascular complications, such as pre-eclampsia and diabetic nephropathy.[21]

2.6. *Environmental Contaminants*

Pollution, especially air pollution, is thought to affect fetal development. Air pollution is a heterogeneous mixture of solid particles and gases, which can have certain effects on the human body.[22] Grippo et al. wrote that there is a small possible impact on

the association of NO_2 (Nitrogen dioxide) with the incidence of spontaneous abortion. However, this finding cannot be confirmed and further research is needed. While exposure to sulfur dioxide is thought to have a strong relationship related to the incidence of spontaneous abortion, the mechanism remains unknown.[23] Some studies suggest that ozone can have an effect on the incidence of spontaneous abortion. Yet, the mechanism through which ozone impacts abortion incidence remains unknown, and further studies are necessary.[22,23]

3. Conclusion

Spontaneous abortion is a reproductive problem that often occurs in women of reproductive age, but its incidence is often overlooked. There are many factors that are thought to influence the incidence of spontaneous abortion, but how some factors, such as environmental pollutants, contribute to abortion remains unknown. Further research is needed to confirm the pathophysiological mechanisms that link these factors to the incidence of spontaneous abortion.

References

1. Dugas C, Slane VH. Miscarriage [Internet]. NCBI. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532992/
2. Alves C, Rapp A. Spontaneous Abortion [Internet]. NCBI. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560521/
3. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Spong CY, Hoffman BL, et al. Abortion. In: Williams' Obstetrics. 25th ed. New York: McGraw-Hill Medical; 2018. p. 520–58.
4. Sauer M V. Reproduction at an advanced maternal age and maternal health. Fertil Steril [Internet]. 2015;103(5):1136–43. Available from: http://dx.doi.org/10.1016/j.fertnstert.2015.03.004
5. Magnus MC, Wilcox AJ, Morken N, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage : prospective register based study. :1–8.
6. Attali E, Yogev Y. The impact of advanced maternal age on pregnancy outcome. Best Pract Res Clin Obstet Gynaecol [Internet]. 2021;70:2–9. Available from: https://doi.org/10.1016/j.bpobgyn.2020.06.006
7. Dimitriadis E, Menkhorst E, Saito S, Kutteh WH, Brosens JJ. Recurrent pregnancy loss. Nat Rev Dis Prim [Internet]. 2020;6(1). Available from: http://dx.doi.org/10.1038/s41572-020-00228-z
8. Carbonnel M, Pirtea P, de Ziegler D, Ayoubi JM. Uterine factors in recurrent pregnancy losses. Fertil Steril [Internet]. 2021;115(3):538–45. Available from: https://doi.org/10.1016/j.fertnstert.2020.12.003
9. Vomstein K, Feil K, Strobel L, Aulitzky A, Hofer-Tollinger S, Kuon RJ, et al. Immunological risk factors in recurrent pregnancy loss: Guidelines versus current state of the art. J Clin Med. 2021;10(4):1–21.
10. Garrido-Gimenez C, Alijotas-Reig J. Recurrent miscarriage: Causes, evaluation and management. Postgrad Med J. 2015;91(1073):151–62.
11. Woolner AMF, Raja EA, Bhattacharya S, Danielian P, Bhattacharya S. Inherited susceptibility to miscarriage: a nested case-control study of 31,565 women from an intergenerational cohort. Am J Obstet Gynecol [Internet]. 2020;222(2):168.e1-168.e8. Available from: https://doi.org/10.1016/j.ajog.2019.08.

013

12. Putri AI, de Sabbata K, Agusni RI, Alinda MD, Darlong J, de Barros B, et al. Understanding leprosy reactions and the impact on the lives of people affected: An exploration in two leprosy endemic countries. PLoS Negl Trop Dis [Internet]. 2022;16(6):1–20. Available from: http://dx.doi.org/10.1371/journal.pntd.0010476
13. Magnus MC, Havdahl A, Morken N, Wensaas K, Wilcox AJ, Håberg SE. Risk of miscarriage in women with psychiatric disorders. 2021;501–6.
14. Yilmaz M, Erdemoglu M, Eroglu RE, Kirat S. Current Approaches in Gynecology and [Internet]. 2022. 67–68 p. Available from: www.iksadyayinevi.com
15. Kalantari N, Gorgani-Firouzjaee T, Moulana Z, Chehrazi M, Ghaffari S. Toxoplasma gondii infection and spontaneous abortion: A systematic review and meta-analysis. Microb Pathog [Internet]. 2021;158(June):105070. Available from: https://doi.org/10.1016/j.micpath.2021.105070
16. Nayeri T, Sarvi S, Moosazadeh M, Amouei A, Hosseininejad Z, Daryani A. The global seroprevalence of anti-toxoplasma gondii antibodies in women who had spontaneous abortion: A systematic review and meta-analysis. PLoS Negl Trop Dis [Internet]. 2020;14(3):1–27. Available from: http://dx.doi.org/10.1371/journal.pntd.0008103
17. Ghasemi FS, Rasti S, Piroozmand A, Bandehpour M, Kazemi B, Mousavi SGA, et al. Toxoplasmosis-associated abortion and stillbirth in Tehran, Iran. J Matern Neonatal Med [Internet]. 2016;29(2):248–51. Available from: http://dx.doi.org/10.3109/14767058.2014.996127
18. Vado-Solís IA, Suárez-Solís V, Jiménez-Delgadillo B, Zavala-Velázquez JE, Segura-Correa JC. Toxoplasma gondii presence in women with spontaneous abortion in Yucatan, Mexico. J Parasitol. 2013;99(2):383–5.
19. Kheirandish F, Ezatpour B, Fallahi S, Tarahi MJ, Hosseini P, Rouzbahani AK, et al. Toxoplasma Serology Status and Risk of Miscarriage, A Case-Control Study among Women with A History of Spontaneous Abortion. PubMed [Internet]. 2019;3(13):184–189. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6642426/
20. Wei Y, Xu Q, Yang H, Yang Y, Wang L, Chen H, et al. Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: A population-based cohort study in China. PLoS Med [Internet]. 2019;16(10):1–15. Available from: http://dx.doi.org/10.1371/journal.pmed.1002926
21. Mitrović M, Stojić S, Tešić DS, Popović D, Rankov O, Tomić Naglić D, et al. The impact of diabetes mellitus on the course and outcome of pregnancy during a 5-year follow-up. Vojnosanit Pregl. 2014;71(10):907–14.
22. Di Ciaula A, Bilancia M. Relationships between mild PM10 and ozone urban air levels and spontaneous abortion: Clues for primary prevention. Int J Environ Health Res. 2015;25(6):640–55.
23. Grippo A, Zhang J, Chu L, Guo Y, Qiao L, Myneni AA, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. Rev Environ Health. 2018;33(3):247–64.