Chapter 2
Early Pregnancy Loss

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Introduction

Pregnancy is a significant event in a woman's life, and emotional attachment to the pregnancy and developing baby may begin early in the first trimester. For most women, experiencing a first trimester loss is a difficult and vulnerable time. When it occurs, the grief can be as profound as for any perinatal or other major loss [1]. Spontaneous abortion (a pregnancy that ends spontaneously before the fetus has reached a viable gestational age) is among the most common complications of pregnancy. Approximately 12–15% of recognized pregnancies and 17–22% of all pregnancies end in spontaneous abortion [2, 3].

The best-documented risk factors for spontaneous abortion are advanced maternal age, a previous spontaneous abortion, and maternal smoking. Most spontaneous abortions are attributed to structural or chromosomal abnormalities in the embryo.

Stages and Types of Spontaneous Abortions

There are various stages and types of spontaneous abortions (threatened, inevitable, incomplete and complete abortions, missed abortion, and fetal/embryonic demise). These types are clearly defined.

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- *Spontaneous abortion/miscarriage*: A pregnancy that ends spontaneously before the fetus has reached a viable gestational age. The World Health Organization defines it as expulsion or extraction of an embryo or fetus weighing ≤500 g (typically corresponds to a gestational age of ≤22 weeks).
- *Threatened abortion*: Bleeding through a closed cervical os during the first half of pregnancy. The bleeding is often painless, although it may be accompanied by mild suprapubic pain. On examination, the uterine size is appropriate for gestational age, and the cervix is long and closed. Fetal cardiac activity can be detectable if the gestation is sufficiently advanced.
- *Inevitable abortion*: When abortion is pending, there may be increased bleeding, intensely painful uterine cramps, and a dilated cervix. The gestational tissue can often be felt or visualized through the internal cervical os.
- *Incomplete abortion*: When the fetus is passed, but significant amounts of placental tissue may be retained, also called an abortion with retained products of conception (RPOC) (commonly occurs after 12 weeks' gestation). On examination, the cervical os is open, gestational tissue may be observed in the vagina/cervix, and the uterus is smaller than expected for gestational age but not well contracted. The amount of bleeding varies but can be severe enough to cause hypovolemic shock. Painful cramps are often present.
- *Complete abortion*: When an abortion occurs (usually before 12 weeks of gestation) and the entire contents of the uterus are expelled. More than one-third of all cases are complete abortions. If a complete abortion has occurred, the uterus is small and well contracted with a closed cervix; slight vaginal bleeding and mild cramping can be present.
- *Missed abortion*: Refers to in utero death of the embryo or fetus prior to the 20th week of gestation, with prolonged retention of the pregnancy (4–8 weeks). Vaginal bleeding may occur, and the cervix is usually closed.
- *Septic abortion*: An abortion accompanied by fever, chills, malaise, abdominal pain, vaginal bleeding, and frequently purulent discharge. Physical examination may reveal tachycardia, tachypnea, lower abdominal tenderness, and a tender uterus with dilated cervix. Infection is usually due to *Staphylococcus aureus*, Gram-negative bacilli, or some Gram-positive cocci. Mixed infections (anaerobic organisms and fungi) can also be encountered. The infection may spread, leading to salpingitis, generalized peritonitis, and septicemia.

Caution Box

- In a patient who presents with vaginal bleeding and abdominal or pelvic pain, although normal and abnormal intrauterine pregnancies are more common, ectopic pregnancy and gestational trophoblastic disease should always be ruled out.

Women with an active spontaneous abortion usually present with a history of amenorrhea, vaginal bleeding, and pelvic pain. The differential diagnosis includes bleeding related to implantation (physiological bleeding), ectopic pregnancy, gestational trophoblastic disease, and cervical, vaginal, or uterine pathology (see the relevant chapters). In addition to the physical examination, ultrasonography is the most useful test for diagnosing and evaluating women suspected of having a spontaneous abortion.

Etiology and Risk Factors

Many factors have been implicated as etiological or risk factors for spontaneous abortions. The most common cause is a genetic abnormality in the fetus, accounting for 50–76% of cases [4, 5]. Yet, a large proportion of spontaneous abortions can be explained by several other etiologies [6], including genetic, placental, and host factors.

In healthy women, maternal age is the most important risk factor for spontaneous abortion. In a large population-based study aimed to estimate the association between maternal age and fetal death (spontaneous abortion, ectopic pregnancy, stillbirth), 13.5% of pregnancies ended with fetal loss. At age 42 years, more than half of the pregnancies resulted in fetal loss. The risk of a spontaneous abortion was 8.9% among women aged 20–24 years and 74.7% among those aged ≥45 years. High maternal age was a significant risk factor for spontaneous abortion irrespective of the number of previous miscarriages, parity, or calendar period [7].

Chromosomal abnormalities account for more than 50% of spontaneous abortions. Most of these abnormalities are aneuploidies. Other abnormalities, such as structural abnormalities, mosaicism, and single gene defects, are responsible for relatively few abortions. The earlier the gestational age at the time of abortion, the incidence of cytogenic defects is higher.

Placental anatomical abnormalities are found in as many as two-thirds of early pregnancy failures. Anatomical evidence of defective placentation is characterized by a thin and fragmented trophoblast shell and reduced cytotrophoblast invasion of the lumen at the tips of the spiral arteries [8]. In most cases of miscarriage, these features are associated with premature maternal circulation throughout the placenta [9–11]. These findings are similar in euploid and most aneuploid abortions but are most profound in hydatiform moles.

Pregnancy losses may be related to the host environment. Congenital or acquired cervical and uterine abnormalities, infections, maternal endocrinopathies and a hypercoagulable state are some factors that have been implicated in the occurrence of spontaneous abortion.

- *Congenital or acquired uterine abnormalities* (i.e., septated uterus, submucosal myomas, intrauterine adhesions) can interfere with implantation and growth. In a recent review of the literature regarding fibroids and their effect on reproductive performance, the authors suggested that the best available evidence indicates that submucous myomas decrease fertility and increase the spontaneous abortion rate.

Myomectomy is likely to be of value. This may be true for intramural myomas as well [12].

