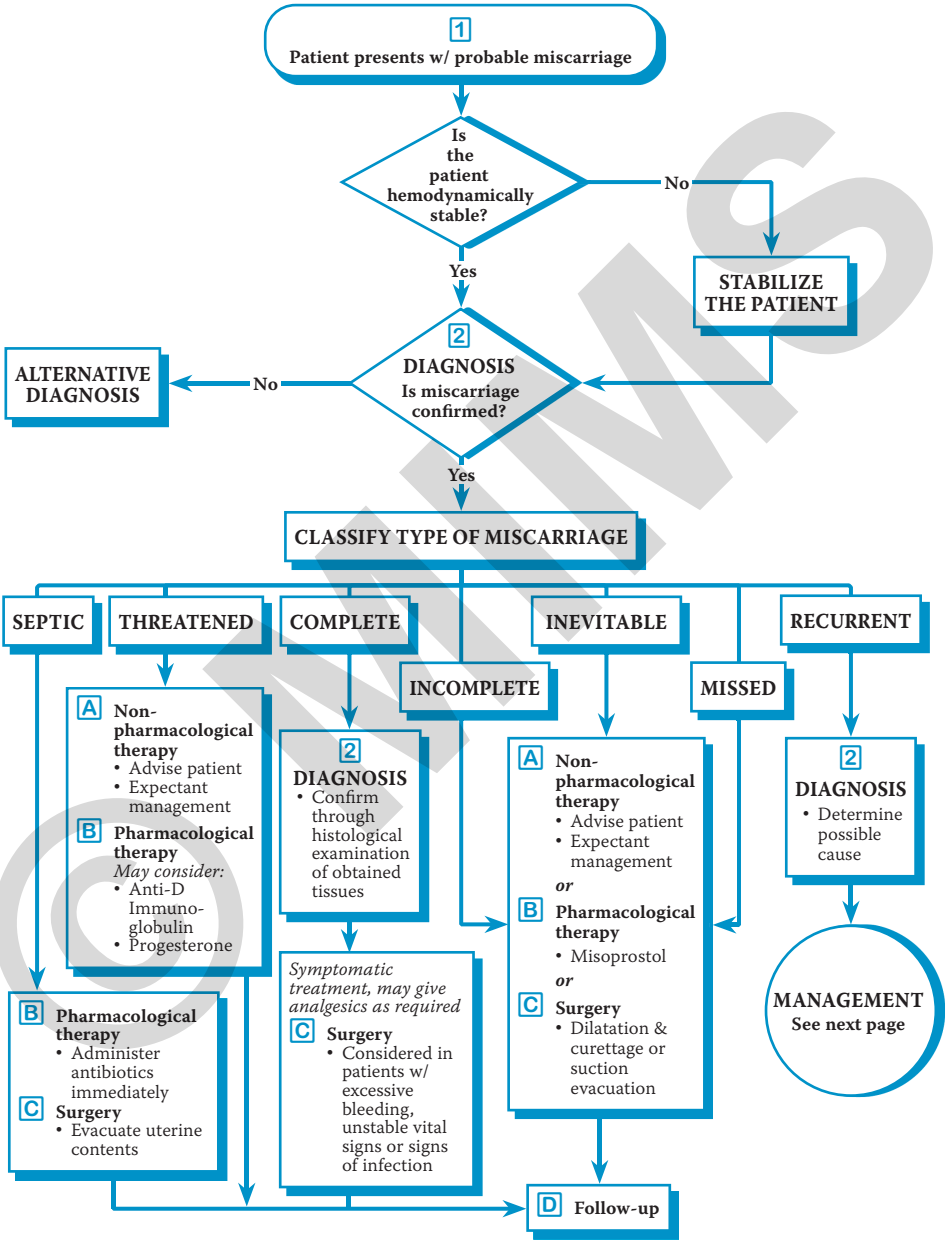
Miscarriage - Spontaneous (1 of 13)



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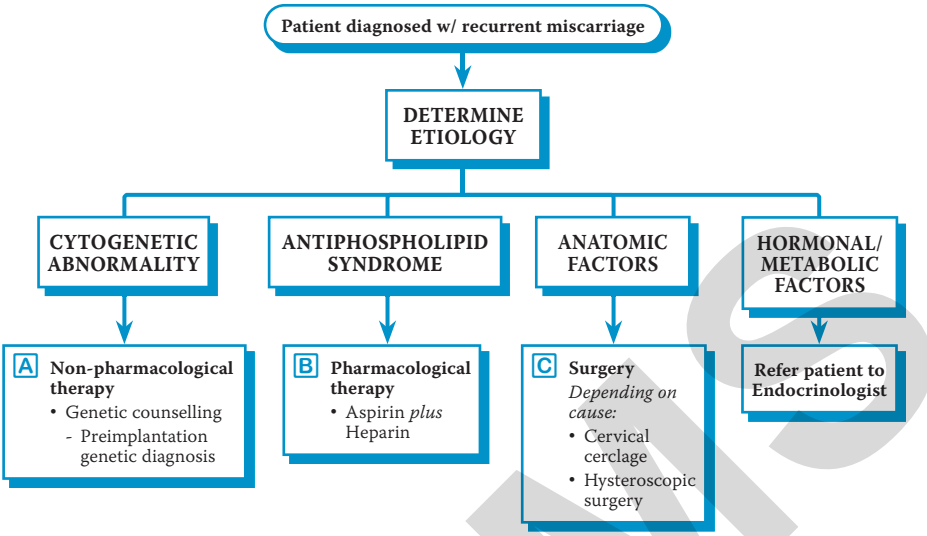

