Section A-Research paper

Brief Overview about Subsequent Miscarriage; Risk Factors and Management

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Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Spontaneous abortion or miscarriage is defined as the loss of pregnancy less than 20 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) estimates it is the most common form of pregnancy loss. It is estimated that as many as 26% of all pregnancies end in miscarriage and up to 10% of clinically recognized pregnancies. Moreover, 80% of early pregnancy loss occurs in the first trimester. The risk of miscarriage decreases after 12 weeks gestation. Most clinically apparent miscarriages (two-thirds to three-quarters in various studies) occur during the first trimester. About 30% to 40% of all fertilized eggs miscarry, often before the pregnancy is known. uterine Early miscarriages can be due to a developmental abnormality of the placenta or other embryonic tissues. In some instances an embryo does not form but other tissues do. This has been called a "blighted ovum".Treatment options include expectant management, medication, or surgical interventions. Decisions are often made jointly with the patient and the obstetrician as to which path to choose. As long as patients are hemodynamically stable and do not require emergency surgery, there is no difference in long-term outcomes when comparing these treatment options. Expectant management is typically limited to those miscarrying in the first trimester due to lack of studies beyond that timeframe and presumed increased risk of bleeding complications beyond that. Approximately 80% of women achieve complete passage of intrauterine contents within 8 weeks.

Keywords: Subsequent Miscarriage

Introduction

Miscarriage also known in medical terms as a spontaneous abortion and pregnancy loss, is the death of an embryo or fetus before the age of viability (it is the age to be able to survive independently) . Some use the cutoff of 20 weeks of gestation, after which fetal death is known as a stillbirth.Previability refers to a fetus weighting < 500 gm or at gestional age (GA)< 20 weeks. **(1) .**

Spontaneous abortion or miscarriage is defined as the loss of pregnancy less than 20 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) estimates it is the most common form of pregnancy loss. It is estimated that as many as 26% of all pregnancies end in miscarriage and up to 10% of clinically recognized pregnancies. Moreover, 80% of early pregnancy loss occurs in the first trimester. The risk of miscarriage decreases after 12 weeks gestation. **(1) .**

The terms miscarriage and abortion are used interchangeably. The term abortion refers to a termination of a pregnancy either natural or induced. There are several terms that describe different states of pregnancy loss. These terms include threatened, inevitable, complete, and missed abortion. Threatened abortion is the presence of vaginal bleeding in early pregnancy but on pelvic exam, the cervical os is closed and the transvaginal ultrasound shows a viable fetus. Inevitable abortion is when there is vaginal bleeding but on

the pelvic exam, the cervical os is open meaning that the fetus or products of conception are expected to pass through the cervix in the near future. On transvaginal ultrasound, there can be either be a viable fetus or not. **(2)** Complete abortion is when there is initially vaginal bleeding and passing of products of conception through the cervix. On transvaginal ultrasound, there would be no remaining products of conception in the uterus. A missed abortion refers to when there was vaginal bleeding and perhaps some passage of tissue or products of conception. On pelvic exam, the cervical os would be closed. On transvaginal ultrasound, there would be retained products of conception and there would not be a viable fetus.

Etiology

The most common cause of spontaneous pregnancy loss in the first trimester is chromosomal abnormalities. In most cases, it is too early to determine the exact cause of the abnormality. The risk of early pregnancy loss decreases with increasing gestational age and is relatively low after 15-weeks gestation in a genetically normal fetus. **(3).**

Epidemiology

The risk of miscarriage is multivariate, and while some maternal risk factors tend to be more important than others, there is no one predictor of future pregnancy loss. Maternal age is an important predictor of the risk of miscarriage. In women ages, 20 to 30 risk of miscarriage less than 20 weeks gestation is 8.9%. This increases to 74.7% for women over 40 yearsAnother important predictor in the risk of early pregnancy loss is prior obstetrical history. The risk of miscarriage in a future pregnancy is approximately 20% after 1 miscarriage, 28% after 2 consecutive miscarriages, and 43% after 3 or more consecutive miscarriages. **(4).**