- *Acute maternal infection* could lead to abortion due to fetal or placental involvement. Infections are an accepted cause of late fetal demise; therefore, it is logical that they are responsible for early fetal losses as well. A large number of organisms have been reported to be associated with spontaneous abortions including, among others, *Listeria monocytogenes*, *Parvovirus B19*, *Rubella*, *Herpes simplex*, *Toxoplasma gondii*, *Mycoplasma hominis*, *Chlamydia trachomatis*, and *Ureaplasma urealyticum.* However, evidence of this relation has not been extensively conformed [13].
- *Maternal endocrinopathies* such as poorly controlled diabetes mellitus [14] and thyroid dysfunction [15, 16] can contribute to a suboptimal host environment. Luteal phase defect is another condition that has been suggested to be associated with spontaneous miscarriage. A successful pregnancy is dependent on sufficient progesterone support. Before the placenta takes over progesterone production, the progesterone produced by the corpus luteum provides the necessary support of early pregnancy. A defect in corpus luteum function is associated not only with implantation failure but with miscarriage. However, the association between corpus luteum defects and miscarriage is controversial. Vitzthum et al. [17] showed that maternal serum progesterone levels around the time of implantation were similar for subsequently lost and ongoing pregnancies.
- *Hypercoagulable state* due to inherited or acquired thrombophilia and abnormalities of the immune system (i.e., systemic lupus erythematosus, antiphospholipid antibody syndrome) may lead to immunological rejection or placental damage and are accepted causes of miscarriage [18].
- *Additional factors* that are considered possible causes of spontaneous abortion include trauma; alloimmune disease; exposure to drugs, substance use, and environmental contaminants; some maternal illnesses; and psychological factors.

When the etiology of abortion in chromosomally and structurally normal embryos of women that are apparently healthy remains unclear, it is considered unexplained. A list of possible causes and risk factors for spontaneous abortions are presented in Table 2.1.

Diagnosis

Women with an active spontaneous abortion usually present with a history of amenorrhea, vaginal bleeding, and pelvic pain. On examination, the cervix is open, and the products of conception can be visualized in the vagina or cervical os if they have not already been passed.

An accurate diagnosis of early pregnancy loss is paramount for appropriately counseling patients about their pregnancy management options. Laboratory and ultrasonographic (US) evaluations are frequently used to diagnose early pregnancy loss.

Table 2.1 Possible causes and risk factors for spontaneous abortion

Embryonic/fetal factors
Chromosomal abnormalities
Other genetic abnormalities: mosaicism, single gene defects
Structural/morphological abnormalities
Placental factors
Placental anatomical abnormalities
Abnormal placentation
Uterine/cervical factors
Cervical os incompetence
Mullerian uterine abnormalities: septated uterus, unicoruate uterus, bicornuate uterus, uterus didelphys
Asherman's syndrome
Endometriosis
Fibroids: submucous and intramural
Maternal factors
Demographic factors: advanced maternal age, two or more previous miscarriages
Maternal illnesses: Wilson's disease, phenylketonuria, cyanotic heart disease, hemoglobinopathies, inflammatory bowel disease
Endocrinopathies: uncontrolled diabetes mellitus, abnormal thyroid function, luteal phase defect
Infection (maternal fever): colonization with *Listeria monocytogenes*, *parvovirus B19*, *rubella*, *herpes simplex*, *Toxoplasma gondii*, *Mycoplasma hominis*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and others
Hypercoagulable state, abnormalities of the immune system: inherited or acquired thrombophilia, APLA syndrome. systemic lupus erythematosus, alloimmune disease
Exposures
Substance use: caffeine, cigarette smoking, alcohol, cocaine
Drugs: NSAIDs, anesthetic gases
Environmental contaminants: lead, formaldehyde, herbicides, solvents, radiation
Other factors
Catastrophic physical trauma
Conception with an IUD
Psychological factors
Unexplained

APLA antiphospholipid antibodies, *NSAIDs* nonsteroidal antiinflammatory drugs, *IUD* intrauterine device

Common indications for US examinations during early pregnancy include vaginal bleeding, pelvic pain, and determination of gestational age [19].

In a patient who presents with vaginal bleeding and abdominal or pelvic pain, although normal and abnormal intrauterine pregnancies are more common, ectopic pregnancy should always be ruled out. Transvaginal (TV)US and measurement of quantitative β-human chorionic gonadotropin (β-hCG) are important for differentiating these diagnoses [19]. The discriminatory level is the level of β-hCG at which a normal intrauterine pregnancy should be visualized. Most commonly, a gestational sac should be visualized in a normal pregnancy via TVUS with a

β-hCG level of > 2,000 mIU/ml [20] or via transabdominal US with a β-hCG level of >6,500 mIU/ml [21]. However, with a β-hCG level >2,000 mIU/ml and no visible intrauterine pregnancy, the possibility of a multiple gestation should be considered.

Barnhart et al. [22] analyzed serum hCG values from 287 subjects who presented during early pregnancy with pain or bleeding and were eventually diagnosed with a viable intrauterine pregnancy. The main purpose of the study was to determine the lower limits of β-hCG increase for viable intrauterine pregnancies to be able to avoid unnecessary interruptions of viable pregnancies. The lowest 99% confidence interval (CI) for serum hCG change was 24% at 1 day and 53% at 2 days. It should be noted that a normal rise in β-hCG levels does not exclude an abnormal intrauterine pregnancy or an ectopic pregnancy; and an abnormal rise in β-hCG levels cannot distinguish between an abnormal intrauterine pregnancy and an ectopic pregnancy. A pseudosac, which consists of blood or fluid within the uterine cavity, is seen in some ectopic pregnancies. Distinguishing between a pseudosac and a gestational sac is important in the diagnosis of early pregnancy. A pseudosac can only be excluded with visualization of a yolk sac or embryo within the gestational sac [23].

The US examination has become the mainstay of early pregnancy diagnosis. It provides a safe, noninvasive diagnosis of normal and abnormal early pregnancy. Table 2.2 summarizes chronological landmarks and sonographic features of normal embryonic development. The safety of US has been investigated with epidemiological studies, looking at markers of normal child development plus childhood cancers in women who have had routine US scans. No woman or baby was shown to be directly affected by the use of diagnostic US [24].