1 SPONTANEOUS MISCARRIAGE

- Loss of pregnancy before 20 weeks gestation or delivery of a fetus weighing <500 g, in the absence of elective medical or surgical measures to terminate pregnancy
  - Early loss is considered if it occurred before menstrual week 12 or in the 1st trimester
  - Late loss refers to those that occurred from menstrual week 12 to 20
- May occur in 15-20% of pregnancies
- 75% of affected women will have a subsequent successful pregnancy but decreases as the number of miscarriages & the age of the mother increase
- Also known as spontaneous abortion, spontaneous pregnancy loss or early pregnancy failure
  - The terms miscarriage, spontaneous pregnancy loss & early pregnancy failure are often used in patients to differentiate those associated w/ elective termination of pregnancy & to acknowledge the emotional aspects of losing a pregnancy

Classifications

Threatened Miscarriage
- Presence of uterine bleeding w/ no cervical dilatation nor passage of fetal tissue

Complete Miscarriage
- Passage of all products of conception w/ no surgical or medical intervention

Incomplete Miscarriage
- Partial passage of fetal tissue through partially dilated cervix

Inevitable Miscarriage
- Presence of cervical dilatation but no passage of fetal tissue

Missed Miscarriage
- Presence of intrauterine fetal demise but no passage of fetal tissue

Recurrent Spontaneous Miscarriage or Recurrent Pregnancy Loss (RPL)
- Spontaneous loss of ≥2 pregnancies & is subdivided into primary & secondary RPL
  - Primary RPL is recurrent loss without ongoing viable pregnancy beyond 24 weeks gestation
  - Secondary RPL is an episode of recurrent loss after ≥1 previous pregnancies progressing beyond 24 weeks gestation
  - Recurrent early pregnancy is loss of ≥2 pregnancies before 10 weeks of gestation
- Prognosis is often favorable even without treatment

1 SPONTANEOUS MISCARRIAGE (CONT'D)

Classifications (Cont'd)

Septic Miscarriage

- Spontaneous miscarriage that is complicated by intrauterine infection that commonly occurs w/ incomplete miscarriage
- Common in illegal induced abortion using nonsterile procedures
- Causative pathogens include *Enterobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, staphylococci, hemolytic streptococci, & some anaerobic organisms (eg *Clostridium perfringens*)
- Signs & symptoms include abdominal or pelvic pain, purulent vaginal discharge, uterine tenderness, &/or systemic signs of infection (eg fever or hypothermia, tachycardia, tachypnea, leukocytosis or leukopenia)

Etiology of Recurrent Spontaneous Miscarriage

- Up to 50-75% of cases will not have a clearly defined etiology

Cytogenetic Abnormalities

- May cause 2-5% of recurrent pregnancy loss
- Studies have shown that most early pregnancy losses are linked w/ sporadic chromosomal anomalies (ie trisomies), which may be age-related
  - There is 9-12% risk of sporadic miscarriage in women <35 years old between 6 & 12 weeks of gestation, which increases in women >35 years old due to high incidence of trisomic pregnancies
- Peripheral karyotyping, if available, may be done to parents to identify any balanced structural chromosomal abnormalities
  - Preimplantation genetic testing (PGT), amniocentesis, or chorionic villus sampling are options to identify genetic abnormality in the offspring when either of the parents has a structural genetic abnormality

Antiphospholipid Syndrome (APS)

- A group of symptoms of vascular thrombosis or unfavorable pregnancy outcomes in association w/ antiphospholipid antibodies
- Antiphospholipid antibodies may cause inhibition of villous cytotrophoblast differentiation & extravillous cytotrophoblast invasion into the decidua, induction of syncytiotrophoblast apoptosis, & initiation of maternal inflammatory pathways on the syncytiotrophoblast surface
- Diagnosed if patient has either 1 of the clinical criteria & 1 of the laboratory criteria
  - Clinical criteria
    - Vascular thrombosis
    - ≥1 unexplained deaths of morphologically normal fetus after the 10th week of gestation by ultrasound or direct examination of the fetus
    - ≥1 premature births of morphologically normal neonate before the 34th week of gestation because of severe preeclampsia/eclampsia or recognized features of placental insufficiency [positive abnormal or non-reassuring cardiotocography features, presence of abnormal wave on Doppler on examination of fetal blood flow, oligohydramnios, low birth weight (<10th percentile)]
    - ≥3 unexplained consecutive spontaneous miscarriages before the 10th week of gestation w/ no maternal anatomic or hormonal abnormalities & paternal & maternal chromosomal causes
  - Laboratory criteria
    - ≥2 positive plasma lupus anticoagulant taken at least 12 weeks apart
    - ≥2 positive serum or plasma anticardiolipin antibody in medium or high titer taken at least 12 weeks apart
    - ≥2 positive serum or plasma anti-β2 glycoprotein-I antibody of IgG &/or IgM isotype in titer >99th percentile taken at least 12 weeks apart)
- May cause 8-42% of recurrent pregnancy loss
  - Thrombophilia is associated more w/ late pregnancy loss than for early pregnancy loss
- Patient should be screened for lupus anticoagulant, anticardiolipin IgG or IgM antibody, anti-β2 glycoprotein-I
- Low-dose Aspirin & Heparin are the standard management for patients diagnosed w/ APS

