17 CHAPTER 17
Pregnancy loss

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LEARNING POINTS

- Failed early pregnancy can be managed expectantly, with misoprostol, or by suction curettage.
- Compared to suction curettage, expectant management of failed early pregnancy is less effective at causing complete abortion; it is associated with more bleeding and unscheduled curettages, but no increased risk of infection.
- Misoprostol, 800 μg administered vaginally and allowed 1 week to work, is approximately 80 to 85% effective at causing expulsion of an anembryonic pregnancy or early embryonic demise.
- In cases of incomplete abortion, expectant management is highly effective. Misoprostol, 600 to 800 μg given vaginally or orally, may speed completion.
- Management options for second-trimester pregnancy loss include dilation and evacuation or labor induction with misoprostol. Modern evidence comparing these techniques is limited.

Introduction

Pregnancy loss in the first or second trimester can result from failure of an embryo to develop, embryonic or fetal death, or spontaneous expulsion of a pregnancy. Much of the literature on pregnancy loss suffers from lack of uniform terminology and definitions. For purposes of national vital statistics reporting in the USA, researchers commonly define *spontaneous abortion* as pregnancy loss prior to 20 weeks' gestation. *Fetal death* is defined as intrauterine fetal demise (IUFD) at 20 weeks' gestation or greater, and a late fetal death is an IUFD after 28 weeks' gestation [1,2]. As early as 1903, Williams stated that the term "miscarriage" was used by laypeople and that clinicians preferred "spontaneous abortion [3]." Application of ultrasonography in contemporary medical practice has allowed for earlier and more precise diagnosis. The term *early pregnancy failure* (EPF) refers to first-trimester pregnancy loss categorized sonographically into two types. A pregnancy that develops without any fetal pole is called an *anembryonic gestation*. The presence of a gestational sac that contains an embryo (at least 5 mm in length) or fetus without evidence of cardiac motion is termed an *embryonic or fetal demise*. Among women with easy access to care, many spontaneous abortions are now identified with minimal or absent symptoms because of the widespread use of sonography.

Of the approximate 205 million pregnancies that occur worldwide each year, 133 million result in live birth, 42 million are terminated by induced abortion, and 30 million end in spontaneous pregnancy loss [4]. In the USA alone, spontaneous abortions exceed 900,000 reported cases annually [1], and many additional cases go unreported [5]. Because pregnancy loss is a frequent occurrence, women's health practitioners must be prepared to diagnose and treat this condition appropriately. After providing some background information on the epidemiology of pregnancy loss, this chapter describes approaches to the diagnosis and modern management of first-trimester pregnancy loss in general and second-trimester pregnancy loss resulting from IUFD. Pregnancy loss in the second trimester also can result from obstetric complications, such as placental abruption, chorioamnionitis, preterm premature rupture of membranes, and advanced cervical dilation with or without bulging membranes. Reviewing the pathophysiology, diagnosis, and management of obstetric complications is beyond the scope of this chapter, but physicians generally use or adapt dilation and evacuation (D&E) or induction techniques (Chapters 11 and 12) to treat such cases of pregnancy loss.

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Epidemiology

Frequency estimates

Spontaneous abortion occurs in 8 to 20% of clinically recognized pregnancies. In the 2002 US National Survey of Family Growth, US women reported that 17% of pregnancies in the previous 5 years resulted in spontaneous abortion; correcting the estimate for the underreporting of induced abortion decreased the proportion to 15% [3]. Although social stigma is unlikely to lead to underreporting of spontaneous abortion, multiple sources agree that these events are underreported. Most studies do not include spontaneous abortion occurring before 5 completed menstrual weeks. The reported frequency of spontaneous abortion depends on the health care system, the source of the information, and the age distribution of the population.

Routine surveillance by the US Centers for Disease Control and Prevention (CDC) tracks births, fetal deaths, and induced abortions, but not pregnancy losses prior to 20 weeks' gestation. In 1999 the CDC estimated the number of clinically recognized pregnancies occurring between 1981 and 1991 to provide denominators for rates of pregnancy-related outcomes. Of all pregnancies that occurred during the study period, 62.5% resulted in live births, 21.9% ended in induced abortion, 13.8% were spontaneous abortions, 1.3% were ectopic, and 0.5% ended with fetal death after 20 weeks' gestation [1]. Applying these percentages to national birth data for the USA between 1991 and 1999, Grimes estimated that approximately 7,882,974 spontaneous abortions and 285,615 fetal deaths occurred during this interval [6]. Assuming consistent rates during this 8-year interval produces estimates of 985,372 spontaneous abortions and 35,702 fetal deaths per year.

The frequency of spontaneous abortion is greatest in the early or mid first trimester and progressively decreases throughout the second trimester. Older estimates suggest that 87% of spontaneous abortions occur before 13 weeks' gestation, 9% at 13 to 15 weeks' gestation, and 4% at 16 to 19 weeks' gestation [7]. A recent study indicates that the subsequent loss rate of pregnancies with fetal heart tones between 10 and 13 weeks' gestation is extremely low. In a large multicenter study of spontaneous pregnancy loss after amniocentesis, the control group included more than 31,000 women who had singleton pregnancies at 10 to 13 weeks' gestation with fetal heart tones and who did not have invasive prenatal diagnostic procedures; the spontaneous loss rate before 24 weeks' gestation was 0.94% [8]. Although infrequent, the rate of loss after documented heart tones increases with maternal age [8].

Risk factors

Many studies agree that the strongest risk factor for spontaneous abortion is advancing maternal age. Both trisomic and chromosomally normal spontaneous abortions increase with age. Monosomy is not associated with increasing maternal age, but all known trisomies are. A Danish study of all pregnancies from 1978 to 1992 with a hospital-based outcome included 101,851 spontaneous abortions [9]. Among women aged 20 to 24, 8.9% of all recorded pregnancies ended in spontaneous abortion compared to 74.7% of pregnancies among women aged 45 or older. In the Jerusalem Perinatal Cohort Study, which included 1,506 women with spontaneous abortions [10], women over age 35 had a markedly increased risk of spontaneous abortion (adjusted odds ratio 8.3, 95% CI 6.7, 10.3) compared to women aged 20 to 24. The risk for spontaneous abortion increased 16% with each additional year of maternal age. That study also showed that the risk increases with advancing paternal age (after adjustment for maternal age), but the effect is not as strong (odds ratio 1.9, 95% CI 1.6, 2.3 for men aged 35 to 39 compared to men aged 25 to 29). The highest risk for spontaneous abortion occurs with advanced age of both the woman and the man.

