EARLY PREGNANCY COMPLICATIONS

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Beyond early pregnancy loss (EPL), the differential diagnosis of pregnancy with bleeding and/or cramping includes

- normal intrauterine pregnancy,
- multiple gestation,
- ectopic pregnancy,
- hydatidiform mole.
INCIDENCE

- Early pregnancy loss (EPL) is the most common complication in early pregnancy.
- The incidence of EPL is as high as 31 percent, though that incidence decreases to approximately 10 percent when considering only losses occurring in clinically recognized pregnancies.
- The incidence of second-trimester loss up to 20 weeks gestation is less than 1 percent.
- The rate of pregnancy loss appears to be further influenced by maternal age and history of prior pregnancy loss.
Early pregnancy loss
nonviable, intrauterine pregnancy within the first trimester (up to 12+6 weeks from the last menstrual period)
termology has included "miscarriage," "blighted ovum," "spontaneous abortion," and "missed abortion"

Early second-trimester pregnancy loss
is one that occurs after 13+0 and prior to 20+0 weeks of gestation
The 20 week cutoff is arbitrary and not related to any physiologic differences between pregnancies less than 20 weeks versus greater than 20 weeks.
By convention, pregnancies lost after 20 weeks are typically referred to as stillbirth or fetal death.

Stillbirth or fetal death – Pregnancy loss that occurs at 20 weeks gestation or later, or at a weight of 350 grams or greater, is generally referred to as a stillbirth or fetal death,
FIRST TRIMESTER BLEEDING

Vaginal bleeding is common in the first trimester (0 to 13+6 weeks).
It may be any combination of light or heavy, intermittent or constant, painless or painful.

Causes

The four major sources of nontraumatic bleeding in early pregnancy are:

- Ectopic pregnancy
- Early pregnancy loss (threatened, inevitable/incomplete, complete)
- Implantation of the pregnancy
- Cervical, vaginal, or uterine pathology (eg, polyps, inflammation/infection, trophoblastic disease)
Bleeding related to early pregnancy loss (also called miscarriage or spontaneous abortion) is the most common nontraumatic cause of first trimester bleeding (prevalence: 15 to 20 % of pregnancies).

Although bleeding may be heavy, almost all women remain hemodynamically stable; only about 1 percent of expectantly managed women require blood transfusion.

Ectopic pregnancy is much less common (prevalence: 2 % of pregnancies), but the most serious etiology of first trimester bleeding as rupture of the extrauterine pregnancy is a potentially life-threatening complication; therefore, this diagnosis must be excluded in every pregnant woman with bleeding.
The source is virtually always maternal, rather than fetal.

Bleeding may result from disruption of blood vessels in the decidua (i.e., pregnancy endometrium) or from discrete cervical or vaginal lesions.
Bleeding and cramping are the most common presenting complaints of symptomatic women with uncomplicated EPL.

Women may also note a loss or reduction of pregnancy symptoms, such as decreased breast tenderness and/or nausea and vomiting. Alternately, some women are asymptomatic, and EPL is discovered incidentally or on routine ultrasound in early pregnancy.

While bleeding in the first trimester of pregnancy is fairly common and occurs in 20 to 30 percent of pregnant women, most women with first-trimester bleeding will not have an EPL.

The volume of vaginal bleeding during EPL varies considerably, and women often report passing clots or tissue.

The pain that occurs with EPL is often crampy in nature and can be mild to severe, especially during passage of gestational tissue.

The pain can be constant or intermittent and is often associated with vaginal bleeding.

As bleeding and cramping are also symptoms of other early pregnancy complications, including ectopic and molar pregnancy, pregnant women with vaginal bleeding or pelvic pain should be evaluated.
Asymptomatic

EPL can be an incidental finding on pelvic ultrasound.

Highly sensitive pregnancy tests and ultrasounds enable diagnosis of pregnancy, and EPL, in women prior to the onset of symptoms.
Complicated EPL

The most common complications associated with EPL are hemorrhage and infection, which can be severe.

- While vaginal bleeding is common in women with EPL, onset of severe hemorrhage can necessitate transfusion and surgical evacuation.

- Women with hemorrhage typically present with heavy vaginal bleeding combined with orthostatic vital signs, anemia, and/or tachycardia. The overall risk of this is low, approximately 1 percent.

- The incidence of intrauterine infection at the time of EPL varies by gestation. It is approximately 15 percent in the first 12 weeks, then as much as 66 percent for losses between 12 and 24 weeks.

