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Early Pregnancy Loss

Early pregnancy loss, or loss of an intrauterine pregnancy within the first trimester, is encountered commonly in clinical practice. Obstetricians and gynecologists should understand the use of various diagnostic tools to differentiate between viable and nonviable pregnancies and offer the full range of therapeutic options to patients, including expectant, medical, and surgical management. The purpose of this Practice Bulletin is to review diagnostic approaches and describe options for the management of early pregnancy loss.

Background

Definition

Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12 6/7 weeks of gestation (1). In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably, and there is no consensus on terminology in the literature. However, early pregnancy loss is the term that will be used in this Practice Bulletin.

Incidence

Early pregnancy loss is common, occurring in 10% of all clinically recognized pregnancies (2–4). Approximately 80% of all cases of pregnancy loss occur within the first trimester (2, 3).

Etiology and Risk Factors

Approximately 50% of all cases of early pregnancy loss are due to fetal chromosomal abnormalities (5, 6). The most common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age and a prior early pregnancy loss (7, 8). The frequency of clinically recognized early pregnancy loss for women aged 20–30 years is 9–17%, and this rate increases sharply from 20% at age 35 years to 40% at age 40 years and 80% at age 45 years (7). Discussion of the many risk factors thought to be associated with early pregnancy loss is beyond the scope of this document and is covered in more detail in other publications (6, 7).

Clinical Considerations and Recommendations

▶ What findings can be used to confirm a diagnosis of early pregnancy loss?

Common symptoms of early pregnancy loss, such as vaginal bleeding and uterine cramping, also are common in normal gestation, ectopic pregnancy, and molar pregnancy. Before initiating treatment, it is important to distinguish early pregnancy loss from other early pregnancy complications. Treatment of an early pregnancy loss before confirmed diagnosis can have detrimental

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consequences, including interruption of a normal pregnancy, pregnancy complications, or birth defects (9). Therefore, a thorough evaluation is needed to make a definitive diagnosis. In combination with a thorough medical history and physical examination, ultrasonography and serum β-hCG testing can be helpful in making a highly certain diagnosis.

Ultrasonography, if available, is the preferred modality to verify the presence of a viable intrauterine gestation. In some instances, making a diagnosis of early pregnancy loss is fairly straightforward and requires limited testing or imaging. For example, early pregnancy loss can be diagnosed with certainty in a woman with an ultrasound-documented intrauterine pregnancy who subsequently presents with reported significant vaginal bleeding and an empty uterus on ultrasound examination. In other instances, the diagnosis of early pregnancy loss is not as clear. Depending on the specific clinical circumstances and how much diagnostic certainty the patient desires, a single serum β-hCG test or ultrasound examination may not be sufficient to confirm the diagnosis of early pregnancy loss.

The use of ultrasound criteria to confirm the diagnosis of early pregnancy loss was initially reported in the early 1990s, shortly after vaginal ultrasonography became widely available. Based on these early studies, a crown–rump length (CRL) of 5 mm without cardiac activity or an empty gestational sac measuring 16 mm in mean gestational sac diameter have been used as diagnostic criteria to confirm early pregnancy loss (10, 11). Recently, two large prospective studies have been used to challenge these cutoffs. In the first study, 1,060 women with intrauterine pregnancies of uncertain viability were followed up to weeks 11–14 of gestation (12). In this group of women, 55.4% received a diagnosis of nonviable gestation during the observation period. A CRL cutoff of 5 mm was associated with an 8.3% false-positive rate for early pregnancy loss. A CRL cutoff of 5.3 mm was required to achieve a false-positive rate of 0% in this study (12). Similarly, the authors reported a 4.4% false-positive rate for early pregnancy loss when using a mean gestational sac diameter cutoff of 16 mm. A mean gestational sac diameter cutoff of 21 mm (without an embryo and with or without a yolk sac) on the first ultrasound examination was required to achieve 100% specificity for early pregnancy loss. In a second study of 359 women from the first study group, the authors concluded that growth rates for the gestational sac (mean gestational sac diameter) and the embryo (CRL) could not predict viability accurately (13). However, the authors concluded that if a gestational sac was empty on initial scan, the absence of a visible yolk sac or embryo on a second scan performed 7 days or more after the first scan was always associated with pregnancy loss (13).