Anatomic Factors

- May be responsible for 1.8-37.6% of recurrent pregnancy loss
  - Studies have shown that patients w/ septate, bicornuate, & arcuate uteri have high incidence of pregnancy loss
- Congenital uterine abnormalities may cause 2nd trimester pregnancy loss & other complications like preterm labor, fetal malpresentation, & increased rates of cesarean delivery
- Cervical weakness is a common cause of 2nd trimester miscarriage which is preceded by spontaneous rupture of membranes or cervical dilatation
- Hysterosalpingography or sonohysterography may be used for screening patients
  - Congenital Mullerian tract anomalies are often detected by hysterosalpingography & more characterized by MRI or 3-D ultrasound imaging

1 SPONTANEOUS MISCARRIAGE (CONT'D)

Etiology of Recurrent Spontaneous Miscarriage (Cont'd)

Hormonal & Metabolic Factors

- Diabetes & thyroid dysfunction should be evaluated in patients w/ recurrent pregnancy loss
  - Thyroid hormone disorders & elevated thyroid peroxidase (TPO) antibodies are associated w/ disorders in folliculogenesis, spermatogenesis, fertilization & embryogenesis which can lead to pregnancy loss
  - Well-controlled diabetes mellitus (DM) & treated thyroid dysfunction are not risk factors for recurrent pregnancy loss
- Prolactin, thyroid stimulating hormone (TSH), or hemoglobin A1c may be used for screening patients
  - Ovulatory dysfunction may be secondary to elevated prolactin levels which may be associated w/ recurrent pregnancy loss through alterations in the hypothalamic-pituitary-ovarian axis that results in impaired folliculogenesis & oocyte maturation, &/or short luteal phase
    - Normalization of prolactin levels w/ dopamine agonist improved subsequent pregnancy outcomes in patients w/ recurrent pregnancy loss
      - Treatment w/ Bromocriptine resulted in 85.7% live born rate
- Inadequate secretion of progesterone in early pregnancy has been associated w/ miscarriage
  - Progesterone supplementation in pregnancy to prevent a miscarriage lacks sufficient evidence
- Presence of polycystic ovary syndrome is associated w/ higher miscarriage rate compared to the general obstetric population
  - Exact mechanism is not known but loss may be due to high luteinizing hormone levels, elevated testosterone & androstenedione concentrations or insulin resistance
- Live birth rate does not improve w/ suppression of high luteinizing hormone levels in women w/ recurrent miscarriage & polycystic ovaries

Infection

- Infective agents that persist in the genital tract & avoid detection or do not cause sufficient symptoms to affect the woman are implicated in the etiology of repeated pregnancy loss
  - *Ureaplasma urealyticum, Mycoplasma hominis,* chlamydia, *Listeria monocytogenes, Toxoplasma gondii,* rubella, cytomegalovirus, herpes virus & other pathogens are identified in women w/ sporadic miscarriage
  - Bacterial vaginosis in the 1st trimester has been shown as a risk factor for 2nd trimester miscarriage
- A study has shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19) in the 1st trimester of pregnancy does not predispose to early pregnancy loss
- Association w/ recurrent pregnancy loss lacks convincing data
  - No clear indication for routine testing for above pathogens
  - Use of antibiotics is not warranted due to lack of prospective studies

Inherited Thrombophilias

- Studies have shown that inherited thrombophilia is associated w/ fetal deaths more than recurrent early pregnancy losses
- Routine testing of women w/ recurrent pregnancy loss for inherited thrombophilias is not recommended
  - Screening may be warranted in patients w/ personal history of venous thromboembolism in the setting of a non-recurrent risk factor or a 1st-degree relative w/ a known or suspected high-risk thrombophilia
- Live birth rate is improved w/ Heparin therapy during pregnancy in women w/ 2nd trimester miscarriage but not w/ recurrent 1st trimester miscarriage due to insufficient evidence

Lifestyle, Environmental, Occupational Factors

- Cigarette smoking, obesity, cocaine use, 3-5 alcoholic drinks per week, & consumption of >3 cups of coffee have been associated w/ risk of miscarriage
  - Cigarette smoking has been shown to have an adverse effect on trophoblastic function & is associated to an increased risk of sporadic pregnancy loss
  - Heavy consumption of alcohol is toxic to the embryo & the fetus; moderate consumption per week may increase the risk of sporadic miscarriage