- Signs and symptoms include abdominal or pelvic pain, uterine tenderness, purulent discharge, and/or systemic signs of infection, such as fever, tachycardia, or hypotension.

- Infectious complications can occur spontaneously or can follow medical or surgical interventions.

- Women who may be less likely to expect or recognize their pregnancy early in gestation, such as adolescents, perimenopausal women, or women with irregular menses, might also be at higher risk of later presentation and/or complications.
Types of miscarriage

Complete early pregnancy loss / miscarriage

When an early pregnancy loss occurs before 12 weeks of gestation, it is common for the entire contents of the uterus to be expelled, thereby resulting in complete pregnancy loss.

If this has occurred

- the uterus is small on physical examination
- well contracted with an open or closed internal cervical os
- scant vaginal bleeding
- and only mild cramping.
- Ultrasound will reveal an empty uterus and no extraterine gestation.

A complete early pregnancy loss can be distinguished from an ectopic pregnancy by

- examining the tissue that was passed to confirm products of conception
- by demonstrating falling rather than rising or plateaued hCG levels
- and by patient description of diminishing bleeding and pain.

No further intervention is needed for complete early pregnancy loss if chorionic villi are identified by pathologic examination of the products of conception. However, if no villi are identified or no specimens are available for pathologic examination, then serum hCG levels should be followed serially until the level is undetectable.
Incomplete early pregnancy loss

When early pregnancy loss is inevitable, the internal os of the cervix is dilated, vaginal bleeding is increasing, and painful uterine cramps/contractions are present.

The gestational tissue often can be felt or seen at the internal cervical os; passage of this tissue typically occurs within a short time.

Management may be expectant, or a medical or surgical intervention to complete the process can be undertaken.

At a more advanced stage, the membranes may rupture and the fetus may be passed, but significant amounts of placental tissue can be retained, resulting in an incomplete early pregnancy loss.

This is most common in the late first trimester and early second trimester.

On examination,

- the internal cervical os is open
- gestational tissue may be observed in the cervical canal
- and the uterine size is smaller than expected for gestational age, but not well contracted.
- The amount of bleeding varies, but can be sufficiently severe to cause hypovolemic shock.
- Painful cramps/contractions are often present.
- Ultrasound reveals tissue in the uterus. Medical or surgical evacuation is generally performed.
Missed miscarriage

A missed abortion refers to in-utero death of the embryo or fetus prior to the 20th week of gestation, with retention of the pregnancy for a prolonged period of time.

- Women may notice that symptoms associated with early pregnancy (eg, nausea, breast tenderness) have abated and they do not “feel pregnant” anymore.
- Vaginal bleeding may occur.
- The internal cervical os usually remains closed.
- Ultrasound reveals an intrauterine gestational sac with or without an embryonic/fetal pole, but no embryonic/fetal cardiac activity.
- Management may be expectant or a medical or surgical intervention to complete process can be undertaken.

Vanishing twin — The term “vanishing twin” has been used to describe a singleton pregnancy which results from very early loss of one member of a multiple gestation.

Vanishing twins are often the product of assisted reproduction techniques and can be associated with vaginal bleeding

- Vaginitis, trauma, tumor, warts, polyps, fibroids — These conditions are diagnosed by visual inspection, with ancillary tests as indicated (eg, wet mount and pH of vaginal discharge, cervical cytology and/or biopsy of mass lesions, ultrasound examination of uterus to detect neoplastic lesions). Even if a lesion appears to be the source bleeding on pelvic examination, it is prudent to always consider the possibility of ectopic pregnancy in women with first trimester bleeding, especially if associated with pain. (See ‘Ectopic pregnancy’ above.)
- Management of bleeding related to these conditions depends upon the specific condition. (Refer to individual topic reviews on each subject).
Threatened early pregnancy loss, diagnostic criteria

- Vaginal bleeding
- Closed cervix
- Sonographic visualization of an intrauterine pregnancy with detectable fetal cardiac activity is diagnostic of threatened early pregnancy loss.

The term "threatened" is used to describe these cases because early pregnancy loss does not always follow vaginal bleeding, even after repeated episodes or large amounts of bleeding.

In fact, 90 to 96 percent of pregnancies with both fetal cardiac activity and vaginal bleeding at 7 to 11 weeks of gestation are not lost; the higher ongoing pregnancy rate is associated with bleeding at the later end of the gestational age range.

- Bleeding in these cases is likely due to disruption of decidual vessels at the maternal-fetal interface. These separations generally cannot be visualized by ultrasound, but sometimes appear as a subchorionic hematoma.