Traditionally, an early pregnancy scan was performed with a transabdominal transducer, but this method was found to be inadequate in up to 42% of women [25]. Transvaginal sonography provides better images owing to the proximity to the pelvic organs. Additionally, a transvaginal scan can be used at an earlier gestational age [26], it gives clearer images, and it can be performed instantly, as the patient needs an empty bladder. Cullen et al. [27] found that vaginal sonography was superior to abdominal sonography for gestations ≤10 weeks, obese patients, and patients with a retroverted uterus [27]. The limitations of vaginal sonography include limited maneuverability. Some women feel it is invasive or are concerned about the safety of their pregnancy and refuse a transvaginal scan.

An intrauterine pregnancy can be diagnosed earliest by sonographic visualization of a gestational sac. Gestational age can be estimated by measuring the mean sac diameter (MSD) – averaging the length, width, and depth of the gestational sac – or the embryonic pole/crown–rump length. A true "crown" and "rump" should be visible at an MSD of 18 mm; before that time, US evaluations include only identification of an embryonic pole (the long axis of the embryo) [23]. When using TVUS, a yolk sac should be visualized when the MSD is ≥8 mm. Similarly, an embryonic pole should be visualized with a MSD of 16 mm [28, 29]. Rowling et al. [30], however, reported that 22% of 135 patients without a yolk sac of 8 mm MSD developed live embryos. Similarly, 8% of 59 patients with a MSD of 16 mm and no visible

Table 2.2 Chronological landmarks and sonographic features of normal embryonic development

Time from last menstrual period	Sonographic features of embryonic development	Clinical recommendation
4^{+3}–5^{+0}	Small gestation sac (2–5 mm) is seen in the endometrium. Sac is spherical; it has a regular outline and is eccentrically located toward the fundus. It is implanted below the surface of the endometrium and is surrounded by echogenic trophoblast	In symptomatic patients, the scan should be repeated in a week, when a yolk sac should be visible
5^{+1}–5^{+5}	Yolk sac becomes visible within the chorionic cavity when the gestational sac diameter is >12 mm	If it is not seen, early embryonic demise is likely; and the scan should be repeated a week later to confirm it
5^{+6}–6^{+0}	Embryonic pole measuring 2–4 mm in length is visible. Heart action could be detected. An embryo is usually visible with a mean gestational sac diameter of >20 mm	If this is not the case, the pregnancy is likely to be abnormal; and another scan should be organized a week later
6^{+1}–6^{+6}	Embryo is kidney bean-shaped, with the yolk sac separated from it by the vitelline duct. Crown–rump length measures 4–10 mm	If the heart rate is not detectable, early embryonic demise is almost certain
7^{+0}–7^{+6}	Crown–rump length measures 11–16 mm. Rhombencephalon becomes distinguishable as a diamond-shaped cavity, enabling distinction of cephalad and caudal. Spine is seen as double echogenic parallel lines. Amniotic membrane becomes visible, defining the amniotic cavity from the chorionic cavity. Umbilical cord can be seen	
8^{+0}–8^{+6}	Crown–rump length is 17–23 mm. Forebrain, midbrain, hindbrain, and skull are distinguishable. Limb buds are visible. Midgut hernia is present. Amniotic cavity expands, and umbilical cord and vitelline duct lengthen	
9^{+0}–10^{+0}	Crown–rump length is 23–32 mm. Limbs lengthen, and hands and feet are seen. Embryonic heart rate peaks at 170–180 bpm	

embryonic pole later developed live embryos. Thus, in patients with borderline US findings and a desired pregnancy, close follow-up with a repeat US examination is necessary before diagnosing an early pregnancy loss [30]. Nyberg et al. [31] used a threshold of 20 mm MSD without a yolk sac or 25 mm without an embryo via abdominal US to diagnosis anembryonic gestations. They study found that an

Table 2.3 Discrimination for β-HCG levels

Sonographic findings	Gestational age (weeks)	β-hCG (mIU/ml)
Gestational sac detection (MSD 2–3 mm)	4.5	1,000 by TVS, 1,800 by TAS
Yolk sac identification (MSD 5–6 mm)	5.0	1,000–7,200
Fetal pole identification	5–7	7,200–10,800
Cardiac activity identification	6–7	>10,800

β-hCG β-human chorionic gonadotropin, *MSD* mean sac diameter, *TVUS* transvaginal ultrasonography, *TAUS* transabdominal ultrasonography

increase in the gestational sac MSD of <3 mm over 5 days or <4 mm over 7 days can also be used to diagnose early pregnancy loss [31]. Gestational cardiac activity should be present by day 35 from the last menstrual period (day 21 from conception) and can be visualized when the embryonic pole is as small as 2 mm. However, lack of detectable cardiac activity in embryos <3 mm is associated with a 41% continuation rate [32]. To diagnose embryonic demise, an embryonic pole should measure >5 mm with no evidence of gestational cardiac activity [32, 33].

Pregnancy viability can be determined using a combination of quantitative β-hCG and US assessments. After implantation of the blastocyst, as early as 8–9 days after ovulation or day 23 of a 28-day cycle, β-hCG is detectable because it is produced in the placenta by the syncytiotrophoblast. The level of β-hCG approximately doubles every 48 h during early pregnancy and is an indicator of normal gestational development [34].

Levels of β-hCG have been correlated with the sonographic findings during early pregnancy [29]. β-hCG levels can assist with the interpretation of the US findings and help distinguish normal from abnormal conditions. When β-hCG is above a specified discriminatory level, structures identifying a normal pregnancy are present [35]. Discriminatory levels for β-hCG that correlate with normal pregnancy development are listed in Table 2.3.

The β-hCG levels are important for both initial and follow-up management of women presenting with first trimester bleeding to confirm and identify normal vs. abnormal development of a pregnancy. β-hCG levels can be used to follow an early pregnancy when US is not available or until US would be of value (e.g., once β-hCG levels reach 1,000 mIU/ml for detection using transvaginal sonography or β-hCG levels of 1,800 mIU/ml for detection using transabdominal sonography). These values may vary based on the institution's US equipment, experience, and analysis.

