

MISCARRIAGE

Dr. Mohammad Ramadneh

Consultant Obstetrician & Gynecologist

Reproductive Endocrinologist

DEFINITION

- Spontaneous miscarriage refers to a pregnancy that ends spontaneously before the fetus has reached a viable gestational age.
- The World Health Organization defines it as expulsion or extraction of an embryo or fetus weighing 500 g or less from its mother
- In Jordan the age of viability is 24 weeks

INCIDENCE

- Spontaneous miscarriage is the most common complication of early pregnancy.
- The frequency decreases with increasing gestational age.
- Eight to 20 percent of clinically recognized pregnancies under 20 weeks of gestation will undergo spontaneous miscarriage; 80 percent of these occur in the first 12 weeks of gestation.
- The overall risk after 15 weeks is low (about 0.6 percent) for chromosomally and structurally normal fetuses, but varies according to maternal age and ethnicity

RISK FACTORS

- Age — Advancing maternal age is the most important risk factor for spontaneous miscarriage in healthy women.
- Previous spontaneous abortion — The risk of miscarriage in future pregnancy is approximately 20 percent after one miscarriage, 28 percent after two consecutive miscarriages, and 43 percent after three or more consecutive miscarriages. By comparison, miscarriage occurred in only 5 percent of women in their first pregnancy or in whom the previous pregnancy was successful.
- Smoking —
- Alcohol —
- Cocaine —
- Nonsteroidal antiinflammatory drugs —
- Fever —
- Caffeine —
- Prolonged time to pregnancy —.
- Low-folate level —.
- Maternal weight — Prepregnancy body mass index less than 18.5 or above 25 kg/m² has been associated with an increased risk of infertility and miscarriage
- Celiac disease — Untreated celiac disease may be associated with a higher risk

ETIOLOGY

- Chromosomal abnormalities — account for approximately 50 percent of all miscarriages.

The earlier the gestational age at abortion, the higher the incidence of cytogenetic defects:

- Autosomal trisomies — 52 percent: Trisomy 16 is the most common autosomal trisomy
- Monosomy X — 19 percent
- Polyploidies — 22 percent
- Other — 7 percent
- Congenital anomalies —
- Trauma — Invasive intrauterine procedures/trauma, such as chorionic villus sampling and amniocentesis
- Host factors — As an example, congenital or acquired uterine abnormalities (eg, uterine septum, submucosal leiomyoma, intrauterine adhesions)
- Acute maternal infection with any of a large number of organisms (eg, *Listeria monocytogenes*, *Toxoplasma gondii*, parvovirus B19, rubella, herpes simplex, cytomegalovirus, lymphocytic choriomeningitis virus) can lead to abortion from fetal or placental infection.
- Maternal endocrinopathies (eg, thyroid dysfunction, Cushing's syndrome, polycystic ovary syndrome)
- A hypercoagulable state due to inherited or acquired thrombophilia and abnormalities of the immune system (eg, systemic lupus erythematosus, antiphospholipid syndrome)
- Unexplained —

CLINICAL MANIFESTATION AND DIAGNOSIS

- **Threatened miscarriage:**
- Bleeding through a closed cervical os in the first half of pregnancy.
- The bleeding is often painless, but may be accompanied by minimal/mild suprapubic pain.
- On examination, the uterine size is appropriate for gestational age and the cervix is long and closed. Fetal cardiac activity is detectable by ultrasound or Doppler examination if the gestation is sufficiently advanced. The exact etiology of bleeding often cannot be determined and is frequently attributed to marginal separation of the placenta.
- 90 to 96 percent of pregnancies with both fetal cardiac activity and vaginal bleeding at 7 to 11 weeks of gestation will result in an ongoing pregnancy, with the higher success rate occurring at the later gestational ages.

- Women with threatened miscarriage have traditionally been managed expectantly until their symptoms resolve,
- The use of progestins to reduce the risk of miscarriage among women with threatened miscarriage is controversial.
- Bed rest is commonly recommended, but randomized trials have not found that bed rest at home or in the hospital is beneficial in preventing fetal loss in women with threatened spontaneous miscarriage.
- Abstinence from sexual intercourse is also typically advised, although there are no data to support this.