Other factors that have been consistently associated with spontaneous abortion include a short interpregnancy interval (generally less than 3 to 6 months) [11], a history of previous spontaneous abortion, and maternal diabetes [10]. Studies are inconsistent regarding previous induced abortion, but a large case-control study found no association [12]. Research examining this issue is limited by underreporting of induced abortions and the methodological difficulties of identifying a suitable control group (Chapter 16).

Smoking is the main clearly defined, modifiable risk factor for spontaneous abortion. Maternal smoking during pregnancy increases the risk of spontaneous abortion in a dose-dependent fashion; however, prepregnancy smoking is unrelated [13,14]. Heavy paternal smoking is also associated with spontaneous abortion [15]. Alcohol consumption and high levels of caffeine intake may be weakly associated with spontaneous abortion [16]. Occupational exposures have been the subject of many studies, but associations are not well defined. In contrast, factors weakly associated with a reduced risk of spontaneous abortion include higher parity, higher maternal or paternal education, and higher social class [10]. Occurrence of spontaneous abortion in the USA does not vary by race; according to national statistics, however, Black race is associated with an increased risk of fetal death at 20 weeks' gestation and beyond [2].

In comparison to first-trimester anembryonic pregnancies, fetal death after 13 weeks' gestation is weakly associated with aneuploidies and more strongly related to thrombophilias [17,18]. Later losses are also related to maternal infections, genetic syndromes, and structural abnormalities.

Morbidity and mortality

Since 1979 the CDC has conducted surveillance of deaths in the USA from all pregnancy outcomes, including spontaneous abortions at less than 20 weeks' gestation. From

1981 to 1991, the overall case-fatality rate was 0.7 per 100,000 spontaneous abortions. The risk of death was higher among non-White women, those over aged 35, and those beyond 12 weeks' gestation [7]. Reported causes of spontaneous abortion-related deaths included infection 59%, hemorrhage 18%, embolism 13%, anesthesia-related complications 5%, and other causes 5%. Disseminated intravascular coagulopathy (DIC) was associated with half of the cases where it was not listed as the primary cause of death [7].

Pregnancies complicated by IUFD may be associated with an increased risk of maternal death, but data are conflicting. A single-institution retrospective analysis found no increased risk of maternal morbidity or mortality associated with IUFD compared to delivery of a viable fetus at a similar gestational age [19]. However, a recent estimation of maternal death rate by pregnancy outcome based on US national statistics suggests that the risk of maternal death is greater with IUFD than with live birth, spontaneous abortion, or legal induced abortion [6]. These data include second- and third-trimester IUFDs and do not report on underlying diagnoses or etiologies of the fetal demise.

Diagnosis

Spontaneous abortion is diagnosed by history of bleeding and pain, physical examination, and by ultrasound examination when available. Serial serum quantitative human chorionic gonadotropin (hCG) monitoring helps in some cases. Because routine, early first-trimester prenatal sonogram for dating or for first-trimester screening is highly prevalent in the USA and many other countries, women often receive the diagnosis of EPF prior to the development of any symptoms.

Sonography

Sonographic findings diagnostic of EPF include either an embryo 5 mm or greater in size without cardiac activity or a mean gestational sac diameter 13 mm or greater with absent yolk sac. A recent report using 5 to 6 mHz transducers found that 100% specificity was not reached until a cutoff of 16 mm (Chapter 6). With or without symptoms, these findings indicate EPF. Because both pregnancy dating and sonography are imperfect, diagnosis of spontaneous abortion in a woman with a wanted pregnancy may require two sonographic assessments to differentiate an EPF from a misdated pregnancy. When no yolk sac is visible, the clinician must also consider the diagnosis of ectopic pregnancy. In addition to ultrasound, serial hCG levels performed approximately 2 days apart can help distinguish normal from abnormal pregnancies. When a yolk sac is not clearly visible on ultrasound and serial hCG levels are not rising normally, uterine evacuation with inspection of tissue for the presence of villi can definitively distinguish between ectopic pregnancy and EPF (Chapter 18).

Early pregnancy failures have been further classified sonographically as anembryonic gestations or embryonic or fetal demises. In the large, multicenter Management of Early Pregnancy Failure (MEPF) trial, US researchers defined anembryonic pregnancy as an empty gestational sac with a mean diameter of at least 16 mm or insufficient growth of the sac over at least 5 days. If the gestational sac contained a yolk sac but hCG levels increased less than 15% over a 2-day period, then EPF was confirmed. Embryonic or fetal demise was diagnosed in the absence of fetal heart motion with an embryonic pole or crown-rump length of at least 5 mm, or the absence of growth over time of a smaller embryo [20].

Clinical diagnosis

The clinical stage of the spontaneous abortion process is described according to the presence or absence of symptoms at the time of presentation, the degree of cervical dilation, and the amount of tissue already passed [21] (Fig. 17.1). Mild bleeding with a closed cervix is prevalent in early pregnancy. In a woman with a positive pregnancy test, this clinical picture is often called *threatened abortion* in the absence of sonographic findings.

If history, examination, or sonogram indicates that the patient has passed tissue, then the diagnosis is either *incomplete abortion* or *complete abortion* depending on the amount of residual tissue in the uterus. No single objective standard differentiates these two entities, and the decision to intervene on clinical grounds often results in a patient receiving a diagnosis of incomplete abortion regardless of whether retained products of conception are present. If the cervix is dilated, contractions are in progress, and no tissue has yet passed, then the clinical diagnosis is imminent or *inevitable abortion*.

The distinctions among these diagnostic subgroups may guide treatment options, and they are generally needed for the purposes of coding and reimbursement in the USA. For instance, the term *missed abortion* is clinically outdated, but it may be the best diagnosis code for an asymptomatic woman with an anembryonic pregnancy or embryonic demise by sonogram. No data indicate that these clinical diagnostic distinctions are useful to ascribe etiology.

The time of diagnosis tends to occur later in women whose early pregnancy loss is diagnosed only with the advent of pain and bleeding; it occurs sooner in women who undergo a routine, early first-trimester sonogram, whether for dating or for first-trimester screening.