Among women who know they are pregnant, the miscarriage rate is roughly 10% to 20%, while rates among all fertilized zygotes are around 30% to 50%.A 2012 review found the risk of miscarriage between 5 and 20 weeks from 11% to 22%**(4).**Up to the 13th week of pregnancy, the risk of miscarriage each week was around 2%, dropping to 1% in week 14 and reducing slowly between 14 and 20 weeks. **(4).**

The precise rate is not known because a large number of miscarriages occur before pregnancies become established and before the woman is aware she is pregnant. Additionally, those with bleeding in early pregnancy may seek medical care more often than those not experiencing bleeding. Although some studies attempt to account for this by recruiting women who are planning pregnancies and testing for very early pregnancy, they still are not representative of the wider population.**(4).**

Maternal comorbidities such as thrombophilia, antiphospholipid antibody syndrome, extremes of maternal weight, and hypertension also increase the risk of miscarriage. Additional maternal risk factors have been identified such as cigarette smoking, large amounts of caffeine use, trauma, and malnutrition.**(5) .**

Symptoms of a miscarriage

Most miscarriages occur before the 12th week of pregnancy.

Signs and symptoms of a miscarriage might include:

Vaginal spotting or bleeding

Pain or cramping in your abdomen or lower back

Fluid or tissue passing from your vagina

Risk factors

Trimesters

First trimester

Most clinically apparent miscarriages (two-thirds to three-quarters in various studies) occur during the first trimester. About 30% to 40% of all fertilized eggs miscarry, often before the pregnancy is known. uterine Early miscarriages can be due to a developmental abnormality of the placenta or other embryonic tissues. In some instances an embryo does not form but other tissues do. This has been called a "blighted ovum". (**6).**

Successful implantation of the zygote into the uterus is most likely eight to ten days after fertilization. If the zygote has not implanted by day ten, implantation becomes increasingly unlikely in subsequent days. (**6).**

A chemical pregnancy is a pregnancy that was detected by testing but ends in miscarriage before or around the time of the next expected period. Chromosomal abnormalities are found in more than half of embryos

miscarried in the first 13 weeks. Half of embryonic miscarriages (25% of all miscarriages) have an aneuploidy (abnormal number of chromosomes). Common chromosome abnormalities found in miscarriages include an autosomal trisomy (22–32%), monosomy X (5–20%), triploidy (6–8%), tetraploidy (2–4%), or other structural chromosomal abnormalities (2%). Genetic problems are more likely to occur with older parents; this may account for the higher rates observed in older women. **(6).**
Luteal phase progesterone deficiency may or may not be a contributing factor to miscarriage.

Chromosomal abnormalities found in first trimester miscarriages

Description	Proportion of total
Normal	45–55%
Autosomal trisomy	22–32%
Monosomy X (45, X)	5–20%
Triploidy	6–8%
Structural abnormality of the chromosome	2%
Double or triple trisomy	0.7–2.0%
Translocation	Unknown

Second and third trimesters

Second trimester losses may be due to maternal factors such as
uterine malformation
growths in the uterus (fibroids)
Cervical problems (cervical incompetence or cervical insufficiency)
second-trimester miscarriages are less likely to be caused by a genetic abnormality; chromosomal aberrations are found in a third of cases. **(6).**
Infection during the third trimester can cause a miscarriage.

