Early pregnancy loss

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ABSTRACT

Previously called spontaneous abortion, early pregnancy loss (EPL) is the preferred term encompassing threatened abortion, incomplete abortion, complete abortion, and anembryonic pregnancy. EPL has many causes, including chromosomal abnormalities, immunologic and infectious causes, and underlying maternal risk factors. Because many patients present with first-trimester bleeding, clinicians must know the appropriate evaluation and management techniques.

Keywords: early pregnancy loss, complete abortion, incomplete abortion, anembryonic pregnancy

Learning objectives

- Differentiate between the terms associated with EPL.
- Summarize the causes of and risk factors for EPL.
- Identify the signs and symptoms most commonly associated with EPL.
- Describe the diagnostic evaluation and management of EPL.

Early pregnancy loss (EPL) is defined as a nonviable intrauterine pregnancy diagnosed up to 12 weeks, 6 days gestation.[1,2] The incidence of EPL is unclear because some losses may occur before the patient knows she is pregnant. In a 1988 study, the incidence of EPL was estimated at 31% and included clinically recognized and unrecognized pregnancies (identified before clinical diagnosis).[3] More recent publications report an incidence of 12.8% to 13.5%; however, this is based on losses in clinically recognized pregnancies only.[4,5] With the avail-

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Key points

- EPL encompasses incomplete abortion, complete abortion, and anembryonic pregnancy.
- The most common cause of an EPL is a chromosomal aberration that occurs at fertilization. A single autosomal trisomy occurs in the vast majority of EPLs.
- First-trimester vaginal bleeding is a common symptom in EPL, so always rule out an ectopic pregnancy.
- A quantitative beta-HCG and ultrasound imaging can help clinicians make an accurate diagnosis.
- Patients who are hemodynamically stable and afebrile often can be managed expectantly or medically with methylergonovine and misoprostol, plus mifepristone if available.

ability of highly sensitive over-the-counter urine pregnancy tests that allow pregnancy detection before formal clinical diagnosis, the incidence of EPL is likely higher than that published for clinically recognized pregnancies. Because EPL is common, clinicians must be familiar with its terminology, maternal risk factors, presentation, diagnosis, and management.

TERMINOLOGY

Historically, EPL has been referred to by many different names, including *miscarriage* and *spontaneous abortion*, which has led to some confusion among patients and clinicians. EPL is a broad term that encompasses many subcategories including threatened, incomplete, and complete abortion. Threatened abortion is defined as symptoms of EPL, such as vaginal bleeding with pelvic pain and cramping, although the cervical os is closed and a viable intrauterine pregnancy is noted on ultrasound. A threatened abortion may evolve into a complete or incomplete abortion.

In an *incomplete abortion*, the patient has a nonviable intrauterine pregnancy noted on ultrasound with products of conception remaining in the uterus.[1] Symptomatic patients have vaginal bleeding, pelvic pain and cramping, and a dilated cervical os. Asymptomatic incomplete abortions often are incidental findings on ultrasound. In contrast, a *complete abortion* is defined as expulsion of all products of conception from the uterus, cervical os closure, and symptom resolution.

Anembryonic pregnancy, previously referred to as blighted ovum, is a condition in which an egg is fertilized and implanted but does not develop into an embryo.[1] Recurrent EPL is defined as the loss of two or more pregnancies in the first trimester; these patients warrant further clinical evaluation.[6]

CAUSES

Patients who suffer an EPL often want to understand the cause. Although EPL has many different causes, the vast majority are due to chromosomal abnormalities (**Table 1**). In 50% to 82% of cases, the cause of EPL is an abnormal fetal karyotype, the most frequent being single autosomal trisomy, particularly trisomy 15, 16, 21, 22.[7–9] Other abnormal karyotypes associated with EPL include triploidy, monosomy X, chromosomal rearrangements, tetraploid, autosomal monosomy, sex chromosome trisomy, or a combination of chromosomal abnormalities.[7,8] EPL secondary to chromosomal abnormalities has a higher rate of occurrence between 5 and 9 weeks gestation.[7]