Based on these studies, the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy created guidelines that are considerably more conservative than past recommendations and also have stricter cutoffs than the studies on which they are based (14) (Table 1). The authors of the guidelines report that the stricter cutoffs are needed to account for interobserver variability; however, this already was accounted for in the original study through its use of multiple ultrasonographers (12, 15). Other important limitations in the development of these guidelines should be recognized. For example, there were few cases at or near the measurements ultimately identified as decision boundaries. Similarly, the time between observing a gestational sac and expecting to see a yolk sac or embryo was increased from 7 days or more in the clinical study (13) to 14 days in the guidelines (14). The basis of this recommendation is unclear.

Obstetrician–gynecologists caring for women experiencing possible early pregnancy loss should consider other clinical factors when interpreting the Society of Radiologists in Ultrasound guidelines, including the woman's desire to continue the pregnancy; her willingness to postpone intervention to achieve 100% certainty of pregnancy loss; and the potential consequences of waiting for intervention, including unwanted spontaneous passage of pregnancy tissue, the need for an unscheduled visit or procedure, and patient anxiety. It is important to include the patient in the diagnostic process and to individualize these guidelines to patient circumstances.

Criteria that are considered suggestive, but not diagnostic, of early pregnancy loss are listed in Table 1 (14). Slow fetal heart rate (less than 100 beats per minute at 5–7 weeks of gestation) (16) and subchorionic hemorrhage also have been shown to be associated with early pregnancy loss but should not be used to make a definitive diagnosis (17). These findings warrant further evaluation in 7–10 days (14).

In cases in which an intrauterine gestation cannot be identified with reasonable certainty, serial serum β-hCG measurements and ultrasound examinations may be required before treatment to rule out the possibility of an ectopic pregnancy. A detailed description of the recommended approach to ectopic pregnancy diagnosis and management is available in Practice Bulletin Number 94, *Medical Management of Ectopic Pregnancy* (18).

▶ *What are the management options for early pregnancy loss?*

Accepted treatment options for early pregnancy loss include expectant management, medical treatment, or

Table 1. Society of Radiologists in Ultrasound Guidelines for Transvaginal Ultrasonographic Diagnosis of Early Pregnancy Loss*

Findings Diagnostic of Early Pregnancy Loss†	Findings Suggestive, but Not Diagnostic, of Early Pregnancy Loss‡
Crown–rump length of 7 mm or greater and no heartbeat	Crown–rump length of less than 7 mm and no heartbeat
Mean sac diameter of 25 mm or greater and no embryo	Mean sac diameter of 16–24 mm and no embryo
Absence of embryo with heartbeat 2 weeks or more after a 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 11 days or more after a scan that showed a gestational sac with a yolk sac	Absence of embryo with heartbeat 7–10 days after an ultrasound scan that showed a gestational sac with a yolk sac
	Absence of embryo for 6 weeks or longer after last menstrual period
	Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)
	Enlarged yolk sac (greater than 7 mm)
	Small gestational sac in relation to the size of the embryo (less than 5 mm difference between mean sac diameter and crown–rump length)

*Criteria are from the Society of Radiologists in Ultrasound Multispecialty Consensus Conference on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, October 2012.

†These are the radiologic criteria only and do not replace clinical judgment.

‡When there are findings suspicious for early pregnancy loss, follow-up ultrasonography at 7–10 days to assess the pregnancy for viability is generally appropriate.

Reprinted from Doubilet PM, Benson CB, Bourne T, Blaivas M, Barnhart KT, Benacerraf BR, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. N Engl J Med 2013;369:1443–51.

surgical evacuation. Although these options differ significantly in process, all have been shown to be reasonably effective and accepted by patients. In women without medical complications or symptoms requiring urgent surgical evacuation, treatment plans can safely accommodate patient treatment preferences. There is no evidence that any approach results in different long-term outcomes. Patients should be counseled about the risks and benefits of each option. The following discussion applies to symptomatic and asymptomatic patients.

Expectant Management

Because of a lack of safety studies of expectant management in the second trimester and concerns about hemorrhage, expectant management generally should be limited to gestations within the first trimester. With adequate time (up to 8 weeks), expectant management is successful in achieving complete expulsion in approximately 80% of women (19). Limited data suggest that expectant management may be more effective in symptomatic women (those who report tissue passage or have ultrasound findings consistent with incomplete expulsion) than in asymptomatic women (20, 21). Furthermore, studies that included women with incomplete early pregnancy loss tend to report higher success rates than those that included only women with missed or anembryonic pregnancy loss (22).