Age

The age of the pregnant woman is a significant risk factor. Miscarriage rates increase steadily with age, with more substantial increases after age 35. In those under the age of 35 the risk is about 10% while it is about 45% in those over the age of 40. Risk begins to increase around the age of 30. Paternal age is associated with increased risk. **(3).**

Obesity, eating disorders

Not only is obesity associated with miscarriage; it can result in sub-fertility and other adverse pregnancy outcomes. Recurrent miscarriage is also related to obesity. Women with bulimia nervosa and anorexia nervosa may have a greater risk for miscarriage. Nutrient deficiencies have not been found to impact miscarriage rates but hyperemesis gravidarum sometimes precedes a miscarriage. **(3).**

Endocrine disorders

Disorders of the thyroid may affect pregnancy outcomes. Related to this, iodine deficiency is strongly associated with an increased risk of miscarriage. The risk of miscarriage is increased in those with poorly controlled insulin-dependent diabetes mellitus. Women with well-controlled diabetes have the same risk of miscarriage as those without diabetes. **(7).**

Food poisoning

Ingesting food that has been contaminated with listeriosis, toxoplasmosis, and salmonella is associated with an increased risk of miscarriage.**(8).**

Amniocentesis and chorionic villus sampling

Amniocentesis and chorionic villus sampling (CVS) are procedures conducted to assess the fetus. A sample of amniotic fluid is obtained by the insertion of a needle through the abdomen and into the uterus. Chorionic villus sampling is a similar procedure with a sample of tissue removed rather than fluid. These procedures are not associated with pregnancy loss during the second trimester but they are associated with miscarriages and birth defects in the first trimester. Miscarriage caused by invasive prenatal diagnosis (chorionic villus sampling (CVS) and amniocentesis) is rare (about 1%). **(9).**

Surgery

The effects of surgery on pregnancy are not well-known including the effects of bariatric surgery. Abdominal and pelvic surgery are not risk factors for miscarriage. Ovarian tumours and cysts that are removed have not been found to increase the risk of miscarriage. The exception to this is the removal of the corpus luteum from the ovary. This can cause fluctuations in the hormones necessary to maintain the pregnancy. **(9).**

Medication

There is no significant association between antidepressant medication exposure and spontaneous abortion.. The risk of miscarriage is not likely decreased by discontinuing SSRIs prior to pregnancy.. Some available data suggest that there is a small increased risk of miscarriage for women taking any antidepressant, though this risk becomes less statistically significant when excluding studies of poor quality**.(10).**

Medicines that increase the risk of miscarriage include:

retinoids

nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen

misoprostol

methotrexate

statins **(11)**

Immunizations

Immunizations have not been found to cause miscarriage. Live vaccinations, like the MMR vaccine, can theoretically cause damage to the fetus as the live virus can cross the placenta and potentially increase the risk for miscarriage. Therefore, the Center for Disease Control (CDC) recommends against pregnant women receiving live vaccinations. However, there is no clear evidence that has shown live vaccinations to increase the risk for miscarriage or fetal abnormalities. **(12).**

Some live vaccinations include: MMR, varicella, certain types of the influenza vaccine, and rotavirus.

Treatments for cancer

Ionizing radiation levels given to a woman during cancer treatment cause miscarriage. Exposure can also impact fertility. The use of chemotherapeutic drugs used to treat childhood cancer increases the risk of future miscarriage.

Pre-existing diseases

Several pre-existing diseases in pregnancy can potentially increase the risk of miscarriage, including diabetes, polycystic ovary syndrome (PCOS), hypothyroidism, certain infectious diseases, and autoimmune diseases. PCOS may increase the risk of miscarriage. Two studies suggested treatment with the drug metformin significantly lowers the rate of miscarriage in women with PCOS, but the quality of these studies has been questioned. Metformin treatment in pregnancy has not been shown to be safe**.(13).** In 2007 the Royal College of Obstetricians and Gynaecologists also recommended against use of the drug to prevent miscarriage. Thrombophilias or defects in coagulation and bleeding were once thought to be a risk in miscarriage but have been subsequently questioned. Severe cases of hypothyroidism increase the risk of miscarriage. The effect of milder cases of hypothyroidism on miscarriage rates has not been established. A condition called luteal phase defect (LPD) is a failure of the uterine lining to be fully prepared for pregnancy. This can keep a fertilized egg from implanting or result in miscarriage. **(14).**