- Management is expectant. The diagnosis and outcome of subchorionic hematoma are discussed in more detail separately.
Classifications of Spontaneous Abortions

Missed
- No vaginal bleeding
- Closed cervical os
- No fetal cardiac activity or empty sac

Threatened
- Vaginal bleeding and cramping
- Cervix closed and soft
- Fetal cardiac activity

Inevitable
- Vaginal bleeding and cramping
- Rupture of membranes
- Dilated cervical os
- Products of conception may be seen or felt at or above cervical os

Incomplete
- Vaginal bleeding and cramping
- Dilated cervical os
- Some products of conception expelled

Complete
- Vaginal bleeding
- Closed cervical os
- Products of conception completely expelled
Types of Miscarriages

**Missed**
- No vaginal bleeding
- Closed cervical os
- No fetal cardiac activity or empty sac

**Threatened**
- Vaginal bleeding
- Closed cervical os
- Fetal cardiac activity

**Inevitable**
- Vaginal bleeding
- Dilated cervical os
- Products of conception may be seen or felt at or above cervical os

**Incomplete**
- Vaginal bleeding
- Dilated cervical os
- Some products of conception expelled & some remain

**Complete**
- Vaginal bleeding
- Closed cervical os
- Products of conception completely expelled
Etiology/causes

Common etiologies/causes of early pregnancy loss (EPL) include:

- chromosomal abnormalities
- maternal anatomic abnormalities
- trauma.
Chromosomal abnormalities

- Chromosomal abnormalities are present in up to 70 percent of pregnancy losses before 20 weeks.
- In a study that evaluated 80 women with pregnancy loss at <20 weeks gestation with chromosomal microarray analysis, genetic abnormalities were reported in 9 percent of pre-embryonic losses, 69 percent of embryos between 6+0 weeks and 9+6 weeks, and 33 percent of fetuses between 10+0 weeks and 19+6 weeks.
- The use of chromosomal microarray likely increased the ability to identify earlier preclinical losses that previously were undetected by karyotype.

Maternal anatomic anomalies

- Anatomic anomalies, such as uterine leiomyomas (fibroids), polyps, adhesions, or septa, may be associated with EPL based on their size and position in relation to the developing pregnancy.
- In a study of 104 women with recurrent pregnancy loss of multiple types, the most common structural diagnoses that likely contributed to the loss were intrauterine adhesions (Asherman syndrome, 15 percent), fibroids (14 percent), uterine septum (3 percent), and endometrial polyps (2 percent).
- The impact of fibroids on pregnancy loss likely varies by other factors, such as distortion of the uterine cavity and/or blood supply.

Trauma

- Significant trauma can cause EPL.
- The developing embryo is relatively protected within the uterus in early pregnancy, but trauma that results in direct impact to the uterus can result in EPL. This can be due to violent trauma (gunshot wounds, penetrating injuries) or iatrogenic trauma, as with chorionic villus sampling and amniocentesis.
Clinical manifestation of miscarriage

Early pregnancy loss (EPL)/ miscarriage

- can be characterized by the presence or absence of symptoms and whether there is complete or incomplete passage of tissue.

- Complete EPL /miscarriage – EPL with complete passage of pregnancy tissue. Complete passage can occur spontaneously (without intervention)

- Incomplete EPL/ miscarriage – EPL with tissue retained within the uterus (fetal or placental tissue). Incomplete EPL can occur after partial spontaneous passage of pregnancy tissue or following medical or surgical treatment. It is often symptomatic, but the absence of symptoms does not exclude the possibility of retained tissue.
  - Threatened miscarriage
  - Inevitable miscarriage
  - Missed
  - septic
Vaginitis, trauma, tumor, warts, polyps, fibroids

- These conditions are diagnosed by visual inspection.
- With ancillary tests as indicated (eg, wet mount and pH of vaginal discharge, cervical cytology and/or biopsy of mass lesions, ultrasound examination of uterus to detect neoplastic lesions).
- Even if a lesion appears to be the source bleeding on pelvic examination, it is prudent to always consider the possibility of ectopic pregnancy in women with first trimester bleeding, especially if associated with pain.
- Management of bleeding related to these conditions depends upon the specific condition.
Physiologic or implantation bleeding

- This is a diagnosis of exclusion.
- It is characterized by a small amount of spotting or bleeding approximately 10 to 14 days after fertilization (at the time of the missed menstrual period),
- is presumed to be related to implantation of the fertilized egg in the decidua (ie, lining of the uterus)
- No intervention is indicated.
Prognosis of EPL

Studies consistently show an association between first trimester bleeding and adverse outcome (e.g., early pregnancy loss, preterm birth, preterm prelabor rupture of membranes, fetal growth restriction) later in pregnancy.