Patients undergoing expectant management may experience moderate-to-heavy bleeding and cramping. Educational materials instructing the patient on when and who to call for excessive bleeding and prescriptions for pain medications should be provided. It also is important to counsel patients that surgery may be needed if complete expulsion is not achieved. Studies among women with early pregnancy loss typically have used ultrasound criteria, patient-reported symptoms, or both to confirm complete passage of gestational tissue. Although there is no consensus in the literature, a commonly used criterion for complete expulsion of pregnancy tissue is the absence of a gestational sac and an endometrial thickness of less than 30 mm (23). However, there is no evidence that morbidity is increased in asymptomatic women with a thicker endometrial measurement (24). Surgical intervention is not required in asymptomatic women with a thickened endometrial stripe after treatment for early pregnancy loss. Thus, the use of ultrasound examination for any diagnostic purpose other than documenting the absence of the gestational sac is not recommended. Other follow-up approaches, such as standardized follow-up phone calls, urine pregnancy tests, or serial quantitative serum β-hCG measurements, may be useful, especially for women with limited access to follow-up ultrasound examination (25). However, these approaches have not

been studied sufficiently among women with early pregnancy loss to provide meaningful guidance.

Medical Management

For patients who are interested in shortening the time to complete expulsion but prefer to avoid surgical evacuation, treatment with misoprostol, a prostaglandin E_1 analogue, is useful. As long as the woman is a candidate for expectant or medical management (eg, without infection, hemorrhage, severe anemia, or bleeding disorders), there are few contraindications to misoprostol besides allergy to the medication. Misoprostol has been studied extensively in early pregnancy loss and it reliably reduces the need for uterine curettage by up to 60% and shortens the time to completion compared with placebo (26). A recent randomized controlled trial comparing vaginal administration of 400 micrograms of misoprostol with 800 micrograms of misoprostol concluded that although the higher dose may shorten the interval to completion and reduced the need for a second dose, success rates were comparable (83.2% versus 87.8%), and fewer adverse effects were reported among women who received the lower dose (27). However, most studies suggest that a larger dose is more effective than a smaller dose, and vaginal or sublingual administration of misoprostol is more effective than oral administration, although the sublingual route is associated with more cases of diarrhea (26). The largest randomized controlled trial conducted in the United States demonstrated complete expulsion by day 3 in 71% of women with first-trimester pregnancy loss after one dose of 800 micrograms of vaginal misoprostol (23). The success rate was increased to 84% after a second dose of 800 micrograms of vaginal misoprostol was administered if needed. Therefore, based on the best available evidence, in patients for whom medical management of early pregnancy loss is indicated, initial treatment using 800 micrograms of vaginal misoprostol generally is recommended, with a repeat dose as needed (see Box 1).

The addition of mifepristone (a progesterone receptor antagonist) to misoprostol has been studied as a treatment for early pregnancy loss, but there is insufficient evidence to conclude that this regimen is superior to misoprostol alone (26). Given that the benefit of adding mifepristone is unclear and that its addition brings increased cost, the routine use of mifepristone in the treatment of early pregnancy loss is not recommended.

A 2013 Cochrane review of limited evidence concluded that among women with incomplete pregnancy loss (ie, incomplete tissue passage), the addition of misoprostol does not clearly result in higher rates of complete evacuation over expectant management (at 7–10 days, success rates were 80–81% versus 52–85%, respectively) (28). Therefore, at this time, there is insufficient evidence to support or refute the use of misoprostol among women with incomplete pregnancy loss.

As with expectant management of early pregnancy loss, women opting for medical treatment should be counseled on what to expect while they pass pregnancy tissue, provided information on when to call regarding bleeding, and given prescriptions for pain medications. Counseling should emphasize that the woman is likely to have bleeding that is heavier than menses (and potentially accompanied by severe cramping). The woman should understand how much bleeding is considered too much. An easy reference for the patient to use is the soaking of two maxi pads per hour for 2 consecutive hours (29). The patient should be advised to call her obstetrician–gynecologist or other gynecologic provider if she experiences this level of bleeding. As with expectant management, it also is important to counsel patients that surgery may be needed if medical management does not achieve complete expulsion.