Mycoplasma genitalium infection is associated with increased risk of preterm birth and miscarriage**. (14).**

Infections can increase the risk of a miscarriage: rubella (German measles), cytomegalovirus, bacterial vaginosis, HIV, chlamydia, gonorrhoea, syphilis, and malaria. **(14).**

Immune status

Autoimmunity is a possible cause of recurrent or late-term miscarriages. In the case of an autoimmune-induced miscarriage, the woman's body attacks the growing fetus or prevents normal pregnancy progression.. Autoimmune disease may cause abnormalities in embryos, which in turn may lead to miscarriage. As an example, Celiac disease increases the risk of miscarriage by an odds ratio of approximately 1.4.. A disruption in normal immune function can lead to the formation of antiphospholipid antibody syndrome. This will affect the ability to continue the pregnancy, and if a woman has repeated miscarriages, she can be tested for it. Approximately 15% of recurrent miscarriages are related to immunologic factors. The presence of anti-thyroid autoantibodies is associated with an increased risk with an odds ratio of 3.73 and 95% confidence interval 1.8–7.6. Having lupus also increases the risk for miscarriage. Immunohistochemical studies on decidual basalis and chorionic villi found that the imbalance of the immunological environment could be associated with recurrent pregnancy loss. **(15).**

Anatomical defects and trauma

Fifteen per cent of women who have experienced three or more recurring miscarriages have some anatomical defect that prevents the pregnancy from being carried for the entire term. The structure of the uterus affects the ability to carry a child to term. Anatomical differences are common and can be congenital.

Type of uterine structure	Miscarriage rate associated with defect
Bicornate uterus	40–79%
Septate or unicornate	34–88%
Arcuate	Unknown
Didelphys	40%
Fibroids	Unknown

(16).

In some women, cervical incompetence or cervical insufficiency occurs with the inability of the cervix to stay closed during the entire pregnancy. It does not cause first trimester miscarriages. In the second trimester, it is associated with an increased risk of miscarriage. It is identified after a premature birth has occurred at about 16–18 weeks into the pregnancy. During the second trimester, major trauma can result in a miscarriage.

Smoking

Tobacco (cigarette) smokers have an increased risk of miscarriage. There is an increased risk regardless of which parent smokes, though the risk is higher when the gestational mother smokes. **(17).**

Chemicals and occupational exposure

Chemical and occupational exposures may have some effect in pregnancy outcomes. A cause and effect relationship almost can never be established. Those chemicals that are implicated in increasing the risk for miscarriage are DDT, lead,**(18).** formaldehyde, arsenic, benzene and ethylene oxide. Video display terminals and ultrasound have not been found to have an effect on the rates of miscarriage. In dental offices where nitrous oxide is used with the absence of anesthetic gas scavenging equipment, there is a greater risk of miscarriage. For women who work with cytotoxic antineoplastic chemotherapeutic agents there is a small increased risk of miscarriage. No increased risk for cosmetologists has been found.

Other

Alcohol increases the risk of miscarriage. Cocaine use increases the rate of miscarriage. Some infections have been associated with miscarriage. These include Ureaplasma urealyticum, Mycoplasma hominis, group B streptococci, HIV-1, and syphilis. Infections of Chlamydia trachomatis, Camphylobacter fetus, and Toxoplasma gondii have not been found to be linked to miscarriage. **(6).**Subclinical infections of the lining of the womb, commonly known as chronic endometritis are also associated with poor pregnancy outcomes, compared to women with treated chronic endometritis or no chronic endometritis. **(19).**

Diagnosis

Ultrasound criteria

A review article in The New England Journal of Medicine based on a consensus meeting of the Society of Radiologists in Ultrasound in America (SRU) has suggested that miscarriage should be diagnosed only if any of the following criteria are met upon ultrasonography visualization**:(20).**