Other causes implicated in EPL include immunologic, infectious, and underlying maternal risk factors. The human immune system is designed to fight foreign invaders, but paradoxically arrests these mechanisms in pregnancy to prevent the mother's immune system from attacking an embryo that carries different genetic information. However, when these immunologic mechanisms are not arrested, EPL may occur. For example, many studies have found a link between a reduced amount or functionality of regulatory T cells (an immunosuppressive type of CD4+ T cell) that leads to a reduced maternal tolerance of the fetus and increased risk of EPL.[10] More recently, the role of the

TABLE 1. Incidence of common chromosomal abnormalities seen in EPL[7]

Chromosomal abnormality	Definition/examples	Incidence (%)
Single autosomal trisomy	One additional autosomal chromosome present, Examples: trisomy 16, trisomy 21 (Down syndrome), trisomy 22	64.6
Triploidy	Three sets of chromosome in each cell, Example: 69XXX	13.1
Monosomy X	An X chromosome is missing, Example: Turner syndrome	10.4
Chromosomal rearrangements	Chromosomal deletions, duplications, inversions, translocations	5.2
Combination of chromosomal abnormalities	Examples: multiple trisomy, trisomy plus monosomy, hypertriploidy	4.2
Tetraploidy	Four sets of chromosomes in each cell, Example: 92XXXX	1.4
Autosomal monosomy	The lack of one member of an autosomal chromosome pair	0.8
Sex chromosome trisomy	An extra sex chromosome, Example: Klinefelter syndrome (XXY), or Jacob syndrome (XYY)	0.3

endometrial decidualization process, the remodeling needed to create an environment best suited for implantation, has received attention as a mechanism of EPL. Decidualization of the endometrium, triggered by progesterone, is kept in homeostatic balance by uterine natural killer cells, and a dysfunction in this homeostasis can increase the likelihood of EPL because of the resulting unfavorable endometrial lining.[11]

Numerous infections are associated with EPL, including cytomegalovirus (CMV), HIV, rubella, dengue fever, herpes simplex virus 1 and 2, parvovirus B19, hepatitis B, human papillomavirus (HPV), and polyomavirus BK. However, there is conflicting evidence linking herpes simplex viruses, parvovirus B19, hepatitis B, HPV, and polyomavirus BK to EPL.[12,13] Bacterial causes of EPL include *Ureaplasma urealyticum* and *Mycoplasma hominis*, bacteria that commonly cause bacterial vaginosis, as well as brucellosis and syphilis. *Chlamydia trachomatis* also may be related but data are conflicting.[13] Malaria has been clearly associated with EPL in many studies, but evidence on toxoplasmosis is conflicting.[13] The proposed mechanisms by which infections cause EPL include transmission of the infection to the utero-placental unit itself, localized immune responses that disrupt blastocyst implantation and placental formation, and hemodynamic compromise arising from maternal sepsis secondary to infection.[9,13]

MATERNAL RISK FACTORS

An estimated 5% to 30% of women with a history of EPL also have an underlying uterine anatomic anomaly.[14] The presence of intrauterine adhesions (also known as Asherman syndrome), uterine fibroids, congenital uterine anomalies such as uterine septa, and endometrial polyps were found to be associated with EPL.[15] Specifically, the congenital anomalies most associated with EPL are unicornuate, bicornuate, septate, and subseptate uteri.[14] Evidence of the effect of uterine fibroids on EPL is conflicting.[16] Although exactly how maternal anatomic uterine abnormalities affect EPL is not clearly known, researchers believe that the endometrium in the areas of anatomic abnormalities may have abnormal blood supply, making it unfavorable for implantation and unable to sustain embryonic growth.[14]