2 DIAGNOSIS

History

- Should include previous obstetric history (ie nature of previous pregnancy losses particularly the actual gestational age), last menstrual period (LMP), presence of pain or bleeding, & if products of conception were passed
  - Classification of miscarriage may primarily be determined by patient's presentation
    - Incomplete miscarriage often presents w/ vaginal bleeding & midline cramping
    - Threatened miscarriage usually presents w/ vaginal bleeding, lower back discomfort, or midline pelvic cramping
- Determine risk factors
  - Advanced maternal & paternal age
    - Maternal age is associated w/ decline in number & quality of remaining oocytes; the older the oocyte, the higher the aneuploidy rate
    - Risk of miscarriage is highest in couples where the woman is ≥35 years old & the man is ≥40 years old
  - Obesity
    - Recent studies have shown that obesity increases the risk of both sporadic & recurrent miscarriage
  - Medical conditions (eg maternal infection, diabetes, thyroid disease)
  - Use of medications such as Misoprostol, retinoids, Methotrexate, etc
  - History of spontaneous miscarriage or multiple elective abortions
  - Conception within 3-6 months after delivery
  - Presence of uterine abnormalities (eg adhesions, leiomyoma) or use of intrauterine device

Physical Exam

- Perform pelvic examination w/ emphasis on possible findings associated w/ uterine or cervical abnormalities
- Examine patient for findings suggestive of diabetes or thyroid disease

Imaging Studies

Ultrasonography

- Preferred imaging study in identifying the status of pregnancy & rule out other possible diagnosis like ectopic pregnancy
  - Transvaginal ultrasonography is 90-100% sensitive & 80-92% specific in determining the product of conception
  - Result showing empty uterus may signal a completed spontaneous miscarriage
  - To know the viability of the fetus, fetal heartbeat should be identified first; if heartbeat is not visible, crown-rump length (CRL) should be measured. If CRL cannot be measured, obtain the mean gestational sac diameter
    - Repeat transvaginal ultrasound after 1 week if CRL is < or > 7.0 mm, or the mean gestational sac diameter is < or > 25 mm, & there is no visible heartbeat; after 2 weeks if transabdominal ultrasound was initially used
- Used to assess uterine anatomy of women w/ recurrent 1st trimester miscarriage & women w/ ≥1 2nd trimester miscarriage
  - Transvaginal 3-dimensional ultrasound is the preferred method to evaluate the uterus due to its high sensitivity & specificity, & the ability to distinguish between septate uterus & bicorporeal uterus w/ normal cervix
- Helps in determining treatment options for patients w/ incomplete, inevitable, or missed miscarriage
  - <40 mm endometrial thickness: Conservative management
  - >40 mm endometrial thickness: Conservative management, medical or surgical evacuation

Others

- Hysteroscopy, laparoscopy, 3-dimensional pelvic ultrasound, or MRI may be used to confirm the presence of uterine anomaly
  - Sonohysterography & hysterosalpingography are noninvasive screening tests used to evaluate uterine cavity & shape
    - Sonohysterography is more accurate in diagnosing uterine anomaly

Laboratory Tests

Serum hCG

- Useful when a complete miscarriage is suspected in the absence of previous ultrasonographic evidence of an intrauterine pregnancy
  - Usually returns to normal in 2-4 weeks
- Also used to diagnose pregnancy of unknown location or asymptomatic ectopic pregnancy

Serum Progesterone

- Progesterone level >25 nmol/L indicates an ongoing pregnancy while those <25 nmol/L is associated w/ pregnancies subsequently confirmed to be non-viable; however some viable pregnancies presented w/ low progesterone levels

Antiphospholipid Antibodies (ie lupus anticoagulant, anticardiolipin antibodies, anti-β_2 glycoprotein I antibodies)

- Should be requested before pregnancy in women w/ recurrent 1st trimester miscarriage & women w/ ≥1 2nd trimester miscarriage

2 DIAGNOSIS (CONT'D)

Laboratory Tests (Cont'd)

Others

- Initial miscarriage management may include checking fluid balance & blood grouping & crossmatching
- If clinically indicated, screen patients for infection (eg *Chlamydia trachomatis, Neisseria gonorrhoeae*, bacterial vaginosis)
  - A blood culture may be requested if patient is febrile
- Women w/ 2nd trimester miscarriage should be screened for inherited thrombophilias (ie factor V Leiden, prothrombin gene mutation, protein S)
- If suggested by history or physical examination, screen patient for thyroid disease or diabetes
  - Screening for TSH & TPO is recommended in patients w/ recurrent pregnancy loss

Histological Examination of Tissues Obtained via Surgical Evacuation

- Confirms the diagnosis & basic pathology of miscarriage & helps rule out ectopic pregnancy or gestational trophoblastic disease