Management

Different types of early pregnancy loss are managed differently. Standard management of early pregnancy loss has been to perform suction dilatation and curettage to evacuate the uterus. This is due to the historical management that was based on the high prevalence of illegal abortions that were a frequent cause of vaginal bleeding

and cramping. When women presented with such symptoms, surgical evacuation was performed to reduce rates of sepsis and hemorrhage [19]. However, other safe options exist for management of early pregnancy loss, including medical and expectant management.

The qualities of the studies on expectant and medical management vary, making them difficult to compare. The studies vary by inclusion criteria (which are often poorly defined) and exclusion criteria; and medical management varies with the dosing regimens and routes of administration, the length of time before considering a treatment successful or unsuccessful, and the definition of success [19].

Moreover, one of the more common criteria used for defining success in early studies of expectant and medical management was a sonographic measurement of the anteroposterior endometrial thickness, with a threshold of <15 mm as diagnostic of RPOC. This was determined to be the lower limit in one study because <15 mm dilatation and curettage would not be performed at the institution where this study took place. Unfortunately, this threshold criterion has been propagated in many studies since then [36]. This 15-mm sonographic criterion for establishing the need for treatment has proven to be misleading and inexact in clinical trials. Accordingly, most of the previously published literature on expectant and medical management is confusing and inaccurate by current standards [19].

Threatened Abortion

Women with a threatened abortion should be managed expectantly until their symptoms resolve, a nonviable pregnancy is definitively diagnosed, or there is progression to an inevitable, incomplete, or complete abortion.

There are no therapeutic interventions that prevent first trimester pregnancy loss. Occasionally, upon sonographic examination of a patient presenting with first trimester vaginal bleeding, a subchorionic hematoma can be seen (Fig. 2.1). Bed rest and abstinence from sexual intercourse are commonly recommended, although there is no evidence that they are beneficial [37]. Administration of progesterone has not been proven effective for preventing early pregnancy loss [38]. A proposed flowchart for the management of first trimester vaginal bleeding is presented in Fig. 2.2.

Septic Abortion

Suspected septic abortion with RPOC is a medical emergency, and management should be immediate. The uterus should be evacuated promptly after initiating antibiotics and stabilizing the patient in cases of suspected septic abortion or RPOC as delay may be fatal [39, 40]. Suction curettage is less traumatic than sharp curettage. If the patient fails to respond to uterine evacuation and antibiotics, a pelvic abscess or clostridial

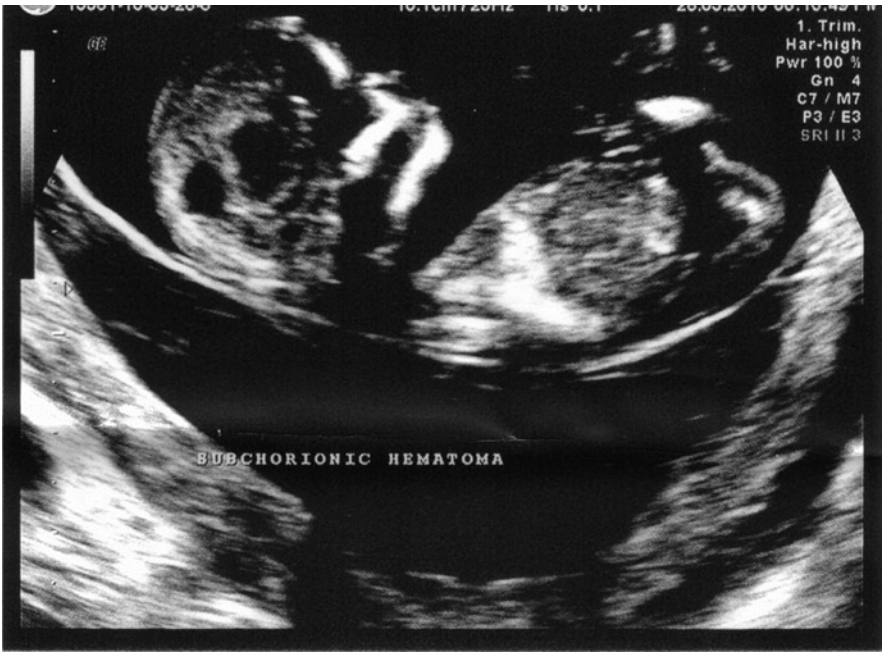

Fig. 2.1 Two-dimensional ultrasonography scan of a subchorionic hematoma in a patient who presented with first trimester vaginal bleeding

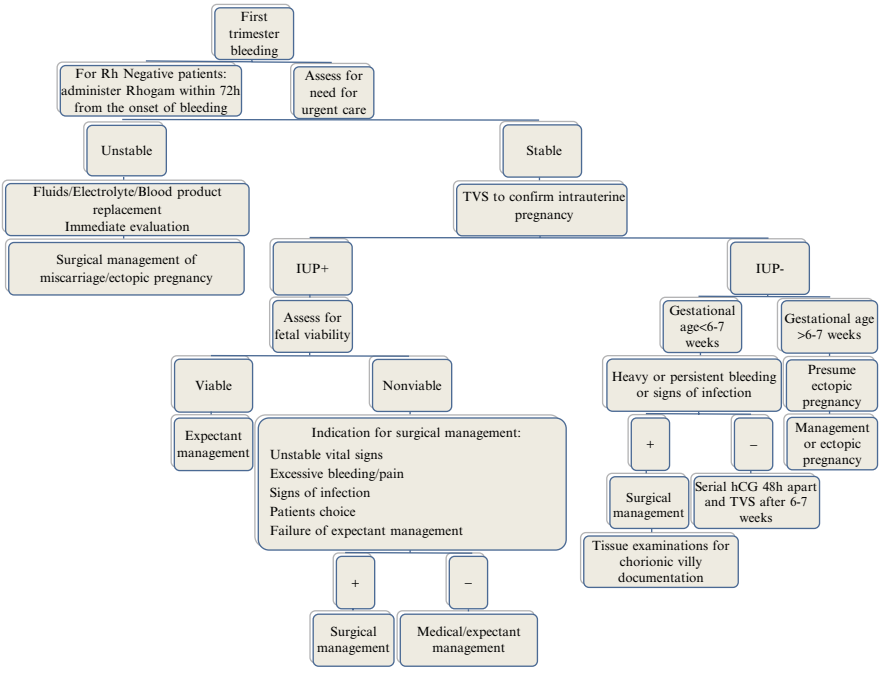

Fig. 2.2 Proposed flowchart for the management of first trimester vaginal bleeding. IUP= intrauterine pregnancy

necrotizing myonecrosis (gas gangrene), although rare, should be suspected. In such cases, laparotomy and possible hysterectomy might be considered.