The prognosis is best when bleeding is light and limited to early pregnancy (i.e., less than 6 weeks of gestation).

The prognosis worsens when bleeding is heavy or extends into the second trimester.

There are no effective interventions, but women can be reassured of the low likelihood of adverse outcome.

In particular, bed rest is unnecessary and will not improve outcome.
Common risk factors for pregnancy loss include:

- increasing maternal age
- medical conditions
- medication and/or substance use
- and environmental exposures.
EPL risk

1. Increasing age
   - Extremes of age increase the risk of pregnancy loss
   - with age >35 years being the most significant risk factor because of the strong association with fetal chromosomal abnormalities
   - the risk of miscarriage (after excluding induced abortions) was lowest (10 percent) in women age 25 to 29 years and rose to a high of 57 percent for women age ≥45 years While the impact of increasing paternal age is somewhat less clear
   - EPL risk does appear to rise with increasing paternal age as well

2. Prior pregnancy loss
   - Prior pregnancy loss appears to increase the risk of subsequent pregnancy loss, independent of maternal age.
   - the risk of miscarriage increased among women whose prior pregnancy ended in a miscarriage
3: Maternal medical conditions

- **Infection**
  - 15 percent of EPL is associated with an infectious etiology. Parvovirus B19 infection in pregnancy has a nearly 8 percent cumulative incidence of loss.
  - Untreated syphilis leads to a 21 percent increased risk of fetal loss and stillbirth.
  - Maternal cytomegalovirus (CMV) infection has a 2.5 increased odds of EPL as compared with noninfection.
  - However, maternal infection with HIV or toxoplasmosis does not appear to be associated with an increased risk of EPL.

- **Obesity**
  - Obesity is more strongly and consistently associated with pregnancy loss than either type 1 or type 2 diabetes. A body mass index greater than 25 was associated with a nearly 70 percent increased odds of EPL after spontaneous or assisted conception.

- **Diabetes**
  - The effects of type 1 and type 2 diabetes on early pregnancy can be extreme, even resulting in lethal fetal anomalies or pregnancy loss. Euglycemia in the preconception and periconception time periods brings this risk back to baseline.

- **Thyroid disease**
  - Both hyper- and hypothyroidism have been associated with increased risk of pregnancy loss.

- **Stress**
  - Both acute and chronic stress can increase the risk of pregnancy loss.

- **Inherited thrombophilias**
  - The effect of inheritable thrombophilias on EPL risk is unclear as the body of evidence conflicts.

- **Pregnancy with intrauterine device (IUD) in place**
  - Though pregnancy with an IUD in place is relatively rare, for those patients who choose to continue their pregnancies, the risk of EPL appears to be higher for women who elect to leave the IUD in place rather than have it removed.
- **4-Medication and substance use**
  - As an example of the complicated nature of medication and EPL risk, the nonsteroidal anti-inflammatory drugs (NSAIDs) aspirin and indomethacin are used for specific obstetric indications (preeclampsia prevention and treatment of acute preterm labor) while other NSAIDs, including ibuprofen and diclofenac, may increase EPL risk.

- **5-Environmental factors and exposures**
  - Exposure to ionizing radiation is associated with EPL, while excessive lead, arsenic, and air pollution exposure appear to increase the risk.

- **6-Race and ethnicity**
  - Increased risk of EPL in women of color compared with white women.

- **7-Subchorionic hematoma**
  - Subchorionic hemorrhage or hematoma is associated with increased risk of EPL, particularly when it amounts to 25 percent or more of the volume of the gestational sac.
  - Women with subchorionic hematoma had double the odds of EPL compared with women without.
  - Location of the hematoma also appears to impact outcome.
DIAGNOSTIC EVALUATION

**History**

- A history of vaginal bleeding and/or crampy pelvic pain in a woman with known pregnancy is suggestive of EPL but is not diagnostic.
- Women with EPL may also note a reduction in pregnancy-related symptoms that were previously present.
- Occasionally, EPL can be diagnosed by history alone in a patient who reports heavy vaginal bleeding with a known intrauterine pregnancy whose subsequent human chorionic gonadotropin (hCG) testing is negative.
- However, in most cases, further evaluation with ultrasound or serial hCG testing is required for definitive diagnosis.