Cytogenetic Analysis of Pregnancy Tissue

- Should be done on products of conception of the third & subsequent consecutive miscarriages
- Provides explanation for the pregnancy loss & helps determine if further examinations or treatments are required
- Allows to know the prognosis of future pregnancy outcome
  - If the miscarried pregnancy has an abnormal karyotype, the next pregnancy has a better prognosis
- Array-based comparative genomic hybridization (array-CGH) is the preferred method
- If results show unbalanced structural chromosomal abnormality, parental peripheral blood karyotyping should also be performed
- Limitations of karyotyping include failure of tissue culture & inability to distinguish between maternal contamination & a normal (euploid) female fetus

A NON-PHARMACOLOGICAL THERAPY

Patient Advice

- Bed rest
  - Encouraged but further study that will show its value in preventing miscarriage is needed
- Lifestyle modification
  - Advise the patient to stop smoking, decrease caffeine & alcohol consumption, & to lose weight
    - These factors may be associated w/ sporadic miscarriage, but relationship w/ recurrent miscarriage is still uncertain & needs further study
- Counseling
  - Physician should provide psychological or psychiatric support to the patient
  - Further intervention measures should be based on the patient & her partner's expectations, coping mechanisms & support systems

Expectant Management/Spontaneous Resolution

- Used for 7-14 days as 1st-line management in patients w/ confirmed miscarriage
- May be considered depending on patient's clinical status, desire to continue pregnancy, & certainty of diagnosis
  - Complete spontaneous expulsion of fetal tissue usually occurs in pregnancies <6 or >14 weeks
  - Has risk of infection or hemorrhage
- Highly effective in patients w/ incomplete spontaneous miscarriage w/ no need for surgical intervention
- Patient should be advised that complete resolution may take several weeks & that overall efficacy rates may be lower than medical or surgical interventions
  - Follow-up scans may be done every 2 weeks until a complete miscarriage is diagnosed
- Should not be considered in a woman at increased risk of hemorrhage & its effects (eg has coagulopathies), who has previous traumatic pregnancy (eg stillbirth, miscarriage, antepartum hemorrhage), or has an infection

Genetic Counselling

- Offers a prognosis for the risk of future pregnancies w/ an unbalanced chromosome complement & the opportunity for familial chromosome studies
- Should be done in patients w/ recurrent pregnancy loss secondary to structural genetic factor
  - Subsequent healthy live birth depends on the involved chromosomes & rearrangement type
  - Treatment options for partners w/ recurrent pregnancy loss & a structural genetic abnormality include preimplantation genetic diagnosis (PGD) for specific translocations, w/ transfer of unaffected embryos, or the use of donor gametes; however, more evidences are needed to demonstrate that in vitro fertilization (IVF)/PGD improves live birth rate compared to natural conception/medical management

B PHARMACOLOGICAL THERAPY

Management for Threatened Miscarriage

Anti-D Immunoglobulin

- May be given to patients who had threatened miscarriage at <12 weeks gestation when bleeding was heavy or associated w/ pain
- In patients who are Rh(D) negative & unsensitized & whose pregnancy is >12 weeks of gestation, Rh(D) immune globulin should be given immediately following surgical intervention of early pregnancy loss or within 72 hours of early pregnancy loss diagnosis w/ medical or expectant management planned in the 1st trimester
- Intramuscular doses are administered into the deltoid muscle
- Not recommended in patients who had a complete miscarriage <12 weeks of gestation where there has been no surgical intervention

Progesterone

- Important hormone for establishing & maintaining pregnancy
- Immediate administration of progestogen proceeding current pregnancy in patients w/ ≥3 consecutive miscarriages has shown benefits
- Studies have shown that progestogens are effective in the treatment of threatened miscarriage w/ no harmful effects to the mother nor to the newborn (ie no evidence of increased rates of pregnancy-induced hypertension or antepartum hemorrhage, no increased occurrence of congenital abnormalities)
- In small studies, Dydrogesterone was shown to be superior than no treatment in continuing pregnancy until 20 weeks of gestation
  - Another study showed that support of corpus luteum w/ Dydrogesterone decreases pregnancy loss in threatened miscarriage during the 1st trimester in women w/ no history of recurrent miscarriage
- Progesterone therapy for threatened miscarriage is given either orally or vaginally, though the optimal dose & route of therapy has not been determined

Management for Incomplete/Inevitable/Missed Miscarriage

Misoprostol

- A prostaglandin analogue that may be given orally or vaginally depending on patient's preference
  - Dosages vary depending on the route of administration & the fetus' gestational age
- Used for initial medical management of incomplete or missed miscarriage in patients w/ no signs of infection, excessive bleeding, or abdominal pain
  - Patients may be given single doses of Misoprostol at 600 mcg orally for incomplete miscarriage while for missed miscarriage 800 mcg intravaginally or 600 mcg sublingually
  - WHO recommends single-dose Misoprostol at 600 mcg orally or 400 mcg sublingually for incomplete abortion <13 weeks gestation
    - Repeat doses may be administered to achieve success
  - WHO recommends Misoprostol 400 mcg orally or sublingually or intravaginally every 3 hours for incomplete abortion ≥13 weeks gestation
    - Repeat doses may be administered to achieve success
  - Counsel patients w/ missed miscarriage that the duration & intensity of lower abdominal cramping & genital blood loss may increase w/ medical therapy
- May also be given for cervical priming 3 hours prior to surgical evacuation of retained products of conception

Management for Recurrent Miscarriage due to Antiphospholipid Syndrome

Aspirin (Low-dose) Plus Heparin

- Should be considered in women w/ antiphospholipid syndrome to prevent further miscarriage
  - Reduces miscarriage rate by 54%
  - Improves live birth rate of women w/ recurrent miscarriage associated w/ antiphospholipid antibodies but needs vigilant antenatal surveillance since these pregnancies are still at risk of complications (ie repeated miscarriage, preeclampsia, fetal growth restriction, preterm birth)
- Heparin therapy during pregnancy may improve live birth rate in patients w/ 2nd trimester miscarriage associated w/ inherited thrombophilias
  - Reduction of pregnancy loss is more effective w/ the addition of unfractionated Heparin than w/ low-molecular-weight Heparin
- Heparin has no potential to cause fetal hemorrhage or teratogenecity but may cause maternal bleeding, hypersensitivity reactions, Heparin-induced thrombocytopenia, & if used long term, osteopenia & vertebral fractures

B PHARMACOLOGICAL THERAPY (CONT'D)

Management for Recurrent Miscarriage w/ No Identifiable Cause

- Progestogens may be used for early & late spontaneous recurrent miscarriage
- Multivitamins & supplementation w/ folic acid are used though w/ no confirmed benefit

Management for Septic Miscarriage

Antibiotics (Broad Spectrum, Parenteral)[1]

- Eg Clindamycin plus Gentamicin w/ or without Ampicillin, Ampicillin plus Gentamicin & Metronidazole, Levofloxacin & Metronidazole, Ticarcillin-clavulanate, Piperacillin-tazobactam, Imipenem
- Administered immediately to patients diagnosed w/ septic miscarriage until the patient has improved & afebrile for 48 hours, then shifted to oral antibiotics to complete for 10-14 days

Others

- Pain reliever & anti-emetics should be offered to patients undergoing medical management
- L-thyroxine is recommended for the treatment of overt hypothyroidism occurring before conception or during early gestation in women w/ RPL

[1]Various antibiotics for septic miscarriage are available. Please see the latest MIMS for specific prescribing information.

C SURGERY

- Surgical management following treatment for early pregnancy loss is not required in asymptomatic patients w/ thickened endometrial stripe

Surgical Uterine Evacuation

- Offered to women who have heavy bleeding & or severe pain, unstable vital signs, when gestational trophoblastic disease or retained early pregnancy tissue is suspected, if w/ infected intrauterine tissue, or depending on patient's preference
  - Retained tissue increases the risk of infection & hemorrhage
- Dilatation & curettage is the traditional treatment for spontaneous miscarriage
- May also be performed using suction evacuation which is associated w/ less blood loss, less pain & shorter duration of the procedure
  - Manual vacuum aspiration technique may be performed in the clinic for uterine evacuation in patients w/ missed & incomplete miscarriage
- Delay surgery for 12 hours to allow antibiotic administration if infection is suspected
  - Patients w/ incomplete miscarriage may be given preoperative antibiotics at least 1 hour prior to uterine evacuation
- Patients undergoing surgical evacuation may be given an oxytocic to bring about uterine evacuation & to prevent bleeding from the procedure
- Possible complications: Uterine perforation, cervical tears, intra-abdominal trauma, hemorrhage, possible blood transfusion, or infection
  - Blood product replacement must be available in cases of bleeding due to coagulation disorders

Cervical Cerclage

- An ultrasound-indicated cerclage should be offered to women w/ singleton pregnancy & a history of one 2nd trimester miscarriage due to cervical factors if a cervical length of ≤25 mm is detected by transvaginal scan before 24 weeks of gestation
- May also be performed in patients w/ 2nd trimester recurrent miscarriages due to insufficient, incompetent or weak cervix
- Associated w/ hazards secondary to surgery & risk of stimulating uterine contractions

Hysteroscopic Surgery

- May be done in patients w/ septate uterus
  - Repair of bicornuate or unicornuate uteri, which have good obstetrical outcomes, is not recommended due to invasiveness of the procedure & higher complication risk
- There is lack of conclusive evidence that surgical treatment in patients w/ Asherman syndrome/intrauterine synechiae, uterine fibroids, or uterine polyps will reduce the risk of pregnancy loss but should still be considered in patients w/ significant uterine cavity defects

D FOLLOW-UP

After Expectant Management

- In patients w/ pregnancy of <6 weeks who had bleeding but no pain, repeat urine pregnancy test after 7-10 days & return for follow-up if positive
  - Negative pregnancy test means that pregnancy has miscarried
- In patients who completed miscarriage during 7-14 days of expectant management, repeat urine pregnancy test after 3 weeks & to return if it showed a positive result
- If bleeding & pain have started & are persisting or worsening, repeat scan after the expectant management period & offer other treatment options (ie continued expectant management, medical management, surgical management)
- In patients who continued the expectant management, review the condition of the patient again 14 days after the first follow-up appointment

After Medical Management

- Advise patient to return for check-up 24 hours after treatment has been given if bleeding has not started
- If there are no worsening symptoms after medical management, urine pregnancy test should be done after 3 weeks
  - Molar or ectopic pregnancy should be ruled out if the test turned out positive

Contraception

- Hormonal contraception & barrier methods may be started immediately following completion of early pregnancy loss
- An intrauterine device may be used if there is no suspicion of septic miscarriage

Dosage Guidelines

DRUGS ACTING ON THE UTERUS		
Drug	**Dosage**	**Remarks**
Dinoprostone	**Missed miscarriage:** 2.5 mcg/min initial IV infusion for the 1st 30 min then increase to 5 mcg/min if needed May increase to 10 mcg/min after 4 hr if response is still unsatisfactory	**Adverse Reactions** • GI effects (N/V, diarrhea); CNS effects (headache, dizziness); Other effects (flushing, shivering, local tissue irritation & erythema at inj site, temporary pyrexia & elevated WBC) **Special Instructions** • Use w/ caution in patients w/ increased intraocular pressure (IOP) or asthma history • Avoid use in patients w/ pelvic infections or hypersensitivity to prostaglandins
Gemeprost	**Intrauterine fetal death in the 2nd trimester of pregnancy:** 1-mg pessary inserted into the posterior vaginal fornix 3 hrly Max of 5 administrations	**Adverse Reactions** • CNS effects (headache, muscle weakness, dizziness); Other effects (vaginal bleeding, mild uterine pain, GI disturbances, flushing, chills, dyspnea, chest pain, palpitations, mild pyrexia, backache) **Special Instructions** • Use w/ caution in patients w/ obstructive airway disease, CV insufficiency, elevated IOP, cervicitis, vaginitis, severe hepatic impairment; may cause uterine rupture • Avoid use in patients w/ renal function disturbance, uterine fragility & scarring & placenta previa • Monitor cardiac & vascular parameters; coagulopathy may occur following intrauterine fetal death
Isoxsuprine	**Uterine hypermotility disorder (ie threatened miscarriage)** **Initial dose:** 100 mg in 500 mL infusion fluid w/ IV infusion rate of 0.5 mL/min (10 drops/min) Increase infusion rate in 10 drops/min increments at 10-min intervals until control is maintained ***or*** 10 mg IM (if IV infusion is not feasible) 3 hrly for 24 hr then 4-6 hrly for 48 hr **Maintenance dose:** 20 mg PO 6-8 hrly when contractions have ceased for at least 12 hr	**Adverse Reactions** • CV effects (hypotension, tachycardia, palpitations, flushing, chest pain); CNS effects (dizziness, nervousness, trembling); GI effects (N/V, abdominal distress, intestinal distention); Other effects (rashes, weakness) **Special Instructions** • May be taken w/ meals, milk or antacids to minimize GI discomfort • Avoid use in patients w/ recent arterial hemorrhage, CV disease, severe anemia • Do not use large vol of fluid to prevent fluid overload • Monitor BP & heart rate

Dosage Guidelines

DRUGS ACTING ON THE UTERUS (CONT'D)		
Drug	**Dosage**	**Remarks**
Oxytocin	**Incomplete, inevitable, or missed miscarriage:** 5-10 IU IM ***or*** 5 IU slow IV, followed by IV infusion at 20-40 mU/min	**Adverse Reactions** • Strong uterine contractions if administered in high doses or to those hypersensitive to it; GI effects (N/V); Metabolic effects (vasopressin-like activity, hyponatremia, water retention); Other effects (anaphylaxis, arrhythmias, hypertensive episodes & pelvic hematoma) **Special Instructions** • Oxytocin should not be used for prolonged periods in resistant uterine inertia, severe preeclampsia, or decompensated CV disorders

PROGESTERONES		
Drug	**Dosage**	**Remarks**
Allylestrenol	**Habitual miscarriage:** 5-10 mg PO 24 hrly as soon as pregnancy has been diagnosed Continue treatment until at least 1 mth after end of critical period **Threatened miscarriage:** 5 mg PO 8 hrly for 5-7 days May extend treatment period if needed Reduce dose gradually after symptoms have disappeared	**Adverse Reactions** • GI effects (N/V); Ophthalmic effects (visual disturbances, proptosis or diplopia, vascular retinal ulcer); Other effect (migraine) **Special Instructions** • May be taken w/ meals if GI upset occurs • Avoid use in patients w/ history of or existing thromboembolic disorders, w/ mammary or genital carcinoma, impaired liver function or w/ active liver disease, undiagnosed or irregular vaginal bleeding • Use w/ caution in patients w/ DM • Discontinue use if visual disturbances, ptosis, vascular retinal lesion or migraine occurs

Dosage Guidelines

PROGESTERONES (CONT'D)		
Drug	**Dosage**	**Remarks**
Dydrogesterone	**Habitual miscarriage:** 10 mg PO 12 hrly on 11th-25th day of the cycle until the 20th wk of pregnancy **Threatened miscarriage:** 40 mg PO at once, then 10 mg PO 8 hrly until symptoms remit	**Adverse Reactions** • GI effects (abdominal pain, N/V); Dermatologic effects (allergic rash, pruritus, urticaria, angioedema); CNS effect (migraines or headache); Other effects (breakthrough bleeding w/ increased dosage, altered liver function, jaundice, hemolytic anemia) **Special Instructions** • Avoid use in patients w/ breast or genital cancer, undiagnosed vaginal bleeding, lactation • Use w/ caution in patients w/ acute or history of liver disease, breakthrough bleeding, galactose intolerance, glucose-galactose malabsorption, history or currently suffering from porphyria or depression &/or aggravated during pregnancy or previous hormone treatment, postmenopausal estrogen deficiency • Periodically perform gynecological & general physical exam & mammogram • Discontinue use if venous thromboembolism, stroke, MI, hepatic adenoma, or gall bladder disease develop
Hydroxyprogesterone caproate	**Habitual miscarriage (associated w/ proven progesterone deficiency):** 250 mg IM after basal body temp rises (around the 18th cycle day) or upon failure of menstruation If pregnancy is proven, 250-500 mg IM at wkly intervals during the 1st half of pregnancy **Imminent miscarriage:** 500 mg IM 2-3 times wkly until bleeding ceases Continue treatment w/ 250 mg IM 2x/wk until bleeding stops despite mobilization	**Adverse Reactions** • GI effects (GI disturbances, appetite or wt changes); Endocrine effects (mild breast tenderness, gynecomastia, changes in libido); Dermatologic effects (acne, rash, melasma or chloasma, urticaria, alopecia, hirsutism); CNS effects (fatigue, drowsiness or insomnia, fever, headache, somnolence); Other effects (abnormal bleeding, fluid retention, premenstrual syndrome-like symptoms, altered liver function tests, jaundice) **Special Instructions** • Avoid use in patients w/ known or suspected breast malignancies or tumors, acute hepatic disease, sensitivity to progestins, undiagnosed urinary tract, uterine or genital bleeding, history of thrombophlebitis, thromboembolic disorders & cerebral apoplexy • Use w/ caution in patients w/ impaired fertility, DM, renal or hepatic impairment, asthma, epilepsy, history of mental depression, conditions which may be aggravated by fluid retention • Perform physical & gynecological exam prior to use

All dosage recommendations are for non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications stated in locally approved product monographs.
Please refer to local product monograph in the latest copy of MIMS or in www.mims.com for country-specific prescribing information.

Dosage Guidelines

PROGESTERONES (CONT'D)		
Drug	**Dosage**	**Remarks**
Progesterone	**Habitual miscarriage:** 100-400 mg vag 8-12 hrly **Threatened miscarriage:** 200-400 mg PO/vag 12-24 hrly until 12th wk of pregnancy **Max dose:** 200 mg/intake	**Adverse Reactions** • Gynecologic effects (irregular menstruation, breakthrough bleeding); CNS effects (somnolence, dizziness, drowsiness); Other effect (hypersensitivity reaction) **Special Instructions** • Avoid use in patients w/ undiagnosed vaginal bleeding, severe hepatic dysfunction, mammary or genital tract carcinoma, thrombophlebitis, thromboembolic disorder, cerebral hemorrhage, porphyria • Use w/ caution in patients w/ hormone-sensitive conditions, infections & mechanical disorders, in patients who need mental alertness (eg driving or using machineries) - Preferably taken at bedtime

VACCINES, ANTISERA & IMMUNOLOGICALS		
Drug	**Dosage[1]**	**Remarks**
Immunoglobulin		
Immunoglobulin, Anti-D [Rho (D) immunoglobulin; Human anti-D Ig]	**Spontaneous miscarriage** **Before 12th wk of pregnancy:** 600-750 IU IM **After 12th wk of pregnancy:** 1250-1500 IU IM administered as soon as possible **After 34 wk gestation:** 600 IU (120 mcg) IM/IV given as soon as possible **Threatened miscarriage** 1500 IU (300 mcg) IM/IV given any time	**Adverse Reactions** • Local effects (pain or tenderness at inj site); CNS effects (fever, malaise, headache); Rare hypersensitivity reactions **Special Instructions** • Avoid use in Rho (D)-positive individuals • Use w/ caution in patients w/ hypersensitivity to thimerosal or human Ig, IgA deficiency • Discontinue use if allergic or anaphylactic-type reaction occurs

[1]Individualize dosage. Some preparations are for IM administration only. Please see the latest MIMS for specific prescribing information.

All dosage recommendations are for non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
Not all products are available or approved for above use in all countries.
Products listed above may not be mentioned in the disease management chart but have been placed here based on indications stated in locally approved product monographs.
Please refer to local product monograph in the latest copy of MIMS or in www.mims.com for country-specific prescribing information.

Please see the end of this section for the reference list.