Management of early pregnancy loss

Spontaneous loss of a desired pregnancy is emotionally distressing for the woman and her partner. Health care personnel can help these patients and their families by showing empathy and support at all times. Women carrying undesired pregnancies may feel relieved that the loss occurred

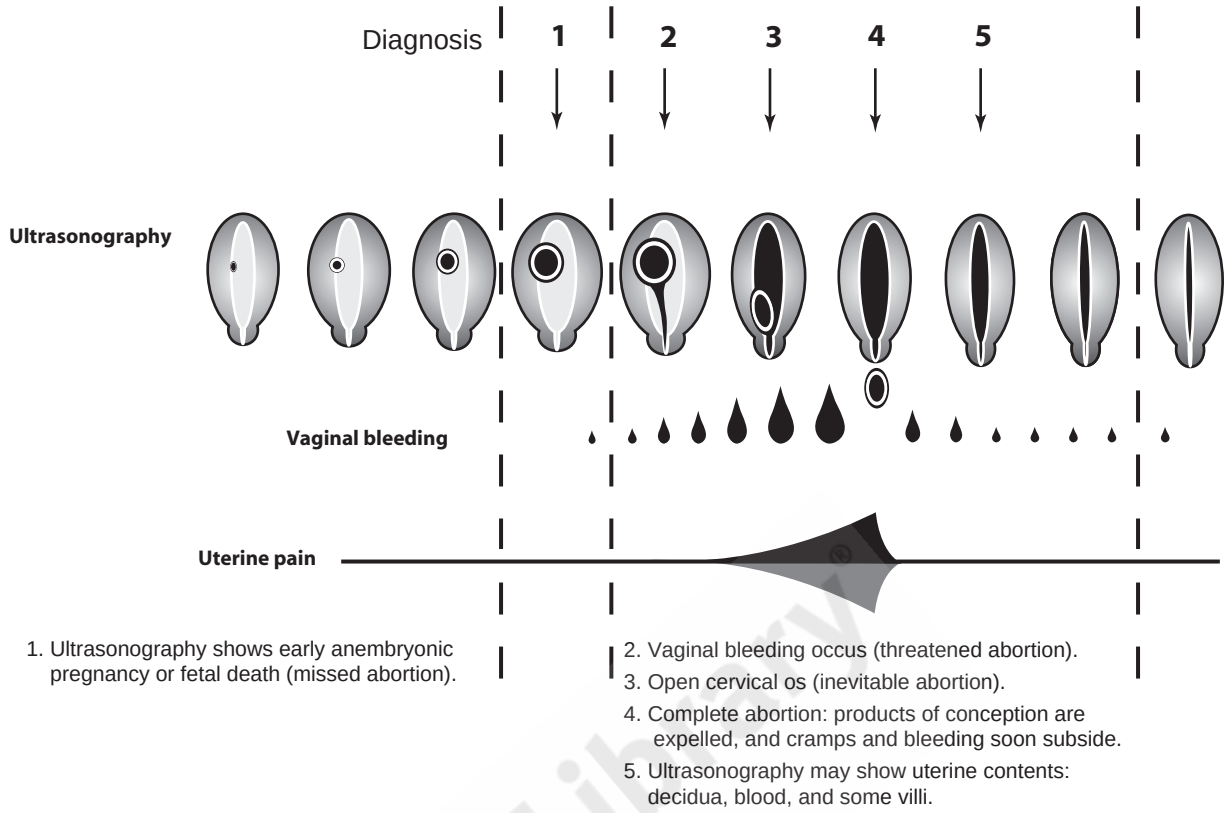

Figure 17.1 Natural course of spontaneous abortion (miscarriage) with opportunities for intervention. (Adapted and reprinted with permission from Ankum et al [21].)

spontaneously, avoiding the need for an induced abortion. Alternatively, some women make the decision to terminate their pregnancy, present for an induced abortion, and are diagnosed with a pregnancy loss incidentally on ultrasound. The provider should inform such patients of the diagnosis, as it may alter their preference for management and their insurance coverage for the procedure. Likewise, equivocal findings should be explained. Anecdotally, most women choose to proceed with the induced abortion as originally planned without a definitive diagnosis, but some women prefer to obtain a follow-up ultrasound for confirmation.

Once the diagnosis of pregnancy loss is established, the clinician should discuss management options with the patient. Options include expectant, medical, and surgical management. A patient in the first or second trimester who is clinically stable with no evidence of hemorrhage or infection does not require immediate uterine evacuation and should be given adequate time to consider her options. When faced with a pregnancy loss, some women request immediate uterine evacuation and others prefer to wait until they feel emotionally ready or can obtain another medical opinion. Patient preference deserves strong consideration when selecting a management option. A study of quality-of-life outcomes found that women managed according to their preference had the best outcomes [22]. The effectiveness of treatment plans, medication-dosing regimens, surgical techniques, and risk of complications vary by gestation. Women who are Rh(D) negative and have had any bleeding during the current pregnancy should receive anti-D immune globulin at the time of their initial assessment. Rh(D)-negative women with no bleeding should receive anti-D immune globulin when they initiate treatment.

Management of first-trimester pregnancy loss

For more than 60 years in the USA, dilation and curettage (D&C) with either a sharp or vacuum curette has been the treatment of choice for early pregnancy loss [23]. As is still the case in some countries with restrictive abortion laws, universal D&C was adopted in the USA to prevent hemorrhage and sepsis in an era when abortion was illegal; antibiotics, synthetic prostaglandins, and ultrasound were unavailable; and a large proportion of women presenting with presumed complications of spontaneous pregnancy loss actually had undergone clandestine and unsafe induced abortions. Despite liberalization of abortion laws and numerous medical advances, routine curettage remains standard treatment for pregnancy loss in many places. Today in countries where abortion is legal, spontaneous abortions usually are truly spontaneous, and they are often diagnosed with ultrasound in asymptomatic women. Moreover, safer vacuum

aspiration methods and prostaglandin analogs such as misoprostol are increasingly available worldwide. In light of these changes, the ideal management of spontaneous pregnancy loss needs to be revisited.

Surgical management

Vacuum aspiration to evacuate a failed pregnancy in the first trimester is performed in a fashion similar to first-trimester pregnancy termination (Chapter 10). Clinicians can use either an electric vacuum source or a handheld manual vacuum aspirator (MVA). The procedure can readily be accomplished using local anesthesia or moderate sedation in an outpatient facility [24] except in certain cases of severe maternal disease or serious pregnancy-related complications (Chapter 7). Surgical management of EPF is the treatment of choice for women who present with heavy vaginal bleeding or signs of infection with possible retained tissue and for those in whom the diagnosis of ectopic pregnancy cannot be excluded. If ultrasound fails to confirm an intrauterine pregnancy prior to uterine evacuation, villi are not identified after uterine aspiration, and serial hCG levels are not falling appropriately, the patient warrants treatment for ectopic pregnancy (Chapter 18).