Follow-up typically includes confirmation of complete expulsion by ultrasound examination, but serial

Box 1. Sample Protocol for Misoprostol Management of Early Pregnancy Loss ⇦

- The recommended initial dose of misoprostol is 800 micrograms vaginally. One repeat dose may be administered as needed, no earlier than 3 hours after the first dose and typically within 7 days if there is no response to the first dose.*
- Prescriptions for pain medications should be provided to the patient.
- Women who are Rh(D) negative and unsensitized should receive Rh(D)-immune globulin within 72 hours of the first misoprostol administration.
- Follow-up to document the complete passage of tissue can be accomplished by ultrasound examination, typically within 7–14 days. Serial serum β-hCG measurements may be used instead in settings where ultrasonography is unavailable. Patient-reported symptoms also should be considered when determining whether complete expulsion has occurred.
- If misoprostol fails, the patient may opt for expectant management, for a time determined by the woman and her obstetrician–gynecologist or other gynecologic provider, or suction curettage.

*Data from Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. N Engl J Med 2005;353:761–9.

serum β-hCG measurement may be used instead in settings where ultrasonography is unavailable. Patient-reported symptoms also should be considered when determining whether complete expulsion has occurred.

Surgical Management

Surgical uterine evacuation has long been the traditional approach for women presenting with early pregnancy loss and retained tissue. Women who present with hemorrhage, hemodynamic instability, or signs of infection should be treated urgently with surgical uterine evacuation. Surgical evacuation also might be preferable in other situations, including the presence of medical comorbidities such as severe anemia, bleeding disorders, or cardiovascular disease. Many women prefer surgical evacuation to expectant or medical treatment because it provides more immediate completion of the process with less follow-up.

In the past, uterine evacuation often was performed with sharp curettage alone. However, studies show that the use of suction curettage is superior to the use of sharp curettage alone (30, 31). Furthermore, the routine use of sharp curettage along with suction curettage in the first trimester does not provide any additional benefit as long as the obstetrician–gynecologist or other gynecologic provider is confident that the uterus is empty. Suction curettage also can be performed in an office setting with an electric vacuum source or manual vacuum aspirator, under local anesthesia with or without the addition of sedation (32, 33). Surgical management in the office setting offers significant cost savings compared with the same procedure performed in the operating room (33–35). Patients often choose management in the office setting for its convenience and scheduling availability (33).

▶ *How do the different management options for early pregnancy loss compare in effectiveness and risk of complications?*

Studies have demonstrated that expectant, medical, and surgical management of early pregnancy loss all result in complete evacuation of pregnancy tissue in most patients, and serious complications are rare. As a primary approach, surgical evacuation results in faster and more predictable complete evacuation (22). The success of surgical uterine evacuation of early pregnancy loss approaches 99% (23). The largest U.S. trial reported that success rates after medical management of anembryonic gestations (81%) was lower than with embryonic or fetal death (88%) or incomplete or inevitable early pregnancy loss (93%) (23). However, a subsequent multivariable analysis of the same data revealed that only active bleeding and nulliparity were strong predictors of success (36). Therefore, medical management is a reasonable option for any pregnancy failure type.

Overall, serious complications after early pregnancy loss treatment are rare and are comparable across treatment types. Clinically important intrauterine adhesion formation is a rare complication after surgical evacuation. Hemorrhage and infection can occur with all of the treatment approaches. In the Management of Early Pregnancy Failure Trial, women randomized to the misoprostol group were significantly more likely to have a decrease in their hemoglobin levels greater than or equal to 3 g/dL than women in the vacuum aspiration group (23, 37). However, rates of hemorrhage-related hospitalization with or without transfusion are similar between treatment approaches (0.5–1%) (23, 38). Pelvic infection also can occur after any type of early pregnancy loss treatment. One systematic review concluded that although infection rates appeared lower among those undergoing expectant management than among those undergoing surgical evacuation (relative risk, 0.29; 95% confidence interval, 0.09–0.97), the overall rates of infection were low (1–2%) (38). Because neither approach was clearly superior, the reviewers concluded that patient preference should guide choice of intervention (38).

The risk of infection after suction curettage for missed early pregnancy loss should be similar to that after suction curettage for induced abortion. Therefore, despite the lack of data, antibiotic prophylaxis also should be considered for patients with early pregnancy loss (39, 40). The use of a single preoperative dose of doxycycline is recommended to prevent infection after surgical management of early pregnancy loss. Some experts have recommended administration of a single 200-mg dose of doxycycline 1 hour before surgical management of early pregnancy loss to prevent postoperative infection. The use of antibiotics based only on the diagnosis of incomplete early pregnancy loss has not been found to reduce infectious complications as long as unsafe induced abortion is not suspected (41). The benefit of antibiotic prophylaxis for the medical management of early pregnancy loss is unknown.

