

Miscarriage Risk Factors and Causes: Review Article

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ABSTRACT

Human reproduction wastes resources horribly. The fact that we have been unable to use the molecular medical biology revolution to address the fundamental question of why the fate of a fertilized egg is so dangerous and unsuccessful as we are in the twenty-first century is frightening. The description that follows briefly reviews the risk factors for miscarriage before moving on to discuss some of the medical causes of miscarriage. This article also explores the issue of pregnancy loss in relation to genetic disorders.

INTRODUCTION

A fetus or embryo that is expelled from the uterus before 20 weeks of gestation or with a birth weight of less than 500 g is said to have experienced a miscarriage. A reasonably frequent pregnancy problem that affects 20% of all pregnancies is threatened miscarriage ⁽¹⁾.

Miscarriage can be subdivided into:

- A. **Complete miscarriage:** Without the necessity for surgical or medical intervention, all progeny have passed.
- B. **Incomplete miscarriage:** Not all of the results of conception have been expelled; those that have been retained may include membranes, the placenta, or parts of the fetus.
- C. **Inevitable miscarriage:** Despite the cervical dilation, the fetus' products have not yet been evacuated.
- D. **Missed miscarriage:** A pregnancy in which the fetus dies but there is no uterine action to release the embryo.
- E. **Recurrent spontaneous miscarriage:** Three or more successive miscarriages.
- F. **Septic miscarriage:** An unplanned pregnancy that is complicated by an infection inside the uterus.
- G. **Threatened miscarriage:** A pregnancy made more difficult by bleeding before 20 weeks of pregnancy ⁽²⁾.

Pathophysiology:

In order to protect differentiating cells from oxidative damage brought on by free radicals, the maternal blood flow through the placenta is physiologically restricted throughout the early stages of pregnancy. Fetomaternal blood flow should start at the edge and slowly move into the center of the growing placenta for optimal development ⁽³⁾.

Roztocka ⁽³⁾ reported that between successful and lost pregnancies, variations in maternal blood flow via the placenta, particularly its marginal zone, were found. **Roztocka** ⁽³⁾ established that premature intervillous blood

flow, particularly that which touches the entire placenta or its central region, has a detrimental effect on pregnancy because it damages the trophoblast. First trimester miscarriages can also be brought on by oxidative damage.

At eight weeks, the intervillous area typically has oxygen tension of less than 20 mm Hg, similar to placental tissue, particularly syncytiotrophoblast, which is very vulnerable to oxidative injury. It results from antioxidants' ineffectiveness on placental tissue up to this point 8-9th week of pregnancy. Increase oxygen tension to exceed 50 mm Hg, precocious maternal arterial blood flow entrance before the end of embryogenesis and the development of the placenta might result in permanent morphological and immunohistochemical alterations as well as syncytiotrophoblast degradation ⁽³⁾.

Alterations in placentation can manifest in the second and third trimesters in addition to their immediate impacts, such as spontaneous miscarriage. Preeclampsia, intrauterine growth restriction, and hypertension in pregnancy—all of which appear at various stages of pregnancy—have all been extensively researched to determine their shared cause ⁽⁴⁾.

Causes of miscarriage: ⁽⁴⁾.

A. Fetal factors which include:

1. Miscarriage with aneuploid chromosomes.
2. Euploid miscarriage (genetic flaws).

B. Maternal factors which include:

1. Anatomic factors:

- a. Congenital abnormality.
- b. Abdominal leiomyoma.
- c. Intrauterine adhesions.
- d. An ineffective cervix.

2. Systemic and localized endocrine abnormalities:

- a. Thyroid condition.
- c. Sugar-related diabetes.
- c. Ovaries that have cysts.
- d. A high amount of androgen.
- e. Luteal phase flaws,

3. Immunological factors.

4. Thrombophilias.

5. Infection causes:

- a. Endometritis, vaginitis, and endocervicitis.
- b. Mycoplasma.
- c. Malaria.
- d. Toxoplasma gondii.
- e. Acquired immunodeficiency syndrome.
- f. Syphilis and Lyme disease that are untreated.
- g. Brucellosis.
- h. Viruses.

C. Paternal factors:

Paternal influences on the development of spontaneous miscarriage are poorly understood. Undoubtedly, sperm chromosomal abnormalities have been linked to miscarriage ⁽⁵⁾.