Although 95% of induced abortions in the USA occur in freestanding clinics or physicians' offices [25], studies from Europe and North America suggest that spontaneous abortions are commonly managed in hospitals with suction curettage in an operating room [26–28]. Data have confirmed the safety of induced abortions performed in nonhospital settings [29], and no evidence suggests that different scenarios are medically necessary for the two conditions [26]. Moreover, one study found that MVA in an outpatient setting using local anesthesia or moderate sedation saved a significant amount of time and money compared to suction curettage in a hospital operating room [30]. A recent study evaluated the treatment preferences and satisfaction of women with EPF who chose between suction curettage in an office or operating room setting. Many women expressed strong preferences, and the priorities of the women differed. Women who preferred the office setting regarded privacy and a desire to avoid drugs and remain awake as highly important. Satisfaction was high in both groups, although underestimating the amount of discomfort of procedures performed without intravenous sedation or general anesthesia was associated with lower levels of satisfaction in the office group. Women in the operating room group were four times more likely to have hemorrhage-related complications, which the authors attributed to use of halogenated gases for general anesthesia [31].

Expectant management

Although suction curettage for first-trimester pregnancy loss is an extremely safe procedure, it may not be necessary in all cases. In a large observational study, 686 women with a failed early pregnancy or incomplete abortion chose between expectant management and suction curettage under general anesthesia. The 478 (70%) women who chose expectant management were followed for 4 weeks, or longer if they requested extended observation, to determine if they completely expelled the products of conception without requiring curettage. Women who initially presented with an incomplete abortion were the most likely to have complete expulsion. Regardless of initial diagnosis, success rates improved the longer women waited before intervention [32] (Table 17.1). Because spontaneous abortion is a physiologic process that often begins with abnormal embryonic development or demise and then progresses with cervical softening, bleeding, uterine contractions, and expulsion, it makes sense that complete abortion rates are higher among those diagnosed later in the process and those given more time (Fig. 17.1).

Several randomized clinical trials have compared expectant management to suction curettage [33–37]. These studies demonstrated a wide range of efficacy of expectant management. Efficacy is influenced by the type of pregnancy failure at the time of initial diagnosis, the interval allowed

Table 17.1 Types of miscarriage and outcome in patients who chose expectant management. Values are numbers (percentages). (Reprinted with permission from Luise et al [32].)

		Complete miscarriage[a]		
Group classification at diagnosis	Patients	By day 7	By day 14	Successful outcome by day 46
Incomplete miscarriage	221 (49)	117 (53)	185 (84)	201 (91)
Missed miscarriage	138 (31)	41 (30)	81 (59)	105 (76)
Anembryonic pregnancy	92 (20)	23 (25)	48 (52)	61 (66)
Total	451 (100)	181 (40)	314 (70)	367 (81)

[a] No suction curettage performed.

Summary: Expectant Management of Early Pregnancy Loss

Based on the evidence to date, it appears that 7 to 14 days of expectant management can enable approximately 75 to 85% of women with an incomplete abortion and 30 to 60% of those with an embryonic demise to avoid suction curettage and its small surgical and anesthetic risks [32,39]. Expectant management is associated with more unscheduled curettages and more bleeding, but no increased risk of infection.

before intervention, and the criteria used for intervention. Specifically, many studies of expectant management routinely performed suction curettage for all women who were noted to have an endometrial thickness on ultrasound greater than 15 mm after a given time interval, including those who were asymptomatic. This practice has likely inflated the published failure rates of expectant management. Nonetheless, these studies consistently showed that expectant management is less effective at achieving complete emptying of the uterus than suction curettage, but most did not observe an increase in complications. A Cochrane review, which included randomized trials conducted through 2005 enrolling a total of 689 women, concluded that expectant management is associated with an increased risk of incomplete abortion (RR 5.37; 95% CI 2.57, 11.22), more unscheduled curettages (RR 4.78; 95% CI 1.99, 11.48), and more bleeding than surgical management, but a decreased risk of infection (RR 0.29; 95% CI 0.09, 0.87) [38]. Most of the trials of expectant management either made no mention of prophylactic antibiotics or reported that they were not used. The Miscarriage Treatment (MIST) trial, a recent randomized trial designed specifically to compare rates of infection among 1,200 women allocated to expectant, medical, or surgical management, found no difference in infection rates among the three groups. No prophylactic antibiotics were used in this study. Significantly more women in the expectant management group required transfusions ($n = 7$, 2%) compared to those in the surgical management group ($n = 0$). Transfusion rates in the medical and surgical management groups did not differ significantly [39].

Medical management

Although expectant management of first-trimester pregnancy loss expands women's treatment options, some women may find the uncertainty about the timing and completeness of pregnancy passage undesirable. Active management with medications gives women more control over the process and may help to avoid surgical intervention.

Mifepristone, an anti-progesterone, and misoprostol, a prostaglandin E1 analog, have been studied extensively for use in early medical abortion. When used in combination, these drugs are highly effective at terminating a pregnancy up to 63 days' gestation (Chapter 9). These same drugs have been studied for treatment of first-trimester pregnancy loss, as has the combination of methotrexate and misoprostol. However, the US Food and Drug Administration (FDA) has not evaluated these medications for this purpose.

Researchers have evaluated mifepristone on its own as treatment for first-trimester pregnancy failure. In a randomized trial, a single 600-mg oral dose led to complete tissue passage for 77% of subjects within 5 days, performing significantly better than the placebo [40]. Medication abortion studies using mifepristone and misoprostol have demonstrated no change in efficacy when mifepristone doses are reduced from 600 to 200 mg [41]. This finding appears to apply to spontaneous abortions as well [42].

Because medical management of spontaneous abortion relies more on uterine expulsion than interruption of an ongoing pregnancy, the mifepristone dose may not be necessary at all. A nonrandomized trial compared the combination of mifepristone and vaginal misoprostol with the same misoprostol dose used alone. The two groups had similar success rates (71 to 74%) [43]. A recent randomized trial comparing misoprostol alone to mifepristone plus misoprostol for EPF also found no difference in success rates with the addition of mifepristone [44]. Similarly, misoprostol combined with methotrexate is no better than misoprostol alone in managing a failed early pregnancy [45]. Whereas adding mifepristone improves the efficacy of medical abortion with misoprostol (Chapter 9), the limited evidence to date suggests that adding mifepristone or methotrexate does not improve the efficacy of misoprostol alone when used for spontaneous abortion. For unclear reasons, success rates for the medical management of EPF remain substantially lower than those reported for medical abortion, regardless of regimen used.

Misoprostol compared to suction curettage

A number of trials have compared misoprostol to suction curettage for the management of failed early pregnancy. These trials have shown success rates of 50 to 90% for women treated medically and 91 to 100% for those treated with electric or manual vacuum aspiration (i.e., no unplanned, repeat procedures) [20,39,46–53]. Although fewer subjects receiving misoprostol achieved success with initial therapy, most were ultimately able to avoid a surgical intervention.