- **Inevitable miscarriage**

- When miscarriage is imminent, bleeding increases, painful uterine cramps/contractions reach peak intensity, and the cervix is dilated.
- The gestational tissue can often be felt or visualized through the internal cervical os

- **Complete miscarriage**

- If a complete miscarriage has occurred, the uterus is small and well contracted with a closed cervix, scant vaginal bleeding, and only mild cramping.

- **Incomplete miscarriage**
- also called an miscarriage with retained products of conception.
- On examination the cervical os is open, gestational tissue may be observed in the vagina/cervix, and the uterine size is smaller than expected for gestational age, but not well contracted.
- The amount of bleeding varies, but can be severe enough to cause hypovolemic shock. Painful cramps/contractions are often present.

- **Missed miscarriage :**
- refers to in-utero death of the embryo or fetus prior to the age of viability, with retention of the pregnancy for a prolonged period of time.
- Women may notice that symptoms associated with early pregnancy (eg, nausea, breast tenderness) have abated and they don't "feel pregnant" anymore; vaginal bleeding may occur.
- The cervix is usually closed.

- A definite diagnosis of nonviable intrauterine pregnancy (missed miscarriage) can be made based upon either of the following criteria:
 1. Absence of embryonic cardiac activity in an embryo with crown-rump length greater than 5 mm.
 2. Absence of a yolk sac when the mean sac diameter is 13 mm.
 3. Absence of an embryonic pole when the mean sac diameter (average of diameters measured in each of three orthogonal planes) is greater than 25 mm measured transabdominally or greater than 18 mm by the transvaginal technique

- **Surgical management**
- The conventional treatment of first or early second trimester failed pregnancy (up to 12 weeks) is dilatation and curettage (D&C) or dilatation and evacuation (D&E) to prevent potential hemorrhagic and infectious complications from the retained products of conception.
- This procedure carries anesthesia risks and complications such as uterine perforation, intrauterine adhesions, cervical trauma, and infection, which might lead to subsequent infertility or ectopic pregnancy

- **Medical treatment**
- Misoprostol (a prostaglandin E1 analog) is the most commonly used such agent.
- The advantages of misoprostol over other drugs (including prostaglandin E2) are its low cost, low incidence of side effects when given intravaginally, stability at room temperature, and ready availability. The risk of a major complication is rare

- **Septic miscarriage**

- Common clinical features of septic miscarriage include fever, chills, malaise, abdominal pain, vaginal bleeding, and discharge, which is often sanguinopurulent.
- Physical examination may reveal tachycardia, tachypnea, lower abdominal tenderness, and a boggy, tender uterus with dilated cervix.
- Infection is usually due to *Staphylococcus aureus*, Gram negative bacilli, or some Gram positive cocci. Mixed infections, anaerobic organisms, and fungi, can also be encountered. The infection may spread, leading to salpingitis, generalized peritonitis, and septicemia.
- Most spontaneous miscarriages are not septic. Septic abortion is, however, a common complication of illegally performed induced abortion. Infrequently, septic miscarriage is related to foreign bodies (eg, intrauterine contraceptive device, laminaria), invasive procedures (eg, amniocentesis, chorionic villus sampling), maternal bacteremia, or incomplete spontaneous or legally induced abortion.

- Suspected septic abortion with retained products of conception should be managed by:
 1. Stabilizing the patient
 2. Obtaining blood and endometrial cultures
 3. Promptly administering parenteral broad spectrum antibiotics
 4. Surgically evacuating the uterine contents
- Evacuation of the uterus should begin **promptly** after initiating antibiotics and stabilizing the patient in cases of suspected septic abortion or retained products of conception as delay in evacuation may be fatal

RECURRENT MISCARRIAGE

- classically refers to the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the age of viability (ectopic, molar, and biochemical pregnancies are not included).
- Approximately 15 percent of pregnant women experience sporadic loss of a clinically recognized pregnancy. Just 2 percent of pregnant women experience two consecutive pregnancy losses and only 0.4 to 1 percent have three consecutive pregnancy losses