D. General causes:

Racial, environmental, and lifestyle variables can all have an impact on pregnancy and contribute to pregnancy loss. The risk of miscarriage is 70% higher in African-American women than it is in Caucasian women. This may be due to a genetic or environmental implantation-placentation defect. It may also be the cause of the higher risk of preterm birth and pre-eclampsia in women who do not miscarry ⁽⁶⁾.

Chronic Debilitating Diseases:

Rarely do persistent wasting illnesses like tuberculosis or carcinomatosis cause early miscarriages ⁽⁶⁾.

Nutrition:

It does not seem that dietary deficiencies in any one vitamin or even mild deficiencies in all nutrients play a significant role in miscarriage. Even at the extreme, a miscarriage is uncommonly caused by hyperemesis gravidarum with severe weight loss ⁽⁷⁾.

Caffeine intake:

Zlatnik ⁽⁷⁾ discovered a connection between caffeine consumption and a rise in miscarriage rates. So it makes sense to limit the caffeine intake before conception and during the first few weeks of pregnancy.

Other factors:

Miscarriage is undoubtedly caused by radiation. The human dose that will cause a miscarriage is not precisely understood, despite the fact that smaller doses are less dangerous. The risk of miscarriage is not increased by exposure to less than five rads. There is no link between the usage of oral contraceptives or spermicidal creams, gels, or jellies and a higher risk of

miscarriage. The risk of miscarriage, and specifically septic miscarriage, significantly increases when intrauterine devices fail to prevent conception. Early in pregnancy, simple abdominal or pelvic surgery does not seem to raise the chance of miscarriage. In most cases, ovarian tumors can be removed without affecting pregnancy. Early excision of the corpus luteum cyst or the ovary in which the corpus luteum is located is a significant exception ⁽⁷⁾.

Zlatnik ⁽⁷⁾ also reported that probable abortifacients include arsenic, lead, formaldehyde, benzene, and ethylene oxide. It was discovered that working with ultrasound had no adverse consequences, however working with nitrous oxide for three or more hours a day in offices without gas-scavenging equipment increased the incidence of spontaneous miscarriage among dental assistants.

E. Fetal factors:

Abnormal Zygotic Development:

1. Chromosomal errors (Aneuploidy):

Where abnormal, an abortus' karyotype can explain the loss, provide evidence for a parent's chromosomal translocation (where an imbalanced translocation is seen), or, when normal, suggest a non-genetic explanation. A normal female karyotype (46, XX) might result from maternal cell contamination of cultured tissue specimens, hence a normal karyotype does not completely rule out genetic explanations for the miscarriage ⁽⁸⁾.

Chromosomal abnormalities are frequent in embryos and fetuses that spontaneously miscarry and are responsible for a large portion, if not all, of pregnancy waste. A chromosomal abnormality of the conceptus is linked to 50–60% of early pregnancy miscarriages, and it becomes less prevalent as pregnancy progresses and is present in 30% of midtrimester losses ⁽⁷⁾.

Monosomy X (45, X) is the most prevalent particular chromosomal anomaly, causing Turner syndrome, which typically causes miscarriage and only rarely live births in females. Autosomal monosomy, on the other hand, is uncommon and unfit for life. Triploidy frequently coexists with hydropic (molar) placental degeneration. Hydatidiform moles that are incomplete (partial) can be trisomic or triploid for chromosome 16. The few that are carried longer, despite the fact that these fetuses typically miscarry early, are invariably severely deformed. The incidence of triploidy is not increased by older mother and paternal ages. Tetraploids are rarely born alive and typically miscarry very early in the pregnancy. Rarely do chromosomal structural defects lead to miscarriage. Some newborns with balanced translocations who are live born may seem normal ⁽⁷⁾.

Holovatiuk ⁽⁹⁾, analyzed data using more recent methods independent of cell culture fluorescence in situ

hybridization. The true rate of chromosomal abnormalities in aborted early pregnancies is closer to 75%, according to more recent rigorous cytogenetic investigations of early missed miscarriages, and roughly 95% of chromosomal abnormalities were caused by maternal gametogenesis faults and 5% by paternal errors.

2. Euploid Miscarriage (genetic defect):

Pregnancies that result in abortion are more likely to be chromosomally normal than aneuploid ones. For instance, whilst euploid losses peaked at about 13 weeks, aneuploid miscarriages peaked at 75% before 8 weeks. When a mother is older than 35 years old, the likelihood of euploid miscarriages rises sharply ⁽⁷⁾.