Caution Box

- In cases of suspected septic abortion or related products of conception evacuation of the uterus should begin promptly after initiating antibiotics and stabilizing the patient.

Complete Abortion

Passage of an intact gestational sac or contractions with scant uterine bleeding and diminishing uterine cramps suggests that a complete abortion has occurred. Tissue that passed should undergo pathological examination to confirm the presence of products of conception. US examination may be useful for confirming the absence of significant amounts of retained intrauterine tissue, but there are no universally defined criteria for an empty uterus.

Complete abortions do not require therapy, it is difficult to reliably distinguish them clinically or sonographically from incomplete abortions. Although, it is clear that surgery is necessary for women with excessive bleeding, unstable vital signs, or obvious signs of infection [41], some clinicians recommend suction curettage for all patients with complete abortions. However, if US shows an empty uterus and the bleeding is minimal, it is reasonable to take no further actions. Serum β-hCG levels should be measured and followed until they are undetected.

Caution Box

- In cases with complete abortion tissue that passed should undergo pathological examination in order to confirm the presence of products of conception.

Inevitable and Incomplete Abortion, Missed Abortion, Embryonic/Fetal Demise (Dead Fetus)

Women with inevitable or incomplete abortion, missed abortion, or embryonic/fetal demise (dead fetus) can be managed surgically, medically, or expectantly.

Surgical Management

The conventional treatment of first or early second trimester pregnancy loss is dilatation and curettage (D&C) or dilatation and evacuation (D&E) to prevent potential

hemorrhagic and infectious complications from the RPOC. The benefits of surgical management include convenient timing for the patient and high success rates, ranging from 93 to 100%, with most studies reporting success rates at or above 98% [19]. Surgical risks include infection, uterine perforation, cervical trauma, and uterine adhesions, which might lead to subsequent infertility or ectopic pregnancy [42]. These complications are relatively rare. Anesthetic risks vary depending on the type of anesthesia used (general anesthesia, intravenous sedation, and local anesthesia). Uterine evacuation can be performed safely and effectively even as an office procedure [43].

Surgical management is appropriate for women with heavy bleeding or sepsis in whom delaying therapy could be harmful as well as for women who do not want to wait for spontaneous or medically induced evacuation of the uterus. Suction curettage is preferable to sharp curettage, which is associated with greater morbidity [44, 45].

Based on a meta-analysis that found women given periabortal antibiotics had a 42% lower risk of infection, some authors recommend antimicrobial administration to reduce the risk of postabortal sepsis (doxycycline 100 mg orally for two doses 12 h apart on the day of the surgical procedure) [46]. However, a single randomized study of intravenous doxycycline at time of curettage for incomplete abortion did not decrease the risk of postoperative febrile morbidity when compared with placebo [47].

In many trials, suction curettage was performed in an operating room. However, given that 93% of induced abortions in the USA in 2000 were performed at an outpatient clinic [48], it seems reasonable that surgical treatment of early pregnancy loss can also be an outpatient procedure. Manual vacuum aspiration consists of a 60-ml syringe attached to a cannula, which provides suction force equal to that of electric vacuum aspiration. Performing D&Cs in a clinic setting rather than in the operating room has decreased overall hospital costs by 41% [49].

Medical Treatment

The availability of effective medical therapies for inducing abortion has created new options for women who want to avoid surgery or when surgical intervention needs to be avoided. With medical management, medications are used to induce expulsion of the products of conception from the uterus. Regimens have typically included a prostaglandin analog (most commonly misoprostol) or a combination of mifepristone or methotrexate with misoprostol [19]. Unfortunately, many studies that have compared medical management with expectant management or surgical management are limited by having different inclusion criteria and patient populations, the inappropriate use of a US diagnosis of failed management, and different follow-up periods before surgical intervention [19].

Misoprostol, a prostaglandin E_1 analog, has been approved by the US Food and Drug Administration (FDA) for the prevention of gastric ulcers. Off-label it has also been used for a variety of obstetrical and gynecological indications, including induction of labor, cervical ripening, and medical abortion. It is the most commonly used

agent for medical abortions. Its safety and effectiveness have been established by multiple randomized controlled trials (RCTs) [50, 51]. The advantages of misoprostol are its low cost [52], it can be administered via several routes (oral, buccal, sublingual, vaginal, and rectal), there is a low incidence of side effects when given intravaginally, it is stable at room temperature, and it is readily available. The risk of a major complication is rare.

Zhang et al. [53] investigated the efficacy of misoprostol for medical management of pregnancy failure during the first trimester. They conducted a large, well-designed trial in which women with missed, incomplete, or inevitable abortion were randomly assigned to receive misoprostol intravaginally or undergo vacuum aspiration. Complete expulsion occurred in 71–84% of medically managed patients. Pregnancy duration did not affect the rate of successful expulsion, but successful expulsion was at a lower percentage with missed abortion compared with incomplete or inevitable abortion (81% vs. 93%). Both medical and surgical therapies were safe, effective, and acceptable to patients [53].

Several trials investigated dosing regimens and routes of administration of misoprostol [54–60]. However, there is no consensus on the optimal choice for either. Success rates for misoprostol ranged from 25% for oral misoprostol in a small study to as high as 95% for oral, sublingual, or vaginal misoprostol in other studies. The oral and sublingual routes seemed to be associated with more side effects, such as diarrhea, nausea, and vomiting when compared with the vaginal route. Repeated dosing does not seem to improve the success rate and results in more side effects [58–60].