▶ *How do the different treatment approaches to early pregnancy loss differ with respect to cost?*

Studies have consistently shown that surgical management in an operating room is more costly than expectant or medical management (42, 43). However, surgical management in an office setting can be more effective and less costly than medical management when performed without general anesthesia and in circumstances

in which numerous office visits are likely or there is a low chance of success with medical management or expectant management (44). Findings from studies comparing the cost-effectiveness of medical and expectant management schemes are inconsistent. However, a U.S. analysis of all three management approaches concluded that medical management with misoprostol was the most cost-effective intervention (43). One limitation of the available studies on cost of early pregnancy loss care is that none of these studies can adequately consider clinical nuances or patient treatment preferences, which can affect patient adherence to the primary treatment regimen and, subsequently, the effectiveness of that treatment. For instance, in one observational study, the effectiveness of medical management of early pregnancy loss was far lower than rates reported in randomized clinical trials, which was due in large part to patients' unwillingness to complete the treatment regimen (45).

▶ *How should patients be counseled regarding interpregnancy interval after early pregnancy loss?*

There are no quality data to support delaying conception after early pregnancy loss to prevent subsequent early pregnancy loss or other pregnancy complications. Small observational studies show no benefit to delayed conception after early pregnancy loss (46, 47). Abstaining from vaginal intercourse for 1–2 weeks after complete passage of pregnancy tissue generally is recommended to reduce the risk of infection, but this is not an evidence-based recommendation.

▶ *How should patients be counseled regarding the use of contraception after early pregnancy loss?*

Women who desire contraception may initiate hormonal contraception use immediately after completion of early pregnancy loss (48). There are no contraindications to the placement of an intrauterine device immediately after surgical treatment of early pregnancy loss as long as septic abortion is not suspected (48). The expulsion rate with immediate intrauterine device insertion after suction curettage in the first trimester is not clinically significantly different than placement 2–6 weeks postoperatively (5% versus 2.7% at 6 months) (49).

▶ *How should patients be counseled regarding prevention of alloimmunization after early pregnancy loss?*

Women who are Rh(D) negative and unsensitized should receive 50 micrograms of Rh(D)-immune globulin immediately after surgical management of early pregnancy loss or within 72 hours of the diagnosis of early pregnancy loss with planned medical management or expectant management in the first trimester (50). It is reasonable to use the more readily available 300-microgram dose if the 50-microgram dose is unavailable.

▶ *What type of workup is needed after early pregnancy loss?*

No workup generally is recommended until after the second consecutive clinical early pregnancy loss (7). Maternal or fetal chromosomal analyses or testing for inherited thrombophilias are not recommended routinely after one early pregnancy loss. Although thrombophilias commonly are thought of as causes of early pregnancy loss, only antiphospholipid syndrome consistently has been shown to be significantly associated with early pregnancy loss (51, 52). In addition, the use of anticoagulants, aspirin, or both has not been shown to reduce the risk of early pregnancy loss in women with thrombophilias except in women with antiphospholipid syndrome (53, 54).

▶ *Are there any effective interventions to prevent early pregnancy loss?*

There are no effective interventions to prevent early pregnancy loss. Therapies that have historically been recommended, such as pelvic rest, vitamins, uterine relaxants, and administration of β-hCG, have not been proved to prevent early pregnancy loss (55–57). Likewise, bed rest should not be recommended for the prevention of early pregnancy loss (58). A 2008 Cochrane review found no effect of prophylactic progesterone administration (oral, intramuscular, or vaginal) in the prevention of early pregnancy loss (59). For threatened early pregnancy loss, the use of progestins is controversial, and conclusive evidence supporting their use is lacking (60). Women who have experienced at least three prior pregnancy losses, however, may benefit from progesterone therapy in the first trimester (7).

Summary of Recommendations and Conclusions

The following recommendation and conclusion are based on good and consistent scientific evidence (Level A):

- In patients for whom medical management of early pregnancy loss is indicated, initial treatment using

800 micrograms of vaginal misoprostol generally is recommended, with a repeat dose as needed.