F- Maternal factors:

1- General causes:

Education level, housing type (public or private), number of children, pre-pregnancy body mass index (BMI), regularity of menstrual cycles, presence of morning sickness during pregnancy, history of prior miscarriages, or pregnancy termination; smoking status, alcohol and caffeine intake, daily phone use of more than two hours, and daily hours spent on a computer; a university degree and a history of mental illness were linked to lower miscarriage rates, while stress is thought to increase miscarriage rates by lowering progesterone levels ⁽¹⁰⁾.

Maternal and paternal age:

According to studies, the mother's and father's ages are strongly related, and the baby's prognosis is worse when both parents are older. It was shown that women over the age of 31 had the highest miscarriage rate. Young maternal age also seems to be a risk factor; patients between the ages of 21 and 30 had the lowest risk, 7.1% ⁽³⁾.

Anatomic factors:

The prevalence of uterine abnormalities is currently estimated to be around 1% in the general population using newer imaging techniques, and it is roughly three times greater in women who experience recurrent pregnancy loss and poor reproductive outcomes ⁽¹⁾.

Uterine leiomyomas:

Fibroids have the potential to lead to miscarriage and pregnancy loss, among other pregnancy-related issues. Numerous studies have demonstrated that the likelihood of spontaneous miscarriage during the first and second trimesters of pregnancy is increased in women who have fibroids, with the submucous fibroid being the most prevalent kind to result in miscarriage ⁽¹¹⁾.

Intrauterine adhesions :

Asherman's syndrome is an acquired disorder brought on by post-traumatic intrauterine adhesions that partially or totally obliterate the uterine cavity, reducing the endometrium's reactivity to steroid hormones in certain places. The prognosis is based on the degree of endometrial damage since substantial dense fibrosis, which is linked to a bad prognosis, may result in permanent loss of endometrial function ⁽¹²⁾.

Systemic and localized endocrine abnormalities:

There may be a number of endocrinological causes for miscarriage.

Thyroid disease:

The majority of research, though not all, have demonstrated a strong connection between thyroid antibody levels and a higher likelihood of miscarriage. However, when compared to individuals with low titres of thyroid autoantibodies, patients with high titres do not exhibit a higher likelihood of miscarriages ⁽⁷⁾.

Diabetes mellitus:

Compared to healthy women, women with type I diabetes have a considerably increased risk of miscarriage and embryopathies, demonstrating the importance of maintaining strict glucose and/or insulin control for safe embryo development ⁽¹³⁾.

Autoimmune factors:

A specific component of the host is the target of an immune reaction in autoimmune disorders, which include several well-known autoimmune conditions as antiphospholipid syndrome and systemic lupus erythematosus. Two of them, lupus anticoagulant and anticardiolipin antibody, have been linked to spontaneous miscarriage. Antiphospholipid antibodies are acquired antibodies that are directed against negatively charged phospholipids found in animals. An immunoglobulin IgG, IgA, or IgM isotype can be present in antiphospholipid antibodies. Placental thrombosis and infarction play a role in how these antibodies cause pregnancy loss in affected women. According to one proposed mechanism, antibodies may prevent prostacyclin, a strong vasodilator and inhibitor of platelet aggregation, from being released into the body. In contrast, thromboxane A₂, a vasoconstrictor and platelet aggregator, is produced by platelets. Additionally, it has been demonstrated that they prevent protein C activation, which causes coagulation and fibrin production ⁽¹³⁾.

2- Alloimmune factors:

According to some research, a healthy pregnancy necessitates the development of blocking substances that stop the mother's immune system from rejecting

paternally produced foreign fetal antigens. Among the potential causes of alloimmune disorders are aberrant maternal cytotoxic antibodies and changes in the function and distribution of natural killer cells in response to fetal or placental antigens⁽¹⁴⁾.

Infectious causes:

An uncommon reason for early miscarriage is infection. Numerous particular infections have been researched. *Campylobacter* and *Brucella* can lead to miscarriage in cattle, but not in humans. Additionally, there is no proof that *Listeria monocytogenes* or *Chlamydia trachomatis* cause miscarriages in people. Herpes simplex virus infection in the first trimester of pregnancy did not raise the incidence in several prospective studies. There is still a lack of proof that *Toxoplasma gondii* causes miscarriages in humans. Data on a connection between some infectious infections and an increase in miscarriage are contradictory. Some studies identified an association between bacterial vaginosis and second-trimester loss but not first-trimester miscarriage⁽¹⁴⁾.

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