Miscarriage diagnosed	Miscarriage suspected
Crown-rump length of at least 7 mm and no heartbeat.	Crown–rump length of less than 7 mm and no heartbeat.
Mean gestational sac diameter of at least 25 mm and no embryo.	Mean gestational sac diameter of 16–24 mm and no embryo.
Absence of embryo with heartbeat at least 2 weeks after an ultrasound scan that showed a gestational sac without a yolk sac.	Absence of embryo with heartbeat 7–13 days after an ultrasound scan that showed a gestational sac without a yolk sac.
Absence of embryo with heartbeat at least 11 days after an ultrasound scan that showed a gestational sac with a yolk sac.	Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac.
	Absence of embryo at least 6 weeks after last menstrual period.
	Amniotic sac seen adjacent to yolk sac, and with no visible embryo.
	Yolk sac of more than 7 mm.
	Small gestational sac compared to embryo size (less than 5 mm difference between mean sac diameter and crown-rump length).

Classification

A threatened miscarriage is any bleeding during the first half of pregnancy. At investigation it may be found that the fetus remains viable and the pregnancy continues without further problems. An anembryonic pregnancy (also called an "empty sac" or "blighted ovum") is a condition where the gestational sac develops normally, while the embryonic part of the pregnancy is either absent or stops growing very early. This accounts for approximately half of miscarriages. All other miscarriages are classified as embryonic miscarriages, meaning that there is an embryo present in the gestational sac. Half of embryonic miscarriages have aneuploidy (an abnormal number of chromosomes). **(6).**

An inevitable miscarriage occurs when the cervix has already dilated, **(21)** but the fetus has yet to be expelled. This usually will progress to a complete miscarriage. The fetus may or may not have cardiac activity.

A complete miscarriage is when all products of conception have been expelled; these may include the trophoblast, chorionic villi, gestational sac, yolk sac, and fetal pole (embryo); or later in pregnancy the fetus, umbilical cord, placenta, amniotic fluid, and amniotic membrane. The presence of a pregnancy test that is still positive, as well as an empty uterus upon transvaginal ultrasonography, does, however, fulfil the definition of pregnancy of unknown location. Therefore, there may be a need for follow-up pregnancy tests to ensure that there is no remaining pregnancy, including ectopic pregnancy.

An incomplete miscarriage occurs when some products of conception have been passed, but some remains inside the uterus. However, an increased distance between the uterine walls on transvaginal ultrasonography may also simply be an increased endometrial thickness and/or a polyp. The use of a Doppler ultrasound

may be better in confirming the presence of significant retained products of conception in the uterine cavity In cases of uncertainty, ectopic pregnancy must be excluded using techniques like serial beta-hCG measurements **(22).**

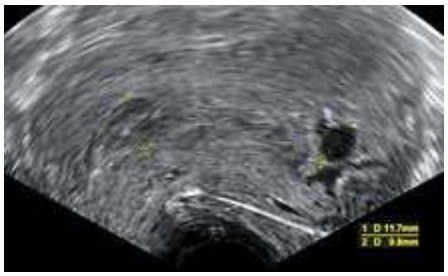
A missed miscarriage is when the embryo or fetus has died, but a miscarriage has not yet occurred. It is also referred to as delayed miscarriage, silent miscarriage, or missed abortion. **(6).**

A septic miscarriage occurs when the tissue from a missed or incomplete miscarriage becomes infected, which carries the risk of spreading infection (septicaemia) and can be fatal. **(6).**

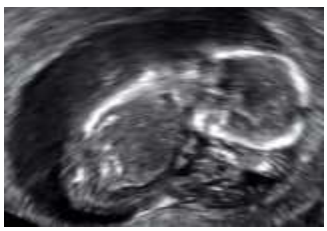
Recurrent miscarriage ("recurrent pregnancy loss" (RPL) or "habitual abortion") is the occurrence of multiple consecutive miscarriages; the exact number used to diagnose recurrent miscarriage varies. If the proportion of pregnancies ending in miscarriage is 15% and assuming that miscarriages are independent events, then the probability of two consecutive miscarriages is 2.25% and the probability of three consecutive miscarriages is 0.34%. The occurrence of recurrent pregnancy loss is 1%. A large majority (85%) of those who have had two miscarriages will conceive and carry normally afterward.**(6).**

The physical symptoms of a miscarriage vary according to the length of pregnancy, though most miscarriages cause pain or cramping. The size of blood clots and pregnancy tissue that are passed become larger with longer gestations. After 13 weeks' gestation, there is a higher risk of placenta retention.