Numerous factors may account for the wide range of success rates with misoprostol, including dose, route of administration, type of spontaneous abortion, definitions of success, indications for suction curettage, and duration of follow-up before surgical intervention. Studies have shown that 800 μg of vaginal misoprostol is more effective than 600 μg given by the same route [54] or 400 μg given orally [55]. Two studies comparing the 800-μg vaginal dose to the same dose given orally showed no difference in effectiveness, with the vaginal route producing more vomiting [56] and the oral

dose producing more diarrhea [57]. Adequate duration of follow-up before surgical intervention may be more important than misoprostol dose. Completion rates were 50 to 60% when researchers offered surgical management 1 to 3 days after treatment [47,52,53] versus 70 to 90% when researchers waited 1 to 2 weeks before considering suction curettage [20,39,46,48,49].

Criteria for surgical intervention also matter. Some researchers intervened when endometrial thickness by ultrasound passed a set cutoff value, whereas others did so only if the gestational sac had failed to pass. One trial using a 15-mm endometrial thickness cutoff found a success rate of only 28% after one misoprostol dose, and 53% after two doses [52]. Alternatively, the MEPF trial, which used a 30-mm endometrial cutoff and 8 days of follow-up, achieved an 84% success rate [20]. In that study, endometrial thickness was a poor predictor of the need for curettage [58]. Medical abortion studies have similarly shown that the only important criterion for determining success of the procedure is passage of the gestational sac (Chapter 9). Although women who ultimately require curettage have a thicker endometrial stripe on average than those who do not, endometrial thickness on ultrasound is a poor predictor of the need for curettage [59].

Efficacy also may vary with type of pregnancy failure. The MEPF trial analyzed success rates by diagnosis and found significantly lower success rates with anembryonic gestations (81%) than with embryonic/fetal deaths or incomplete abortions (88 and 93%, respectively) [20]. Incomplete abortions, which begin spontaneously and are near completion, may have the highest success rates with medical management. Trials specifically looking at the medical management of incomplete abortions show success rates of 80 to 96% [39,46,48,49]. Reported success rates are lower if women with incomplete abortions are allowed only 1 to 3 days to pass retained tissue before surgical intervention (50 to 71%) [39,47]. Other predictors of success with medical management of early pregnancy failure include spontaneous vaginal bleeding within the 24 hours preceding misoprostol use and parity less than two [60].

Most studies found increased bleeding [39,46–49,61] or a larger drop in hemoglobin concentration [53,61] with misoprostol than with surgical therapy, but the clinical significance of this difference has been questioned. In the MEPF study, the average drop in hemoglobin was only 0.5 g/dl greater for those in the medical group than the surgical group; however, more medically treated women dropped their hemoglobin by more than 3 g/dl or reached a nadir more than 10 g/dl from their baseline. Additionally, more women in the misoprostol group found their bleeding unacceptable (12% vs. 5% in the surgical group) [61]. The MEPF and the MIST trials as well as others found that women treated with misoprostol had more days of bleeding than those treated surgically [39,46].

The MEPF and MIST trials found no significant difference in infection rates when comparing misoprostol to surgical management [20,39]. Other studies have found higher rates of antibiotic use and infection in the subjects randomized to surgical therapy [47,48].

Studies have shown variable results regarding pain. Some studies found that subjects in the misoprostol groups required more analgesia than those in the surgical groups [20,47,52], whereas others have shown the opposite [48,49]. The choice of analgesia used during the surgical procedure likely influences these results.

Misoprostol can produce gastrointestinal side effects, such as nausea and diarrhea. These side effects occur more frequently with oral or sublingual misoprostol than with vaginal administration [57,62,63]. When compared to surgical management, trials have shown higher rates of gastrointestinal side effects in women using oral or vaginal misoprostol [47,49]. The MEPF trial found that, compared to those having surgery, significantly more subjects receiving vaginal misoprostol experienced nausea (53% vs. 29%), vomiting (20% vs. 7%), and diarrhea (24% vs. 10%) [20].

Misoprostol compared to expectant management

A number of trials have compared misoprostol to expectant management for first-trimester pregnancy loss. In cases of early demise or anembryonic gestation, all trials showed that misoprostol was superior to no therapy or placebo, with success rates of 72 to 83% at 1 to 2 days of follow-up for the misoprostol groups versus 12 to 17% with placebo [64–66]. A longer, 7-day follow-up period increased success rates to 87% for misoprostol and 29% for placebo [67]. In contrast, several studies specifically looking at incomplete abortion did not show an advantage to misoprostol over expectant management. The 70 to 100% success rates for the misoprostol groups did not differ significantly from the 75 to 86% success with 7 to 14 days of expectant management [39,67,68]. However, a meta-analysis comparing the efficacy of expectant, medical, and surgical management of first-trimester spontaneous abortion suggests that medical management is more effective than expectant management for incomplete abortion [69]. Additionally, an expert panel suggests that medical management is a reasonable option for women with an incomplete abortion who prefer immediate treatment and wish to avoid surgery [70].

Most studies found no differences in bleeding between misoprostol treatment and expectant management [39,54,66,67]. In the MIST study, seven transfusions occurred in the expectant group, three in the medical group, and none in the surgical group. This difference was only statistically significant when comparing expectant to surgical management [39]. Two small studies found more fever or infection with misoprostol use than with expectant management [54,68]; whereas the MIST study, designed to look at