- The use of anticoagulants, aspirin, or both has not been shown to reduce the risk of early pregnancy loss in women with thrombophilias except in women with antiphospholipid syndrome.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- Ultrasonography, if available, is the preferred modality to verify the presence of a viable intrauterine gestation.
- Surgical intervention is not required in asymptomatic women with a thickened endometrial stripe after treatment for early pregnancy loss.
- The routine use of sharp curettage along with suction curettage in the first trimester does not provide any additional benefit as long as the obstetrician–gynecologist or other gynecologic provider is confident that the uterus is empty.
- Women who are Rh(D) negative and unsensitized should receive 50 micrograms of Rh(D)-immune globulin immediately after surgical management of early pregnancy loss or within 72 hours of the diagnosis of early pregnancy loss with planned medical management or expectant management in the first trimester. It is reasonable to use the more readily available 300-microgram dose if the 50-microgram dose is unavailable.

The following recommendation and conclusion are based primarily on consensus and expert opinion (Level C):

- Accepted treatment options for early pregnancy loss include expectant management, medical treatment, or surgical evacuation. In women without medical complications or symptoms requiring urgent surgical evacuation, treatment plans can safely accommodate patient treatment preferences.
- The use of a single preoperative dose of doxycycline is recommended to prevent infection after surgical management of early pregnancy loss.

Proposed Performance Measure

The proportion of Rh(D)-negative, unsensitized women who receive Rh(D)-immune globulin immediately after surgical management or within 72 hours of diagnosis with planned medical management or expectant management of early pregnancy loss

References

1. National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. NICE Clinical Guideline 154. Manchester (UK): NICE; 2012. Available at: http://www.nice.org.uk/guidance/cg154/resources/guidance-ectopic-pregnancy-and-miscarriage-pdf. Retrieved January 20, 2015. (Level III) ⇦
2. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189–94. (Level II-3) [PubMed] ⇦
3. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril 2003;79:577–84. (Level II-2) [PubMed] [Full Text] ⇦
4. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril 1996;65:503–9. (Level II-3) [PubMed] ⇦
5. Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: a case-control study. Hum Reprod 2002; 17:446–51. (Level II-2) [PubMed] [Full Text] ⇦
6. Alijotas-Reig J, Garrido-Gimenez C. Current concepts and new trends in the diagnosis and management of recurrent miscarriage. Obstet Gynecol Surv 2013;68:445–66. (Level III) [PubMed] ⇦
7. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2012; 98:1103–11. (Level III) [PubMed] [Full Text] ⇦
8. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ 2000;320:1708–12. (Level II-3) [PubMed] [Full Text] ⇦
9. Barnhart KT. Early pregnancy failure: beware of the pitfalls of modern management. Fertil Steril 2012;98:1061–5. (Level III) [PubMed] [Full Text] ⇦
10. Brown DL, Emerson DS, Felker RE, Cartier MS, Smith WC. Diagnosis of early embryonic demise by endovaginal sonography. J Ultrasound Med 1990;9:631–6. (Level III) [PubMed] ⇦
11. Pennell RG, Needleman L, Pajak T, Baltarowich O, Vilaro M, Goldberg BB, et al. Prospective comparison of vaginal and abdominal sonography in normal early pregnancy. J Ultrasound Med 1991;10:63–7. (Level II-3) [PubMed] ⇦
12. Abdallah Y, Daemen A, Kirk E, Pexsters A, Naji O, Stalder C, et al. Limitations of current definitions of miscarriage using mean gestational sac diameter and

crown-rump length measurements: a multicenter observational study. Ultrasound Obstet Gynecol 2011;38:497–502. (Level II-3) [PubMed] [Full Text] ⇦

13. Abdallah Y, Daemen A, Guha S, Syed S, Naji O, Pexsters A, et al. Gestational sac and embryonic growth are not useful as criteria to define miscarriage: a multicenter observational study. Ultrasound Obstet Gynecol 2011;38:503–9. (Level II-3) [PubMed] [Full Text] ⇦

14. Doubilet PM, Benson CB, Bourne T, Blaivas M, Barnhart KT, Benacerraf BR, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. N Engl J Med 2013;369:1443–51. (Level III) [PubMed] [Full Text] ⇦

15. Pexsters A, Luts J, Van Schoubroeck D, Bottomley C, Van Calster B, Van Huffel S, et al. Clinical implications of intra- and interobserver reproducibility of transvaginal sonographic measurement of gestational sac and crown-rump length at 6-9 weeks' gestation. Ultrasound Obstet Gynecol 2011;38:510–5. (Level II-3) [PubMed] [Full Text] ⇦

16. Doubilet PM, Benson CB, Chow JS. Long-term prognosis of pregnancies complicated by slow embryonic heart rates in the early first trimester. J Ultrasound Med 1999;18:537–41. (Level II-3) [PubMed] [Full Text] ⇦

17. Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol 2011;117:1205–12. (Meta-analysis) [PubMed] [*Obstetrics & Gynecology*] ⇦

18. Medical management of ectopic pregnancy. ACOG Practice Bulletin No. 94. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;111:1479–85. (Level III) [PubMed] [*Obstetrics & Gynecology*] ⇦

19. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ 2002;324:873–5. (Level III) [PubMed] [Full Text] ⇦

20. Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Hum Reprod 2004;19:266–71. (Level I) [PubMed] [Full Text] ⇦

21. Ngai SW, Chan YM, Tang OS, Ho PC. Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. Hum Reprod 2001;16:1493–6. (Level I) [PubMed] [Full Text] ⇦

22. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP. Expectant, medical, or surgical management of first-trimester miscarriage: a meta-analysis. Obstet Gynecol 2005;105:1104–13. (Meta-analysis) [PubMed] [*Obstetrics & Gynecology*] ⇦

23. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. N Engl J Med 2005;353:761–9. (Level I) [PubMed] [Full Text] ⇦

24. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J. Endometrial thickness after misoprostol use for early pregnancy failure. NICHD Management of Early Pregnancy Failure Trial. Int J Gynaecol Obstet 2004;86:22–6. (Level III) [PubMed] [Full Text] ⇦

25. Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception 2011;83:504–10. (Level III) [PubMed] [Full Text] ⇦

26. Neilson JP, Hickey M, Vazquez JC. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD002253. DOI: 10.1002/14651858.CD002253.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦

27. Petersen SG, Perkins A, Gibbons K, Bertolone J, Devenish-Meares P, Cave D, et al. Can we use a lower intravaginal dose of misoprostol in the medical management of miscarriage? A randomised controlled study. Aust N Z J Obstet Gynaecol 2013;53:64–73. (Level I) [PubMed] [Full Text] ⇦

28. Neilson JP, Gyte GM, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD007223. DOI: 10.1002/14651858.CD007223.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦

29. Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, Creinin MD, editors. Management of unintended and abnormal pregnancy: comprehensive abortion care. Hoboken (NJ): Wiley-Blackwell; 2009. (Level III) ⇦

30. Tunçalp Ö, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD001993. DOI: 10.1002/14651858.CD001993.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦

31. Rogo K. Improving technologies to reduce abortion-related morbidity and mortality. Int J Gynaecol Obstet 2004;85(suppl 1):S73–82. (Level III) [PubMed] [Full Text] ⇦

32. Goldberg AB, Dean G, Kang MS, Youssof S, Darney PD. Manual versus electric vacuum aspiration for early first-trimester abortion: a controlled study of complication rates. Obstet Gynecol 2004;103:101–7. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦

33. Dalton VK, Harris L, Weisman CS, Guire K, Castleman L, Lebovic D. Patient preferences, satisfaction, and resource use in office evacuation of early pregnancy failure. Obstet Gynecol 2006;108:103–10. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦

34. Blumenthal PD, Remsburg RE. A time and cost analysis of the management of incomplete abortion with manual vacuum aspiration. Int J Gynaecol Obstet 1994;45:261–7. (Level III) [PubMed] ⇦

35. Choobun T, Khanuengkitkong S, Pinjaroen S. A comparative study of cost of care and duration of management for first-trimester abortion with manual vacuum

aspiration (MVA) and sharp curettage. Arch Gynecol Obstet 2012;286:1161–4. (Level II-3) [PubMed] ⇦