A combination of a progesterone antagonist (mifepristone) with misoprostol has also been used. However, the value of adding a progesterone antagonist is questionable and expensive. It has been reported that misoprostol alone or a combination of misoprostol and mifepristone had similar success rates in the treatment of early pregnancy failure [61, 62].

Patients who are treated medically are instructed to go to the emergency department if they develop excessive bleeding. Tissues that are passed vaginally at home should be placed in a container and brought to the hospital for analysis.

Expectant Management

Expectant management is an alternative for women with early pregnancy failure at less than 13 weeks of gestation who have stable vital signs and no evidence of infection. Expectant management allows spontaneous passage of the products of conception, allows women to avoid surgical and anesthesia risks, and may be perceived as a “more natural” option. Risks and side effects include an unpredictable duration of time until resolution, the possibility of increased pain and bleeding, and the potential need for emergent surgical evacuation [19].

A systematic Cochrane database review that included five randomized trials concluded that compared to surgical management expectant management was

associated with a higher risk of incomplete abortions, the need for unplanned surgical evacuation of the uterus, and bleeding; however, it was also concluded that it was not an unreasonable approach if the woman preferred nonintervention [63]. Randomized trials comparing medical with expectant management have reported similar rates of successful evacuation [64, 65]. Differences in success rates could be attributed to the length of expectant management, the medical regimen used, and the type of early pregnancy failure (incomplete abortion vs. missed abortion or fetal demise). With expectant management, most expulsions occur during the first 2 weeks after diagnosis, although the duration may extend to 3–4 weeks. Incomplete miscarriage is more likely than a missed abortion to proceed to expulsion within 2 weeks [66, 67].

Medical or surgical treatment should be offered if spontaneous expulsion does not occur. Following spontaneous or medically induced expulsion, the uterine cavity should undergo US evaluation when RPOC are suspected. Some physicians perform this examination routinely.

Postabortion Care

After surgical evacuation or if medical management or expectant management is planned, women who are Rh(D)-negative and unsensitized should receive Rh(D)-immune globulin. A dose of 50 μg is effective through the 12th week of gestation due to the small volume of red blood cells in the fetoplacental circulation, although the more readily available 300 μg dose is normally given.

Women are advised to refrain from coitus and the use of tampons for at least 2 weeks after evacuation of the uterus. Postponing pregnancy for 2–3 months is usually advised, although there seems to be no greater risk of adverse outcomes with a shorter interpregnancy interval [68]. Any type of contraception, including placement of an intrauterine device [69], may be started immediately.

Caution Box

- Mild vaginal bleeding can persist for a couple of weeks after the abortion. If heavy bleeding, fever, or abdominal pain develops patients should be referred without delay for a medical examination.
- Women who are Rh(D)-negative and unsensitized should receive Rh(D)-immune globulin, after surgical evacuation or at the time of diagnosis of early pregnancy failure if medical management or expectant management is planned.

Mild vaginal bleeding can persist for a couple of weeks after the abortion. If heavy bleeding, fever, or abdominal pain develops, patients should be referred without delay for a medical examination. Menses typically resumes within 6 weeks.

If normal menses does not resume, the presence of a new pregnancy or gestational trophoblastic disease should be considered. On rare occasions, intrauterine adhesions (Asherman's syndrome) occur after surgical evacuation of the uterus. Serum hCG levels normally return to normal within 2 weeks after an abortion [22]. Follow-up hCG testing is unnecessary if the normal menstrual cycle resumes.

It is important to acknowledge the patient's (and partner's) grief and provide empathy and support as well as a referral to professional counseling in some cases. Risk factors for abnormal grief following a miscarriage include a history of or current depression, anxiety, or other psychiatric disorder; neurotic personality traits; and lack of social support [70]. If the etiology of the loss is known or suspected, the couple should be informed and counseled about recurrence risks. If the etiology is not known, it is important to reassure the patient and alleviate any feelings of guilt or blame.

Prognosis

Many women may feel anxiety and have concerns regarding the possibility of another loss in a future pregnancy. Women could be reassured that one previous miscarriage does not necessarily increase the risk of another one. Nevertheless, the overall risk of another miscarriage is not insignificant [71].

The overall risk of miscarriage in a future pregnancy is approximately 20% after one miscarriage, 28% after two miscarriages, and 43% after three or more miscarriages [72]. There also appears to be an increased risk of preterm delivery of subsequent pregnancies [73]. Second trimester pregnancy loss is significantly associated with recurrent second-trimester loss and future spontaneous preterm birth. After a second trimester pregnancy loss, one study reported that 39% of women had a preterm delivery in their next pregnancy, 5% had a stillbirth, and 6% had a neonatal death [74]. Interestingly, three more recent studies reported that an initial miscarriage is associated with a higher risk of obstetrical complications in the following pregnancy [75–77]. Nevertheless, the long-term conception rate and pregnancy outcome are similar for women who underwent medical or surgical evacuation for early pregnancy loss [78].

Summary

Spontaneous abortions are among the most common complications of pregnancy. Many risk factors for spontaneous abortion, including advanced maternal age and a previous spontaneous abortion, have been reported. Most spontaneous abortions are attributed to structural or chromosomal abnormalities in the embryo.

There are various stages and types of spontaneous abortions. Women usually present with a history of amenorrhea, vaginal bleeding, and pelvic pain. Ultrasonography is

the most useful test for diagnosing and evaluating women suspected of having a spontaneous abortion.

There are no useful interventions to prevent first trimester pregnancy loss. In most patients, surgical, medical, and expectant management ultimately result in evacuation of the products of conception. Surgical evacuation seems more successful than medical or expectant management. The success of medical and expectant management depends on the length of time allowed before a secondary surgical intervention and on the type of nonviable pregnancy. Postabortal infection rates are similar for all three strategies, and the frequency of other complications is low. The choice of treatment should take into account the patient's preferences.