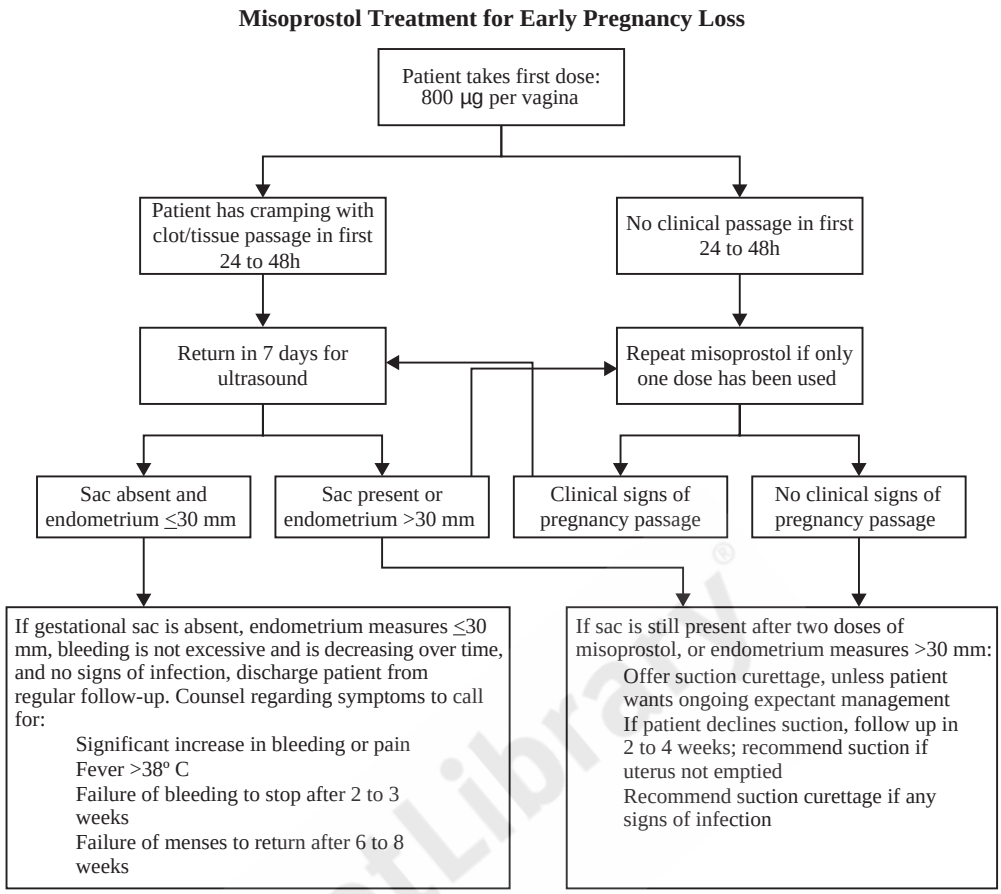

Figure 17.2 Algorithm for the use of misoprostol for management of early pregnancy loss.

infectious complications, found no difference with medical, surgical, or expectant management [39].

Management of second-trimester pregnancy loss because of fetal demise

Most patients diagnosed with a fetal death in the second trimester prefer active management because carrying a demised fetus, especially late in gestation, is stressful [17]. However, in a hemodynamically stable patient with no evidence of infection, uterine evacuation is not urgent. Patients with fetal demise should be given adequate time to process the diagnosis and consider their management options.

A study from the early 1960s suggested that 80 to 90% of women with fetal death spontaneously labored within 2 weeks of the fetal demise [71]; however, a recent expert opinion suggests that the interval may be considerably longer [17]. We could not identify any recent studies specifically evaluating expectant management of fetal demise in the second trimester. Potential risks of expectant management include delivery outside of a clinical setting, hemorrhage from maternal coagulopathy, and infection.

Summary: Medical Management of Early Pregnancy Loss

Available data indicate that 60 to 90% of patients who prefer to avoid surgical management may be able to do so with misoprostol. Based on studies in a large number of subjects, the best dose to maximize effectiveness and minimize side effects among women with an anembryonic pregnancy or embryonic demise is 800 μg per vagina, with the possibility of repeating the dose in 24 hours (Fig. 17.2). For women with an incomplete abortion and no evidence of infection, expectant management is a highly effective and reasonable option. Women with an incomplete abortion who prefer active management can receive an 800-μg vaginal dose or a 600-μg oral dose of misoprostol [70]. Success is further optimized by allowing at least 1 week before diagnosing a treatment failure and avoiding surgical intervention as long as the gestational sac has passed. In the absence of a gestational sac, decisions for surgical intervention should be made on clinical grounds (e.g., heavy or persistent bleeding or clinical infection with concern for retained products of conception). Although misoprostol therapy is consistently superior to expectant management in the case of early fetal/embryonic death or anembryonic gestation, it offers less benefit in cases of incomplete abortion where expectant management is highly effective.

Older studies reported a 25% rate of coagulopathy among women with fetal demise for more than 4 weeks [17]. More recently, of 238 women with IUFD, most were delivered within 1 week of the demise and 3% of women with no co-existing obstetric disease had coagulation abnormalities. Pregnancy-related conditions, especially abruption and uterine perforation, were associated with an increased risk of coagulation abnormalities [72]. Whether uterine evacuation of a recently demised fetus carries an increased risk of hemorrhage and DIC compared to induced abortion at a similar gestational age is unknown. In cases of fetal demise, some providers recommend preprocedure laboratory evaluation for coagulation defects (platelet count, prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]).

Women desiring active management of an IUFD in the second trimester are generally managed either with D&E in locations where providers with the requisite skills are available or by induction of labor, often with misoprostol.

Surgical management

D&E for the indication of fetal demise is performed in the same way as D&E for second-trimester pregnancy termination (Chapter 11). Long-standing demise may make fetal tissue softer and easier to remove. Complications include hemorrhage, infection, retained tissue requiring reevacuation, cervical laceration, and uterine perforation (Chapter 15). Similar to cases of second-trimester induced abortion, the risk of serious complications is low but increases with advancing gestational age.

No epidemiologic evidence suggests that amniotic fluid embolism (AFE) is more likely to occur with uterine evacuation of a demised fetus than with induced abortion at a comparable gestational age. This extremely rare complication was primarily associated with older uterine instillation methods for abortion [73], but a few cases of AFE have been reported in women having second-trimester D&Es for fetal demise [74, 75]. The incidence of AFE in the second trimester is unknown but is likely lower than in the third trimester. A population-based study of singleton births in California from 1994 to 1995 reported an incidence of AFE of 1 in 20,646 with a 26% maternal mortality [76].

A variety of infections can cause fetal death. However, aside from cases of septic abortion, we could find no evidence suggesting that D&E performed for IUFD is associated with any higher risk of endometritis or sepsis than D&E performed for induced abortion. Similarly, no data have compared the infection rates associated with modern methods of labor induction and those associated with D&E when used for the management of IUFD.

The possible increased risks of hemorrhage, DIC, and maternal death with late second-trimester fetal demise warrant consideration as to the ideal location for managing these patients. Women faced with fetal demise often have an option for hospital-based care that patients having induced abortions may not. However, many hospitals have no provider of D&E services, leaving only the option of induction of labor. Because the absolute risks of major complications using modern D&E or induction techniques for fetal demise are not known, evidence to guide recommendations is lacking. Providers should consider the facility's capacity to manage complications and the proximity to emergency referral resources when making decisions about the appropriate setting.