36. Creinin MD, Huang X, Westhoff C, Barnhart K, Gilles JM, Zhang J. Factors related to successful misoprostol treatment for early pregnancy failure. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. Obstet Gynecol 2006;107:901–7. (Level II-2) [PubMed] [*Obstetrics & Gynecology*] ⇦
37. Davis AR, Hendlish SK, Westhoff C, Frederick MM, Zhang J, Gilles JM, et al. Bleeding patterns after misoprostol vs surgical treatment of early pregnancy failure: results from a randomized trial. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. Am J Obstet Gynecol 2007;196:31.e1–31.e7. (Level I) [PubMed] [Full Text] ⇦
38. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD003518. DOI: 10.1002/14651858.CD003518.pub3. (Meta-analysis) [PubMed] ⇦
39. Achilles SL, Reeves MF. Prevention of infection after induced abortion: release date October 2010: SFP guideline 20102. Society of Family Planning. Contraception 2011;83:295–309. (Level III) [PubMed] [Full Text] ⇦
40. Sawaya GF, Grady D, Kerlikowske K, Grimes DA. Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis. Obstet Gynecol 1996;87:884–90. (Meta-analysis) [PubMed] [*Obstetrics & Gynecology*] ⇦
41. Prieto JA, Eriksen NL, Blanco JD. A randomized trial of prophylactic doxycycline for curettage in incomplete abortion. Obstet Gynecol 1995;85:692–6. (Level I) [PubMed] [*Obstetrics & Gynecology*] ⇦
42. Petrou S, McIntosh E. Women's preferences for attributes of first-trimester miscarriage management: a stated preference discrete-choice experiment. Value Health 2009;12:551–9. (Level III) [PubMed] ⇦
43. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod 2005;20:2873–8. (Level III) [PubMed] [Full Text] ⇦
44. Rausch M, Lorch S, Chung K, Frederick M, Zhang J, Barnhart K. A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss. Fertil Steril 2012;97:355–60. (Level III) [PubMed] [Full Text] ⇦
45. Colleselli V, Schreiber CA, D'Costa E, Mangesius S, Wildt L, Seeber BE. Medical management of early pregnancy failure (EPF): a retrospective analysis of a combined protocol of mifepristone and misoprostol used in clinical practice. Arch Gynecol Obstet 2014;289:1341–5. (Level II-3) [PubMed] ⇦
46. Vlaanderen W, Fabriek LM, van Tuyll van Serooskerken C. Abortion risk and pregnancy interval. Acta Obstet Gynecol Scand 1988;67:139–40. (Level II-3) [PubMed] ⇦
47. Goldstein RR, Croughan MS, Robertson PA. Neonatal outcomes in immediate versus delayed conceptions after spontaneous abortion: a retrospective case series. Am J Obstet Gynecol 2002;186:1230–4; discussion 1234–6. (Level III) [PubMed] [Full Text] ⇦
48. U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep 2010;59(RR-4):1–86. (Level III) [PubMed] [Full Text] ⇦
49. Bednarek PH, Creinin MD, Reeves MF, Cwiak C, Espey E, Jensen JT. Immediate versus delayed IUD insertion after uterine aspiration. Post-Aspiration IUD Randomization (PAIR) Study Trial Group. N Engl J Med 2011;364:2208–17. (Level I) [PubMed] [Full Text] ⇦
50. American College of Obstetricians and Gynecologists. Prevention of Rh D alloimmunization. ACOG Practice Bulletin 4. Washington, DC: ACOG; 1999. (Level III) ⇦
51. McNamee K, Dawood F, Farquharson R. Recurrent miscarriage and thrombophilia: an update. Curr Opin Obstet Gynecol 2012;24:229–34. (Level III) [PubMed] ⇦
52. McNamee K, Dawood F, Farquharson RG. Thrombophilia and early pregnancy loss. Best Pract Res Clin Obstet Gynaecol 2012;26:91–102. (Level III) [PubMed] [Full Text] ⇦
53. Empson MB, Lassere M, Craig JC, Scott JR. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002859. DOI: 10.1002/14651858.CD002859.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
54. de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD004734. DOI: 10.1002/14651858.CD004734.pub4. (Meta-analysis) [PubMed] [Full Text] ⇦
55. Rumbold A, Middleton P, Pan N, Crowther CA. Vitamin supplementation for preventing miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004073. DOI: 10.1002/14651858.CD004073.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦
56. Lede RL, Duley L. Uterine muscle relaxant drugs for threatened miscarriage. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD002857. DOI: 10.1002/14651858.CD002857.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
57. Devaseelan P, Fogarty PP, Regan L. Human chorionic gonadotrophin for threatened miscarriage. Cochrane Database of Systematic Reviews 2010, Issue 5. Art. No.: CD007422. DOI: 10.1002/14651858.CD007422.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
58. Aleman A, Althabe F, Belizán JM, Bergel E. Bed rest during pregnancy for preventing miscarriage. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD003576. DOI: 10.1002/14651858.CD003576.pub2. (Meta-analysis) [PubMed] [Full Text] ⇦
59. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003511. DOI: 10.1002/14651858.CD003511.pub3. (Meta-analysis) [PubMed] [Full Text] ⇦

60. Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005943. DOI: 10.1002/14651858.CD005943.pub4. (Meta-analysis) [PubMed] [Full Text] ⇦

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–July 2014. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

The American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

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