Additional uterine factors associated with EPL include subchorionic hematoma (blood clots in the placental layers) and intrauterine device (IUD) use. The risk of EPL is significantly increased if a subchorionic hematoma is diagnosed on ultrasound before 7 weeks gestation and if the hematoma is greater than 50% the size of the gestational sac.[17] Conceptions with IUD in situ are at increased risk of EPL; removing the IUD early in the pregnancy reduces the risk.[18,19]

Thrombophilias have been implicated as a cause of pregnancy loss; however, more recent studies have shown little to no increased risk of EPL in patients with inherited thrombophilias. The exception is a possible slight increased risk in those with Factor V Leiden and possibly MTHFR homozygosity, but evidence of the latter is conflicting.[20] Of the acquired thrombophilias, those with anticardiolipin antibodies, such as systemic lupus erythematosus, are most associated with early and recurrent pregnancy loss.[20]

Endocrine disorders including diabetes mellitus types 1 and 2, polycystic ovarian syndrome, and thyroid disease also are associated with EPL, particularly in patients whose disorders are not well controlled, such as those with thyrotoxicosis or poor glycemic control associated with diabetes.[21–24] Although not all of the exact mechanisms are known, the hormonal and metabolic abnormalities that result from these endocrine disorders likely impair the development of quality endometrium and prevent successful implantation, thus resulting in EPL.[21–24]

Outcomes of previous pregnancies also can play a role in the risk of EPL. A history of previous EPL by itself is a risk factor for a recurrence, which increases with the number of EPLs.[5] Preterm delivery, stillbirth, cesarean section, or gestational diabetes in previous pregnancies also are risk factors for EPL.[5]

Maternal age plays a significant role in EPL—the risk of EPL is slightly increased for women under age 20 years, then decreases, with the lowest risk of miscarriage at age 27 years.[5] The risk increases significantly after age 30 years, reaching a 53% risk of EPL by age 45 years.[5] This correlates with abnormal karyotypes being the most common cause of EPL, as women of advanced maternal age (age 35 years and older) have significantly higher rates of fetal chromosomal abnormalities, particularly single autosomal trisomies including trisomies 15, 21, and 22.[7] Although age can be considered a modifiable risk factor, it also could be considered a nonmodifiable risk factor in the situation of unplanned pregnancy.

Black ethnicity is associated with increased risk of EPL. A large retrospective study revealed an increased incidence of EPL in Black African and Black Caribbean women compared with White European women.[25] Whether this increased incidence was caused by genetic mechanisms or the presence of other confounding risk factors is unclear.

Modifiable risk factors in EPL have been extensively studied. Alcohol use during pregnancy is the highest modifiable risk factor after maternal age at conception.[26] Maternal BMI of 25 and greater, or less than 18.5, also is associated with increased risk of EPL; 3.7% of EPLs can be prevented by being in a normal weight category before conception.[26] Other modifiable risk factors that have long been implicated in increasing the risk of EPL include the use of tobacco, cocaine, and cannabis.[27,28] Maternal stress, particularly about legal or substance use issues, is another modifiable risk factor; however, evidence of this has been conflicting.[29,30]

Use of certain medications has been associated with EPL. Nonsteroidal anti-inflammatory drugs (NSAIDs) used for 15 or more days around the time of conception are associated with an increased risk of EPL.[31] Many antibiotic classes have been loosely associated with an increased risk of pregnancy loss before 20 weeks, including azithromycin, clarithromycin, metronidazole, sulfonamides, tetracyclines, and fluoroquinolones.[32]

Clinicians must be well educated on the vast number of risk factors associated with EPL in order to more safely prescribe medications to women of childbearing age. It is important to deliver clear patient education and prenatal counseling about modifiable risk factors and management of underlying chronic disease. Similarly, clinicians also must take into consideration the medical conditions associated with EPL and consider workup for these in patients who have had a second consecutive EPL. Maternal risk factors associated with EPL are summarized in **Table 2**.