RISK FACTORS AND ETIOLOGY

Etiology of recurrent pregnancy loss in a series of 545 women

Etiology	Percent
Immunologic	25
Anatomic	22
Endocrinologic	20
Microbiologic	6
Genetic	3
Unknown	40

- **Immunologic factors**

- Antiphospholipid syndrome — Several autoimmune diseases have been linked to poor obstetric outcome, but antiphospholipid syndrome (APS) is the only immune condition in which pregnancy loss is a diagnostic criteria for the disease.
- Adverse pregnancy outcomes include:
 - • three or more consecutive miscarriages before 10 weeks of gestation
 - • one or more morphologically normal fetal losses after the 10th week of gestation
 - • one or more preterm births before the 34th week of gestation owing to placental disease
- Five to 15 percent of patients with RM may have AP

Inherited thrombophilic

- Inherited thrombophilic defects Both inherited and acquired thrombophilias, including:
 1. activated protein C resistance (most commonly due to factorV Leiden mutation)
 2. deficiencies of protein C/S
 3. antithrombin III,
 4. hyperhomocysteinaemia
 5. prothrombin gene mutation

- **Anomalies**

- Congenital uterine anomalies are present in 10 to 15 percent of women with RM versus 7 percent of all women, includes:
 1. The septate uterus is the uterine anomaly associated with the poorest reproductive outcome and the most common uterine abnormality associated with RM
 2. Leiomyoma — Submucous leiomyomas that protrude into the endometrial cavity can impede normal implantation as a result of their position, poor endometrial receptivity of the decidua overlying the myoma, or degeneration with increasing cytokine production.
 3. Endometrial polyps —
 4. Intrauterine adhesions —
 5. Cervical insufficiency —

- **Endocrine factors**

Endocrine factors may account for 15 to 60 percent of RM.

- Luteal phase defect —
- Diabetes mellitus —
- Polycystic ovary syndrome —
- Thyroid antibodies and disease —
- Hyperprolactinemia — .

- **Genetics**

- Three to 5 percent of couples with RM have a major chromosomal rearrangement (versus 0.7 percent of the general population); usually a balanced translocation (60 percent reciprocal, 40 percent Robertsonian) or, less commonly, an inversion.
- One or both partners may harbor lethal genes in a heterozygous or balanced combination that does not affect them, but causes pregnancy loss when inherited by the embryo in a homozygous or unbalanced state.
- Balanced translocations are more common in the female than the male and more likely to result in pregnancy loss if the translocation is of maternal origin.

INVESTIGATION

- **Antiphospholipid antibodies**
 - All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies.
 - To diagnose antiphospholipid syndrome it is mandatory that the woman has two positive tests at least 12 weeks apart for either lupus anticoagulant or anticardiolipin antibodies of immunoglobulin G and/or immunoglobulin M

- **Karyotyping Cytogenetic**

- analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).
- Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality.

- **Anatomical factors**

- All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy.
- Suspected uterine anomalies may require further investigations to confirm the diagnosis, using hysteroscopy, laparoscopy or three-dimensional pelvic ultrasound

- **Thrombophilias**

- Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S

Treatment options for recurrent miscarriage

- **Antiphospholipid syndrome**

Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage

Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity

- **Genetic factors**

- The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist.
- Preimplantation genetic screening with in vitro fertilisation treatment in women with unexplained recurrent miscarriage does not improve live birth rates

- **Congenital uterine malformations**
- There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage
- Cervical weakness and cervical cerclage Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit.
- Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance.
- In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation.

- **Endocrine factors**

- There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage
- There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage
- Suppression of high luteinising hormone levels among ovulatory women with recurrent miscarriage and polycystic ovaries does not improve the live birth rate
- There is insufficient evidence to evaluate the effect of metformin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage

- **Immunotherapy**

- Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained recurrent miscarriage does not improve the live birth rate

- **Inherited thrombophilias**

- There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia.
- Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias

- **Unexplained recurrent miscarriage**

- Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit