
Evidence Based Management of Early Pregnancy Risks

Clinical specialty: Obstetrics and Gynecology

Intended users: Physicians and students

Source of Evidence: The Cochrane Library and DARE

JC Objective

To discuss the evidence for the management of Early Pregnancy Risks

Miscarriage (Spontaneous abortion)

Miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. This includes all pregnancy losses from the time of conception until 24 weeks of gestation. Advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation. Early pregnancy loss occurs <12 weeks.

Threatened miscarriage

- Diagnosis: Bleeding is Minimal with no or mild lower abdominal cramping Pain. The cervical os is closed. Ultrasound shows a positive Fetal life.
- Interventions
 1. There is insufficient evidence to support the routine use of **progesterone (e.g. dydrogesterone or micronized progesterone)** for the treatment of threatened miscarriage
 2. There is insufficient evidence to support the routine use of **hCG** in the treatment of threatened miscarriage.
 3. There is insufficient evidence to support the routine use of **uterine muscle relaxant** drugs (including tocolytic and antispasmodic agents), in the treatment of threatened miscarriage.
 4. There is insufficient evidence of high quality that supports a policy of **bed rest**. Although there is no definite evidence that bed rest can affect the course of pregnancy, abstinence from active environment for few days may help women feel safer and provide emotional relief.
 5. There is insufficient evidence of high quality that supports a policy of **avoidance of sexual intercourse**

Inevitable miscarriage

- Diagnosis: Bleeding is excessive with lower abdominal cramping Pain. The cervical os is opened and products of conception can be felt.
- Interventions: evacuation of retained products of conception

Incomplete Miscarriage

- Diagnosis:
 1. Clinical: \pm Bleeding and/or abdominal pain.
 2. Ultrasound: Any endometrial thickness; heterogeneous tissues (\pm sac) distorting midline endometrial echo.
- Intervention: evacuation of retained products of conception

Complete miscarriage

- Diagnosis:
 1. Clinical: Cessation of vaginal bleeding and abdominal pain.
 2. Ultrasound: Endometrial thickness $<$ 15 mm; no evidence of retained products of conception.
- No Intervention required.

Missed/Anembryonic Miscarriage

- Diagnosis: Bleeding is absent and there is no Pain. The cervical os is closed. TVUS shows fetal pole $>$ 6 mm with no fetal heart activity or Gestational sac diameter \geq 20 mm with no fetal pole or yolk sac
- Intervention
 1. First Trimester
 - a. Surgical (suction evacuation or curettage) versus medical (mifepristone and/or misoprostol) management: Surgical management is more likely than medical management to induce complete evacuation of conception products (ARR 32.8%, 95% CI: 14.4, 51.1) (NNT of 3 and NTN of 2).
 - b. Medical versus expectant management: Medical management is more likely than expectant management to induce complete evacuation of conception products (ARR 49.7%, 95% CI: 28.3, 71.1) (NNT of 2 and NTN of 1).
 - c. vaginal versus oral misoprostol: no difference
 2. Second trimester
 - a. Dilation and evacuation is superior to
 - (1) Prostaglandin F2 α .
 - (2) mifepristone and misoprostol
 - b. The combination of mifepristone and misoprostol has the highest efficacy and shortest abortion time interval among medical methods.
 - c. Where mifepristone is not available, misoprostol alone is a reasonable alternative.
 - d. The optimal route for misoprostol is vaginally, preferably using tablets at 3-hourly intervals.

Notes

1. Surgical evacuation should be offered to women who prefer that option. Clinical indications include:
 - a. persistent excessive bleeding,
 - b. hemodynamic instability,
 - c. evidence of infected retained tissue
 - d. suspected gestational trophoblastic disease.
2. Complications of surgery include perforation, cervical tears, intraabdominal trauma, intrauterine adhesions and hemorrhage.
3. There is insufficient evidence to recommend routine antibiotic prophylaxis prior to surgical evacuation.
4. Antibiotic prophylaxis should be given based on clinical indications (septic miscarriage).

Recurrent Pregnancy Loss

The loss of three or more consecutive pregnancies. It affects 1% of couples trying to conceive.

Risk Factors

- Unexplained
- Maternal age (20–24 yrs: 11%; 25–29 yrs: 12%; 30–34 ys: 15%; 35–39 yrs: 25%; 40–44 yrs: 51%).
- Number of previous miscarriages (40% after three consecutive pregnancy losses)
- Antiphospholipid syndrome (the most important **treatable** cause): anticardiolipin, LAC
- Inherited thrombophilia: activated protein C resistance (most commonly due to factor V Leiden mutation), deficiencies of protein C/S and antithrombin III, hyperhomocysteinemia and prothrombin gene mutation
- Chromosomal
 1. Parental chromosomal rearrangements: In 2–5% of couples with recurrent miscarriage, one parent carries a balanced structural chromosomal anomaly: most commonly a balanced translocation.
 2. Embryonic chromosomal abnormalities
- Endocrine factors: DM, thyroid dysfunction, PCOS, insufficient corpus luteum
- Congenital uterine malformations: septate, arcuate
- Cervical weakness (incompetent cervix) is a recognized cause of second-trimester miscarriage
 1. There is currently no satisfactory objective test that can identify women with cervical weakness in the non-pregnant state.
 2. The diagnosis is usually based on a history of second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation.
- Bacterial vaginosis in the first trimester is a risk factor for second-trimester miscarriage and PTL

Workup: for possible risk factors

Intervention

- Unexplained recurrent miscarriage: an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered **supportive care** alone.
- Antiphospholipid syndrome
 1. Pregnant women with antiphospholipid syndrome **should** be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage.
 2. Neither corticosteroids nor IV 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.
- inherited thrombophilia
 1. Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias.
 2. One RCT demonstrated the efficacy of the LMWH enoxaparin for the treatment of women with a history of a single second-trimester miscarriage who carry the factor V Leiden or prothrombin gene mutation or have protein S deficiency. The live birth rate of women treated with enoxaparin was 86% compared with 29% in women taking low-dose aspirin alone (OR 15.5, 95% CI 7–34).
 3. 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. Observational studies showed that heparin may improve the live birth rate for these women.

- Cervical weakness: an ultrasound-indicated cerclage should be offered in women with
 1. cervical length of ≤ 25 mm (by TVUS) AND
 2. a history of one second-trimester miscarriage attributable to cervical weakness AND
 3. a singleton pregnancy
- Endocrine factors
 1. Progesterone versus placebo or no treatment

Outcome	RR (95% CI)	RRR	Absolute effects			
			Risk with Control	ARR with Progesterone (95% CI)	NNT	NTN
Miscarriage (women with recurrent miscarriage ONLY)	0.48 (0.29 to 0.79)	52%	38 Miscarriage per 100	20 fewer Miscarriage per 100 (from 8 fewer to 27 fewer)	5	4

No differences between the route (oral, intramuscular, vaginal) versus placebo or no treatment

2. There is **insufficient evidence** to evaluate the effect of hCG supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.
 3. Metformin
 - a. In women with PCOS and infertility: metformin has **no effect** on the sporadic miscarriage risk when administered **before pregnancy**.
 - b. There is **insufficient evidence** to evaluate the effect of metformin supplementation **in pregnancy** to prevent a miscarriage in women with recurrent miscarriage.
 4. Suppression of high LH levels among ovulatory women with recurrent miscarriage and PCOS **does not** improve the live birth rate
- Septate Uterus: uterine septum resection. (insufficient evidence)

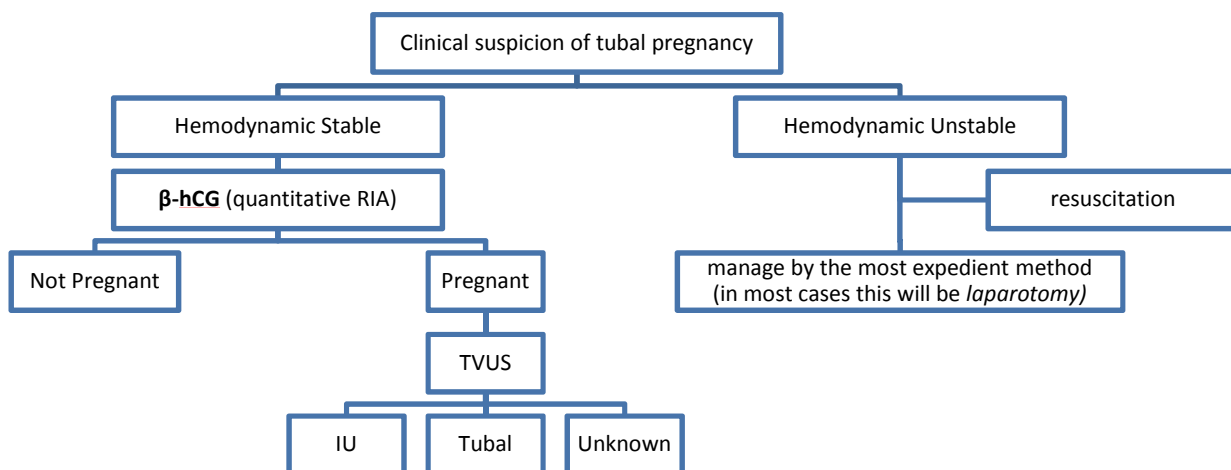
Tubal Pregnancy

Risk factors

- Half the women who have a tubal pregnancy have no known risk factors
- Factors strongly associated with risk of tubal pregnancy include:
 1. Damage to Fallopian tubes from previous PID.
 2. Previous tubal pregnancy.
 3. Damage to Fallopian tubes from tubal surgery:
 - a. Sterilization — although rare, if a pregnancy does occur there is a 15% risk that it will be ectopic.
 - b. Reversal of sterilization.
 - c. Tubal reconstruction and repair.
 4. Current use of a copper IUD or LNG-IUS.
 5. Assisted reproduction techniques

Diagnosis

- Lower abdominal pain, abnormal bleeding, amenorrhea
- Hemodynamic status, abdominal tenderness and guarding rigidity, cervical motion tenderness
- Quantitative b-hCG (RIA), TVUS, laparoscopy. Diagnostic algorithm MUST be available



Interventions

- Surgical
 1. Approach: laparotomy, laparoscopy
 2. Maneuver: salpingectomy, salpingotomy/salpingostomy
 3. Effect of interventions
 - a. Approach: depends on hemodynamic stability
 - (1) Management of tubal pregnancy in the presence of *hemodynamic instability* should be by the most expedient method. In most cases this will be *laparotomy*.
 - (2) For *hemodynamically stable* women: laparoscopy versus laparotomy
 - (a) laparoscopic salpingostomy is less successful than laparotomy in the elimination of the tubal pregnancy (OR 0.28, 95% CI 0.09 to 0.86). This mainly resulted from the significant higher persistent trophoblast rate of laparoscopic surgery (OR 3.5, 95% CI 1.1 to 11).
 - (b) subsequent intrauterine pregnancies: (OR 1.2, 95%CI 0.59 to 2.5)
 - (c) recurrent ectopic pregnancy rate (OR 0.47, 95% 0.15 to 1.5).

- b. Maneuver: depends on presence of contralateral tubal disease **AND** desire for fertility
 - (1) In the presence of a healthy contralateral tube there is no clear evidence that salpingotomy/salpingostomy should be used in preference to salpingectomy.
 - (2) Salpingotomy/salpingostomy should be considered as the primary treatment when managing tubal pregnancy in the presence of contralateral tubal disease **AND** the desire for future fertility
 - (3) Salpingostomy versus salpingotomy: no difference
 - (4) Salpingostomy alone versus combined with prophylactic single dose of methotrexate IM within 24 hours postoperatively: salpingostomy alone was less successful (OR 0.25, 95% CI 0.08 to 0.76), due to the higher incidence of persistent trophoblast (OR 4.1, 95% CI 1.3 to 13).
- Medical
 1. If medical therapy is offered, women should be given clear information (preferably written) about the possible need for further treatment and adverse effects following treatment. Women should be able to return easily for assessment at any time during follow-up.
 2. Suitable candidates
 - a. undisturbed (unruptured) tube
 - b. no active bleeding
 - c. blood in the Douglas pouch < 100 ml
 - d. initial serum hCG < 3000 iu/L
 - e. gestational sac diameter < 3 cm
 - f. no fetal components or cardiac pulsation
 3. Regimen:
 - a. Systemic
 - (1) fixed multiple dose im
 - (2) single dose im
 - (3) variable dose im
 - b. Local
 - (1) Under TVUS guidance
 - (2) Under laparoscopic guidance
 4. Effect of Interventions
 - a. Systemic MTX versus laparoscopic salpingostomy
 - (1) primary treatment success: OR 1.84 [0.73, 4.65]
 - (2) persistent trophoblast: no difference
 - (3) tubal preservation: no difference
 - (4) tubal patency: no difference
 - (5) subsequent intra uterine pregnancy: no difference
 - (6) recurrent tubal pregnancy: no difference
 - b. local MTX versus laparoscopic salpingostomy: no difference
- Expectant: Suitable candidate: stable clinically, initial hCG <1000 iu/L, decreasing hCG
- Nonsensitized women who are RH negative should receive anti-D immunoglobulin.

Prognosis

- Death is rare, but is the leading cause of pregnancy-related death in the first trimester
- Recurrence is 8–14%, but rises to 25% in women with two or more previous tubal pregnancies