TABLE 2. Maternal risk factors associated with EPL[5,7,14-32]

Past medical history
- Previous pregnancy loss
- Preterm delivery
- Stillbirth
- Cesarean section
- Gestational diabetes

Uterine abnormalities
- Asherman syndrome
- Uterine fibroids*
- Congenital uterine anomalies
- Subchorionic hematoma
- IUD in situ

Thrombophilias
- Anticardiolipin antibody disorders (systemic lupus erythematosus, antiphospholipid antibody syndrome)
- Factor V Leiden
- MTHFR homozygosity*

Endocrine disorders
- Type 1 or 2 diabetes
- Thyroid disease
- Polycystic ovarian syndrome

Nonmodifiable risk factors
- Age greater than 30 years
- Black ethnicity

Modifiable risk factors
- Alcohol, tobacco, cocaine, or marijuana use in pregnancy
- BMI of 25 or greater or less than 18.5
- Stress*
- NSAID use in first trimester
- Certain antibiotic classes (azithromycin, clarithromycin, metronidazole, sulfonamides, tetracyclines, and fluoroquinolones)**

* Conflicting data exist about the effect on EPL
** Evidence is weak about the effect on EPL

COMMON PRESENTATIONS

Vaginal bleeding in the first trimester is a common symptom of EPL, and ectopic pregnancy should always be considered in the differential diagnosis and promptly ruled out. Vaginal bleeding in EPL can be described as being similar to that of a heavy menstrual cycle and can contain clots or tissue, but light spotting can occur as well. Moderate to heavy bleeding with pelvic pain or cramping is associated with an increased incidence of EPL.[33] Pelvic cramping without bleeding is not associated with EPL.[33] Patients who experience emesis during the first trimester have a decreased incidence of EPL.[33] Nausea, another common early pregnancy symptom, has no association with the incidence of EPL.[33] Although symptoms of bleeding, lower abdominal cramping, and vomiting are common in the first trimester in healthy patients, they also can be found in other disorders, such as ectopic pregnancy or molar pregnancy. A thorough history, physical examination, and diagnostic workup can confirm the diagnosis.

ASYMPTOMATIC PATIENTS

Although the majority of women experiencing an EPL will experience some symptoms, a small percentage will not. In this subset of women, the pregnancy loss is diagnosed as an incidental finding on ultrasound. Previously this was called *missed abortion*; however, the new terminology describes this as an asymptomatic incomplete abortion. The incidence of asymptomatic EPL was found to be about 38% of all EPLs in a nationwide registry study in Finland.[34] This percentage has increased and is likely due to increased sensitivity of home pregnancy tests and ultrasound imaging.

PHYSICAL EXAMINATION

The physical examination of a patient with a possible EPL should always include an assessment of the patient's hemodynamic status to ensure that she is stable. Patients with symptoms of possible EPL should undergo a speculum examination. However, the physical examination findings can vary in symptomatic and asymptomatic patients with EPL. Cervical dilation with bleeding or tissue in the vagina is commonly seen; however, a closed cervix without active bleeding does not rule out an EPL.

A bimanual examination can help a clinician better assess for cervical dilation if it is not visibly seen on speculum examination. Assess for adnexal tenderness, cervical motion tenderness, and peritoneal signs—patients with ectopic pregnancies can have a similar presentation to EPL.[2] Assessment of fundal height by bimanual examination may be helpful to compare with estimated gestational age obtained by last menstrual period, because complete molar pregnancies will typically have a larger fundal height measurement than would be expected for gestational age. The clinician may attempt to assess fetal heart tones if the estimated gestational age is at least 10 weeks; however, heart tones typically are not heard until 12 weeks. Although history and physical examination are important in the

evaluation of a possible EPL, they cannot be used alone to reach a definitive diagnosis.