Women who are unstable because of bleeding or infection and women who want an immediate, definitive treatment should undergo surgical management. Of women undergoing medical management, 70–90% have a successful outcome. This strategy is preferable for women who want to avoid a surgical procedure but do not want to wait for a spontaneous abortion to occur. Women who are stable hemodynamically, who do not want a medical or surgical intervention, and who are willing to wait days to weeks for expulsion to occur may choose expectant management. Bleeding and cramping may be prolonged, and surgical evacuation may still be required; but as many as 80% of women have a successful outcome with expectant management alone. Expectant management for 1 month appears to be a safe, effective alternative to immediate surgical evacuation. In addition, sonographic classification of the miscarriage at presentation appears to be predictive of successful outcome without surgical intervention.

The long-term conception rate and pregnancy outcome are similar for women who undergo medical or surgical evacuation for early pregnancy loss. Although there are several treatment options available to women who are diagnosed with early pregnancy failure, counseling needs to be individualized to patient expectations and preferences.

With a thorough understanding of the experience and process of first trimester loss, and appreciation of its emotional impact and significance, and making an educated choice of management physicians can provide sensitive and complete care to women at this important time.

References

1. Brier N. Grief following miscarriage: a comprehensive review of the literature. J Womens Health (Larchmt). 2008;17:451–64.
2. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996;65:503–9.
3. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C. A prospective study of early pregnancy loss. Hum Reprod. 1996;11:406–12.
4. Guerneri S, Bettio D, Simoni G, Brambati B, Lanzani A, Fraccaro M. Prevalence and distribution of chromosome abnormalities in a sample of first trimester internal abortions. Hum Reprod. 1987;2:735–9.
5. Ohno M, Maeda T, Matsunobu A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi. Obstet Gynecol. 1991;77:394–8.

6. Gracia CR, Sammel MD, Chittams J, Hummel AC, Shaunik A, Barnhart KT. Risk factors for spontaneous abortion in early symptomatic first-trimester pregnancies. Obstet Gynecol. 2005;106:993–9.
7. 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.
8. Hustin J, Jauniaux E, Schaaps JP. Histological study of the materno-embryonic interface in spontaneous abortion. Placenta. 1990;11:477–86.
9. Jauniaux E, Gulbis B, Burton GJ. The human first trimester gestational sac limits rather than facilitates oxygen transfer to the foetus – a review. Placenta. 2003;24:S86–93.
10. Jauniaux E, Zaidi J, Jurkovic D, Campbell S, Hustin J. Comparison of colour Doppler features and pathological findings in complicated early pregnancy. Hum Reprod. 1994;9:2432–7.
11. Jauniaux E, Greenwold N, Hempstock J, Burton GJ. Comparison of ultrasonographic and Doppler mapping of the intervillous circulation in normal and abnormal early pregnancies. Fertil Steril. 2003;79:100–6.
12. Olive DL, Pritts EA. Fibroids and reproduction. Semin Reprod Med. 2010;28:218–27.
13. Matovina M, Husnjak K, Milutin N, Ciglar S, Grce M. Possible role of bacterial and viral infections in miscarriages. Fertil Steril. 2004;81:662–9.
14. Mills JL, Simpson JL, Driscoll SG, Jovanovic-Peterson L, Van Allen M, Aarons JH, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med. 1988;319:1617–23.
15. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. JAMA. 2004;292:691–5.
16. Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. Thyroid. 2010;20:989–93.
17. Vitzthum VJ, Spielvogel H, Thornburg J, West B. A prospective study of early pregnancy loss in humans. Fertil Steril. 2006;86:373–9.
18. Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. Fertil Steril. 2002;77:342–7.
19. Chen BA, Creinin MD. Contemporary management of early pregnancy failure. Clin Obstet Gynecol. 2007;50:67–88.
20. Bateman BG, Nunley Jr WC, Kolp LA, Kitchin 3rd JD, Felder R. Vaginal sonography findings and hCG dynamics of early intrauterine and tubal pregnancies. Obstet Gynecol. 1990;75:421–7.
21. Kadar N, DeVore G, Romero R. Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy. Obstet Gynecol. 1981;58:156–61.
22. Barnhart KT, Sammel MD, Rinaudo PF, Zhou L, Hummel AC, Guo W. Symptomatic patients with an early viable intrauterine pregnancy: HCG curves redefined. Obstet Gynecol. 2004;104:50–5.
23. Goldstein SR. Sonography in early pregnancy failure. Clin Obstet Gynecol. 1994;37:681–92.
24. Sawyer E, Jurkovic D. Ultrasonography in the diagnosis and management of abnormal early pregnancy. Clin Obstet Gynecol. 2007;50:31–54.
25. Shillito J, Walker JJ. Early pregnancy assessment units. Br J Hosp Med. 1997;58:505–9.
26. Fossum GT, Davajan V, Kletzky OA. Early detection of pregnancy with transvaginal ultrasound. Fertil Steril. 1988;49:788–91.
27. Cullen MT, Green JJ, Reece EA, Hobbins JC. A comparison of transvaginal and abdominal ultrasound in visualizing the first trimester conceptus. J Ultrasound Med. 1989;8:565–9.
28. Levi CS, Lyons EA, Lindsay DJ. Early diagnosis of nonviable pregnancy with endovaginal US. Radiology. 1988;167:383–5.
29. Dighe M, Cuevas C, Moshiri M, Dubinsky T, Dogra VS. Sonography in first trimester bleeding. J Clin Ultrasound. 2008;36:352–66.
30. Rowling SE, Coleman BG, Langer JE, Arger PH, Nisenbaum HL, Horii SC. First-trimester US parameters of failed pregnancy. Radiology. 1997;203:211–7.
31. Nyberg DA, Mack LA, Laing FC, Patten RM. Distinguishing normal from abnormal gestational sac growth in early pregnancy. J Ultrasound Med. 1987;6:23–7.