Fig(1): Transvaginal ultrasonography after an episode of heavy bleeding in an intrauterine pregnancy that had been confirmed by previous ultrasonography. There is some widening between the uterine walls, but no sign of any gestational sac, thus, in this case, being diagnostic of a complete miscarriage.



Fig(2): Transvaginal ultrasonography, with some products of conception in the cervix (to the left in the image) and remnants of a gestational sac by the fundus (to the right in the image), indicating an incomplete miscarriage



Fig(3): A 13-week fetus without cardiac activity located in the uterus (delayed or missed miscarriage)

Management

Treatment options include expectant management, medication, or surgical interventions. **(23).**
Decisions are often made jointly with the patient and the obstetrician as to which path to choose. As long as patients are hemodynamically stable and do not require emergency surgery, there is no difference in long-term outcomes when comparing these treatment options.Expectant management is typically limited to those miscarrying in the first trimester due to lack of studies beyond that timeframe and presumed increased risk of bleeding complications beyond that. Approximately 80% of women achieve complete passage of intrauterine contents within 8 weeks. **(23).**
Medical management can be used in the absence of contraindications, including severe anemia, bleeding disorders, or infection. Misoprostol, a prostaglandin analog, is given in 1 or 2 doses to achieve induced passage of intrauterine contents. Misoprostol can be taken in the oral form, sublingual, or as a vaginal suppository. Most women will achieve complete expulsion within 3 days, and very few need subsequent uterine curettage. Surgical evacuation is another option in the treatment of early pregnancy loss and is achieved either with sharp curettage or suction curettage. Surgical evacuation is preferred in women who present with hemorrhage, hemodynamic instability, or signs of infection because these conditions require urgent treatment. This is also the preferred method of treatment for women with comorbid conditions such as cardiovascular disease, infection, severe anemia, or bleeding disorders.
While success rates for surgical evacuation reach 99%,**(24).** the risk of complications among all 3 treatment options remains low and is equivocal in women without comorbid conditions or contraindications to one form or another. Hemorrhage and infection appear to be the 2 most common complications across all three treatment types.Another important consideration that must be taken into account when evaluating pregnant females with complaints consistent with miscarriage is their Rh status. This is important due to the fact that the fetus could differ in Rh type from the mother. If mother and fetus have different Rh types, this sets up a scenario where the mother could be exposed to a differing Rh from exposure to the fetal blood type. This could cause the mother to produce antibodies against the different Rh to which it was exposed. These antibodies can then cross the placenta and affect the fetus. This can then present serious consequences to the fetus and cause the fetus to develop a high output cardiac failure state known as hydrops fetalis, which is nearly 100% fatal. All women who have a blood type that is Rh(D) negative who are diagnosed with early pregnancy loss, and have not been sensitized, should receive Rh(D)-immune globulin 50 micrograms (or 300 micrograms if available) to prevent alloimmunization. Rh(D)-immune globulin should be administered as early as possible, within 72 hours, of diagnosis of miscarriage and immediately following surgical intervention. **(25).**
To date, there exists no proven strategy to prevent early pregnancy loss. Suggestions such as pelvic rest and hormone administration have not been proven. However, some physicians advocate progestin administration early to women who have experienced multiple prior miscarriages. Anticoagulants or aspirin administration has only been proven to be beneficial in women with antiphospholipid antibody syndrome. **(25).**

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