Medical management

Many women with fetal demise undergo labor induction rather than surgery. Labor-induction procedures commonly take place in hospital settings, where patients can be monitored for heavy bleeding or fever, receive analgesics and antiemetics as needed, and undergo surgical removal of the placenta if required. As with other labor inductions, medication choices include oxytocin, PGE_2 (dinoprostone or sulprostone), or misoprostol, although higher doses are often required in the second trimester compared to later in gestation.

Regimens are well defined for second-trimester medical abortion (Chapter 12). The FDA has approved use of dinoprostone vaginal suppositories for second-trimester labor induction. Among patients undergoing induced abortion or treatment of fetal demise, a 20-mg dose of PGE_2 was no more effective than 10 mg followed by high-dose oxytocin. Patients receiving the higher dose experienced more fever and vomiting, and one case of hypotension and two cases of refractory fever occurred in this group [77]. Dinoprostone is a relatively expensive drug that requires refrigeration, limiting its practicality for this indication.

Numerous studies have confirmed the safety and efficacy of misoprostol for labor induction, although FDA labeling for misoprostol does not include this indication. Misoprostol's low cost and stability at room temperature make it a popular option for this purpose. When compared to oxytocin regimens, misoprostol resulted in faster delivery times and higher rates of complete abortion within 24 hours (>90% success vs. 62 to 85%). These studies included patients with both ongoing pregnancies and demised fetuses, and they used 400 μg of misoprostol orally every 4 hours [78] or a 600-μg vaginal loading dose followed by 400 μg vaginally every 4 hours [79]. When given at a lower dose less frequently, 200 μg every 12 hours, misoprostol was inferior to high-dose oxytocin [80].

Misoprostol appears equivalent to dinoprostone when using doses of 600 μg vaginally every 12 hours or a 600-μg vaginal dose followed by 400 μg orally every 12 hours [81]. Equivalence to PGE_2 has been demonstrated with misoprostol doses as low as 100 to 200 μg vaginally every 12 hours [82], with the advantage of producing less severe pain, fever, and vomiting [83]. Using 100 μg of misoprostol vaginally

every 4 hours may be more effective than PGE_2, although in one study this regimen was associated with more bleeding and incomplete expulsion [84].

These trials combined women undergoing induced abortion and those with fetal demise. However, studies comparing these two groups have consistently shown faster induction to delivery times in cases of fetal demise. Both PGE_2 [83,85,86] and misoprostol demonstrate mean delivery times of 10 to 13 hours with fetal demise [83,87–90]. Other studies have shown that the misoprostol dose can be lowered in cases of fetal demise. For induced abortions, a dose of 400 μg per vagina every 6 hours is more effective than 200 μg by the same route every 6 or 12 hours [87,91], or 400 μg given orally every 6 hours [92]. In cases of fetal demise a dose of 200 μg vaginally every 6 hours appears as effective as the 400-μg dose [87,91].

Dosing interval may be important in accelerating uterine evacuation. Studies of labor induction for fetal demise that used 100 to 200 μg of misoprostol every 12 hours showed a wide range of 24-hour completion rates, with some studies reporting rates under 80% [82,91,93] and others 92 to 94% [94,95]. Studies that compared twice-daily to more frequent dosing found higher 24-hour completion rates when doses were given every 4 to 6 hours, but similar completion rates at 48 hours [91,93].

As with first-trimester misoprostol studies, research protocols for second-trimester induction are heterogenous. In some studies, researchers place laminaria tents within the cervix prior to administering the study drugs [79,80]. However, one trial showed that placing laminaria at the time of the first vaginal dose of misoprostol added no benefit [96], while another found slower induction to delivery times [97]. Outside of the USA, mifepristone is used extensively in combination with misoprostol for second-trimester induction abortion, resulting in higher efficacy and shortened induction-to-abortion intervals compared to using misoprostol alone (Chapter 12). A small trial that included women with fetal demise compared mifepristone to laminaria given 1 day before second-trimester induction of labor with misoprostol. This study found a shorter induction-to-delivery time with mifepristone [98]. Studies vary in terms of giving oxytocin routinely [81,83], and many studies combine second- and third-trimester inductions [82,93,94]. Despite this heterogeneity, most trials of misoprostol for labor induction for fetal demise show mean induction-to-delivery intervals of 10 to 16 hours [82,83,86–88,90,93,99,100], and completion rates of 80 to 100% within 24 hours [86,88,90,91,93,100,101].

The American College of Obstetricians and Gynecologists (ACOG) discourages use of misoprostol when a patient has a scarred uterus and a viable fetus [102]. Studies of second-trimester induction of labor with misoprostol have included women with a uterine scar, as the smaller uterus is likely to confer less risk of rupture. Although a few case reports have described uterine rupture with second-trimester use of misoprostol [82,91], uterine rupture can occur with oxytocin as well [103,104]. Dickinson retrospectively reviewed 101 cases of second-trimester misoprostol use in women with prior cesarean sections. No cases of uterine rupture occurred, and the frequency of major complications or blood loss was not increased when compared to women with an unscarred uterus [105].

Summary: Medical Management of Fetal Demise

Based on the evidence to date, a recent expert panel recommends using 200 μg of misoprostol vaginally every 6 hours for women with IUFD at 13 to 17 weeks' gestation (maximum daily dose 1600 μg), 100 μg of misoprostol vaginally every 6 hours for women with IUFD at 18 to 26 weeks' gestation (maximum daily dose 800 μg) and 25 to 50 μg of misoprostol every 4 hours for women with IUFD from 27 to 43 weeks' gestation (maximum daily dose 600 μg). If the first dose does not induce regular contractions, the next dose may be doubled. Women with previous cesarean sections should receive lower range doses of misoprostol, and doses should not be doubled [106]. Pretreatment with mifepristone appears beneficial. Patients who have uterine scars should be counseled about the rare risk of uterine rupture, which could potentially occur with any medical induction method.

D&E compared to induction of labor for fetal demise

We could identify no studies that specifically compared the relative safety of induction of labor using misoprostol with D&E in cases of fetal demise. One recent observational study found a higher rate of retained placenta with misoprostol induction abortions than D&E techniques [107]. In this study, which included women with IUFD, patients undergoing labor induction were at increased risk of induction failure or retained tissue requiring curettage. The authors found no significant increased risk of transfusion, intravenous antibiotics, cervical laceration, organ damage, or hospital readmission. However, the only two cases of major organ damage requiring repair occurred among women with failed medical inductions: one woman with a prior cesarean scar experienced uterine rupture, and another had a uterine perforation on rescue D&E.