DIAGNOSTIC CONSIDERATIONS

Patients with a positive urine pregnancy test and symptoms suspicious for an EPL should have a quantitative beta-HCG), complete blood cell count, and confirmation of Rh status. Correlation between beta-HCG and transvaginal ultrasound findings is critical so that a viable pregnancy is not misdiagnosed as an EPL, which could lead to unnecessary treatment of an otherwise desired and viable pregnancy. A gestational sac found on ultrasound should correspond to a beta-HCG level of 390 to 3,510 mIU/mL; a yolk sac, 1,094 to 17,716 mIU/mL; and a fetal pole, 1,294 to 47,685 mIU/mL.[35] Serial beta-HCG levels and transvaginal ultrasounds may be helpful in clinical situations in which the diagnosis is unclear. Quantitative beta-HCG levels that do not double within 72 hours are highly suspicious for an abnormal pregnancy but should not be used alone to diagnose an EPL. Serum progesterone less than 35 nmol/L is associated with EPL but cannot be used alone to diagnose an EPL.[36] Patients with heavy bleeding and evidence of hemodynamic compromise should also have a type and crossmatch, and consideration should be given to obtaining a disseminated intravascular coagulopathy panel. Administer Rho (D) immunoglobulin within 72 hours to a patient with first-trimester bleeding who is Rh negative and antibody screen negative.[1]

> Ultrasonography is essential in diagnosing an EPL.

Ultrasonography is essential in diagnosing an EPL. Common findings include a mean gestational sac of 25 mm or greater with no embryo, crown-rump length of 7 mm or greater with no cardiac activity, an empty gestational sac by 12 weeks 6 days gestation, and a gestational sac with an embryo or fetus with no cardiac activity.[1,37] In patients with disparate findings, rechecking the quantitative beta-HCG in 48 to 72 hours and repeating the ultrasound in 7 to 10 days may be appropriate as long as the patient is hemodynamically stable.

MANAGEMENT

The management of a patient with an EPL depends on the presentation and diagnosis. If a patient is hemodynamically stable, less than 13 weeks 6 days pregnant, and afebrile, consider expectant management, with patient education to monitor for excessive bleeding or signs of infection. A complete abortion in a patient who is Rh positive requires no medical or surgical management, but the patient should be appropriately counseled on expectations for future pregnancies. If another pregnancy is desired, pelvic rest is recommended for 2 weeks following resolution of symptoms, following which the patient may resume further attempts at conception.[1] Provide contraceptive counseling if subsequent pregnancy is not desired. Patients who are Rh negative should receive Rho (D) immunoglobulin.

In a patient with an incomplete abortion who is afebrile and hemodynamically stable, one dose of mifepristone 200 mg orally (if available) 24 hours before a single dose of misoprostol 800 mcg vaginally can be used. If mifepristone is unavailable, misoprostol alone can still be used.[1] If products of conception are still retained after 1 week and the patient is hemodynamically stable and afebrile, consider a repeat dose of misoprostol. Bleeding can be managed with methylergonovine 0.2 mg orally every 6 to 8 hours, but the patient should be counseled to report worsening of symptoms immediately. Surgical intervention is required if the patient is more than 13 weeks pregnant, hemodynamically unstable, septic, bleeding heavily, and if products of conception remain intact.[1] The follow-up of a patient who experiences an EPL includes serial beta-HCGs to ensure appropriate decline and reimaging with ultrasound to ensure that all products of conception have been passed.

An EPL diagnosis can be devastating to patients and their partners, and often is associated with other physical and psychologic diagnoses. Feelings of guilt, shame, and isolation are common and can lead to diagnoses of depression and anxiety.[38,39] History of EPL can also have long-term implications on maternal health. Recent studies have shown an increased incidence of type 2 diabetes, hypercholesterolemia, and hypertension in women with a past medical history of EPL.[40] Clinicians in all areas of primary care, emergency medicine, urgent care, and obstetrics and gynecology must be familiar with this outcome, given its prevalence and physical and emotional effect on patients.

CONCLUSION

EPL is a common occurrence during the reproductive years, so clinicians should be aware of common findings associated with the different types of EPLs. Clinicians also should be comfortable with the initial assessment and management of a patient with a possible EPL, so that the highest quality care can be delivered. **JAAPA**

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