32. Goldstein SR. Significance of cardiac activity on endovaginal ultrasound in very early embryos. Obstet Gynecol. 1992;80:670–2.
33. 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.
34. Snell BJ. Assessment and management of bleeding in the first trimester of pregnancy. J Midwifery Womens Health. 2009;54:483–91.
35. Peisner DB, Timor-Tritsch IE. The discriminatory zone of beta-hCG for vaginal probes. J Clin Ultrasound. 1990;18:280–5.
36. Nielsen S, Hahlin M. Expectant management of first-trimester spontaneous abortion. Lancet. 1995;345:84–6.
37. Aleman A, Althabe F, Belizán J, Bergel E. Bed rest during pregnancy for preventing miscarriage. Cochrane Database Syst Rev. 2005;CD003576.
38. Wahabi HA, Abed Althagafi NF, Elawad M. Progestogen for treating threatened miscarriage. Cochrane Database Syst Rev. 2007;CD005943.
39. Stubblefield PG, Grimes DA. Septic abortion. N Engl J Med. 1994;331:310–4.
40. Finkielman JD, De Feo FD, Heller PG, Afessa B. The clinical course of patients with septic abortion admitted to an intensive care unit. Intensive Care Med. 2004;30:1097–102.
41. Forna F, Gülmezoglu AM. Surgical procedures to evacuate incomplete abortion. Cochrane Database Syst Rev. 2001;CD001993.
42. Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure. Hum Reprod. 2001;16:365–9.
43. Harris LH, Dalton VK, Johnson TR. Surgical management of early pregnancy failure: history, politics, and safe, cost-effective care. Am J Obstet Gynecol. 2007;196:445.e1–5.
44. Grimes DA. Unsafe abortion: the silent scourge. Br Med Bull. 2003;67:99–113.
45. Grimes DA, Benson J, Singh S, Romero M, Ganatra B, Okonofua FE, et al. Unsafe abortion: the preventable pandemic. Lancet. 2006;368:1908–19.
46. 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.
47. Prieto JA, Eriksen NL, Blanco JD. A randomized trial of prophylactic doxycycline for curettage in incomplete abortion. Obstet Gynecol. 1995;85:692–6.
48. Finer LB, Henshaw SK. Abortion incidence and services in the United States in 2000. Perspect Sex Reprod Health. 2003;35:6–15.
49. 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.
50. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2006;3:CD002253.
51. Blum J, Winikoff B, Gemzell-Danielsson K, Ho PC, Schiavon R, Weeks A. Treatment of incomplete abortion and miscarriage with misoprostol. Int J Gynaecol Obstet. 2007;99: S186–9.
52. Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. Hum Reprod. 2005;20:1067–71.
53. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005;353:761–9.
54. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol. 1997;89:768–72.
55. Ngoc NT, Blum J, Westheimer E, Quan TT, Winikoff B. Medical treatment of missed abortion using misoprostol. Int J Gynaecol Obstet. 2004;87:138–42.
56. Gilles JM, Creinin MD, Barnhart K, Westhoff C, Frederick MM. National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial. A randomized

trial of saline solution-moistened misoprostol versus dry misoprostol for first-trimester pregnancy failure. Am J Obstet Gynecol. 2004;190:389–94.
57. Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. Hum Reprod. 2003;18:2315–8.
58. Tang OS, Ong CY, Tse KY, Ng EH, Lee SW, Ho PC. A randomized trial to compare the use of sublingual misoprostol with or without an additional 1 week course for the management of first trimester silent miscarriage. Hum Reprod. 2006;21:189–92.
59. Phupong V, Taneepanichskul S, Kriengsinyot R, Sriyirojana N, Blanchard K, Winikoff B. Comparative study between single dose 600 microg and repeated dose of oral misoprostol for treatment of incomplete abortion. Contraception. 2004;70:307–11.
60. Nguyen TN, Blum J, Durocher J, Quan TT, Winikoff B. A randomized controlled study comparing 600 versus 1,200 microg oral misoprostol for medical management of incomplete abortion. Contraception. 2005;72:438–42.
61. Grønlund A, Grønlund L, Clevin L, Andersen B, Palmgren N, Lidegaard Ø. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. Acta Obstet Gynecol Scand. 2002;81:1060–5.
62. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956–60.
63. Nanda K, Peloggia A, Grimes D, Lopez L, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database Syst Rev. 2006;CD003518.
64. Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. Br J Obstet Gynaecol. 1999;106:804–7.
65. Shelley JM, Healy D, Grover S. A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage. Aust N Z J Obstet Gynaecol. 2005;45:122–7.
66. Casikar I, Bignardi T, Riemke J, Alhamdan D, Condous G. Expectant management of spontaneous first-trimester miscarriage: prospective validation of the '2-week rule'. Ultrasound Obstet Gynecol. 2010;35:223–7.
67. 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.
68. 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.
69. Grimes D, Schulz K, Stanwood N. Immediate postabortal insertion of intrauterine devices. Cochrane Database Syst Rev. 2002;CD001777.
70. Stratton K, Lloyd L. Hospital-based interventions at and following miscarriage: literature to inform a research-practice initiative. Aust N Z J Obstet Gynaecol. 2008;48:5–11.
71. Thorstensen KA. Midwifery management of first trimester bleeding and early pregnancy loss. J Midwifery Womens Health. 2000;45:481–97.
72. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. BMJ. 1989;299:541–5.
73. Swingle HM, Colaizy TT, Zimmerman MB, Morriss Jr FH. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. J Reprod Med. 2009;54:95–108.
74. Edlow AG, Srinivas SK, Elovitz MA. Second-trimester loss and subsequent pregnancy outcomes: what is the real risk? Am J Obstet Gynecol. 2007;197:581.e1–6.
75. Kashanian M, Akbarian AR, Baradaran H, Shabandoust SH. Pregnancy outcome following a previous spontaneous abortion (miscarriage). Gynecol Obstet Invest. 2006;61:167–70.
76. Bhattacharya S, Townend J, Shetty A, Campbell D, Bhattacharya S. Does miscarriage in an initial pregnancy lead to adverse obstetric and perinatal outcomes in the next continuing pregnancy? BJOG. 2008;115:1623–9.

77. Weintraub AY, Sergienko R, Harlev A, Holcberg G, Mazor M, Wiznitzer A, et al. An initial miscarriage is associated with an increased rate of adverse pregnancy outcomes in the following pregnancy. Presented at the 31st Annual Meeting of the Society of Maternal Fetal Medicine (SMFM). San Francisco, CA, USA, 7–12 February 2011.
78. Tam WH, Tsui MH, Lok IH, Yip SK, Yuen PM, Chung TK. Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage. Hum Reprod. 2005;20: 3355–9.

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