Evaluation of second-trimester fetal loss

For patients who desire future pregnancy, a single second-trimester fetal death should prompt a fetal karyotype analysis, inspection of the fetus for abnormalities, and placental pathologic analysis [108]. Confirmation of a chromosomal problem may reduce the need for other testing. Obtaining a full karyotype of the pregnancy requires recovery and culture of embryonic tissue or chorionic villi. The cells will grow in culture only if sent as a fresh specimen (not in formalin); even fresh specimens will fail to grow in culture approximately 5% of the time [109]. If cells fail to grow

in culture, then the florescence *in situ* hybridization (FISH) test can be performed. With FISH testing, probes for select chromosomes enable identification of the number of those chromosomes per cell. The test does not screen for all chromosomal abnormalities; however, by selecting the chromosomes most commonly associated with pregnancy loss, approximately 80% of aneuploid pregnancies can be identified [110]. No studies have specifically compared the success of cell culture with specimens obtained surgically versus those passed spontaneously. Fresher specimens, cultured soon after removal or expulsion from the uterus, may yield better cell growth.

Autopsy of medically delivered intact fetuses has been shown to alter the final diagnosis and patient counseling in 27% of cases with normal chromosomes [111]. Induction of labor and often intact D&E (Chapters 11 and 20) enable removal of an intact fetus for inspection and grieving purposes. Evidence of placental infarction may warrant maternal thrombophilia and antiphospholipid antibody screening. Infectious and toxicology screening may depend on maternal clinical status and fetal and placental pathology [17].

Septic abortion

Women having a spontaneous abortion who are hemodynamically unstable or have signs of sepsis, including high fever and white blood cell count, altered mental status, hypovolemia, hypotension, or tachycardia, should receive broad-spectrum intravenous antibiotic therapy and undergo prompt uterine evacuation. Patients who fail to respond to these measures or those with an acute abdomen may require laparotomy and possible hysterectomy. In these severe cases, the diagnosis of clostridial sepsis should be considered. Cases of *Clostridium sordellii* sepsis have been reported after both spontaneous and medically induced abortions [112]. Management of clostridial sepsis is similar to management of septic abortion from other pathogens, although patients may have a greater need for hysterectomy and a worse prognosis (Chapter 15).

Women presenting with spontaneous abortion without sepsis but with signs of infection including abdominal pain, fever, uterine tenderness, and/or abnormal bleeding should receive broad-spectrum antibiotics. In addition, uterine evacuation is warranted for women with suspected retained products of conception. It also should be considered when sonography suggests no retained products but the patient fails to respond quickly to broad-spectrum antibiotics alone [113]. Parenteral antibiotic regimens recommended by the CDC for the treatment of pelvic inflammatory disease are appropriate [114].

Although two randomized trials comparing doxycycline to placebo for prophylaxis prior to suction curettage for incomplete abortion showed no reduction in infection with doxycycline, multiple trials and a meta-analysis indicate that universal antibiotic prophylaxis reduces the risk of postabortal infection after surgical abortion (Chapters 14 and 15). No evidence to date supports the routine use of prophylactic antibiotics in cases of expectant or medical management of pregnancy loss.

Counseling, education, and consent for patients with pregnancy loss

Counseling patients with pregnancy loss includes focusing on their emotional needs, treatment options, and their desire for future pregnancies. The loss of a wanted pregnancy often exacts a high emotional toll. In such cases, providers can acknowledge the sadness of the loss, the prospects of attempting another pregnancy, and the improbability that the woman's own behavior caused the loss. The counselor should obtain a pregnancy history, as prior live births or losses may affect the patient's perspective as well as her odds of complications in the future.

In order to give informed consent, patients must understand the risks and benefits of each treatment alternative and have ample opportunity to ask and receive answers to their questions (Chapter 5). Given that the risks of suction curettage are similar when performed for pregnancy loss or induced abortion, many providers use similar consent forms for surgical management regardless of diagnosis. Unlike for induced abortion in the USA, no state mandates special consent forms for management of fetal demise; however, procedures and consent for disposal of the products of conception may differ by state.

For medical management of spontaneous abortion, important risks to discuss include bleeding, infection, incomplete uterine evacuation, and failure of the treatment requiring vacuum aspiration. With up to two vaginal doses of 800-μg misoprostol, failure rates after first-trimester medical management are approximately 15% if patients wait at least 1 week to pass the pregnancy [20,56,67]. With second-trimester misoprostol treatment, at least 85% of patients will pass the pregnancy within 24 hours [91,99,101], and 90 to 100% will do so within 48 hours [82,90,93].

Other factors may also influence the choice of management options. In the first trimester, medical management allows a patient to complete expulsion in the privacy of her own home, usually avoiding surgical risks. However, she must be prepared to bleed more heavily than she might with surgical management [47,61] and to self-treat any pain or cramping. Patients using home medical management must have access to a telephone and transportation, if needed for emergency care.

In the second trimester, available medical resources may limit a woman's options. Many hospital facilities do not have skilled surgical abortion providers on-site, so labor induction is the only alternative. Medical treatment may be preferred by patients who desire comprehensive fetopsy as part of the

evaluation for fetal demise or who simply prefer to deliver an intact fetus. Furthermore, some patients may wish to see or hold their fetus for grieving purposes. Intact D&E (Chapter 11) also may have these advantages. Because intact D&E depends on achieving adequate cervical dilation, however, not all procedures result in an intact fetus even in the most experienced hands. Counselors need to explain these benefits and limitations before the patient decides on a treatment method.

Follow-up

Some evidence suggests that routine follow-up is not necessary for many women after uncomplicated first-trimester induced abortion [115], but the same may not hold true for women experiencing loss of a desired pregnancy. Studies suggest that after a spontaneous abortion, many women appreciate the opportunity to follow up with their care provider to have their loss acknowledged and their grief legitimized and to have the opportunity to discuss possible underlying etiologies and the risk of recurrence [116,117].

Conclusion

Pregnancy loss is a common condition that requires adept management by practitioners of women's health care. Diagnosis can be made clinically or more precisely using ultrasonography. Early pregnancy failures can be managed expectantly, with medication, or surgically. Expectant management is a safe option for clinically stable women with incomplete abortions. Medical management with misoprostol allows most women with early pregnancy failure to complete their abortion and avoid surgery. Vacuum aspiration remains the most effective and efficient way to ensure complete uterine evacuation, and it can be accomplished easily in the outpatient setting using manual or electric suction devices. Management options for second-trimester fetal demise include labor induction or D&E where clinicians with the requisite skills are available. Patients experiencing loss of a desired pregnancy benefit from a follow-up visit to acknowledge the loss and discuss its implications. Those desiring pregnancy and experiencing multiple early losses or a second-trimester loss may benefit from referral to counselors or specialists to address their complex needs.

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