**Physical examination**

- Patients who present with bleeding in pregnancy first undergo a speculum examination to assess the source and quantity of bleeding.
- Signs suggestive of EPL include bleeding coming from the cervix and an open cervical os.
- Traditionally, the findings of vaginal bleeding with an open cervix were diagnosed as an "inevitable abortion."
- A bimanual examination can also determine whether the cervix is open and whether there is tissue within the cervical canal.
- Lastly, absence of fetal heart tones on handheld Doppler in a pregnancy of 12 weeks or greater should prompt further evaluation for pregnancy loss,
Imaging

- When available, transvaginal ultrasound is generally performed in all pregnant women with signs or symptoms suggestive of pregnancy loss to confirm both an intrauterine gestation and evidence of viability.

- Women whose ultrasound demonstrates an intrauterine pregnancy but no fetal cardiac activity undergo repeat ultrasound at a future date to assess for interval change, unless diagnostic criteria for EPL are met.

- If transabdominal ultrasound is done instead, but is unable to demonstrate cardiac activity in an intrauterine pregnancy, then transvaginal ultrasound should be performed.

- Women with a positive pregnancy test but no intrauterine pregnancy seen on ultrasound are diagnosed as having a pregnancy of unknown location and followed carefully with repeat imaging and possibly serial serum hCG levels.

- These women may have an early intrauterine pregnancy, an ectopic pregnancy, or a molar pregnancy.

- The timing of initial ultrasound in asymptomatic pregnant women varies.

- We advise that a pelvic ultrasound be deferred until at least six weeks gestation from the last menstrual period to avoid unnecessary evaluations for pregnancy of unknown location.

- An initial ultrasound for a patient at seven to eight weeks gestation is more likely to identify the presence of fetal cardiac activity and thus avoid the need for a follow-up ultrasound.

- Women with risk factors for pregnancy loss may undergo ultrasound at the initial prenatal visit, while for others the first ultrasound may occur at the time of first-trimester aneuploidy screening or at the time of second-trimester fetal anatomy assessment.
If ultrasound is available, serum hCG and progesterone have limited utility in the diagnostic evaluation of pregnant women suspected of having EPL.

hCG is useful if a sac is not seen on ultrasound to help determine if there is concern for ectopic pregnancy.

A dramatic drop in hCG >25 percent over 48 hours in the setting of uterine bleeding is highly suggestive of EPL and may be especially helpful if ultrasound is not easily available.

By contrast, hCG testing is commonly performed as part of the assessment for pregnancy of unknown location and is often helpful in excluding ectopic pregnancy.

In general, once an intrauterine gestational sac is seen on ultrasound, the diagnosis of pregnancy loss is made based on the ultrasonographic criteria below, and laboratory testing is not indicated.

Given the substantial variation in hCG levels at any gestational age, one hCG value is rarely suggestive of pregnancy loss, and a single hCG value <4000 milli-international units/mL should be interpreted with great caution.
It is important to consider that the rate of hCG increase and trends may be unpredictable, particularly at low levels. Three serial hCGs are typically needed to establish a trend. In normal pregnancies, average hCG levels plateau at approximately 8 to 11 weeks and then decline.

Serum hCG testing is sometimes performed in conjunction with an ultrasound to assess the viability of a pregnancy.

In counseling patients about the probability of a continuing pregnancy given a single hCG level and their ultrasound findings, we use data from an analysis of 651 pregnancies that concluded that discriminatory hCG levels at which structures would be predicted to be seen 99 percent of the time were 3510 milli-international units/mL for gestational sac; 17,716 milli-international units/mL for yolk sac; and 47,685 milli-international units/mL for fetal pole.

Serum progesterone has been used to assess pregnancy viability, as low serum progesterone levels are associated with EPL. In a study of 360 pregnant women with bleeding in early pregnancy at 6 to 10 weeks gestation, a cutoff of <35 nmol/L led to a positive predictive value for EPL of 68 percent and a negative predictive value of 91 percent.

Serum progesterone testing may be appropriate in some clinical settings to assess a patient’s risk of EPL in the setting of bleeding, but it is not used for the diagnosis of EPL.
Once an intrauterine pregnancy is identified on ultrasound, pregnancy loss is diagnosed if any subsequent ultrasound (performed routinely or for symptoms) shows no intrauterine pregnancy or loss of previously seen cardiac activity.

In patients who have an initial transvaginal ultrasound that demonstrates an intrauterine pregnancy without fetal cardiac activity, the diagnosis of early pregnancy loss (EPL) is based on the following criteria, which achieve essentially 100 percent specificity and positive predictive value (ie, no chance of a viable pregnancy) A gestational sac ≥25 mm in mean diameter that does not contain a yolk sac or embryo.

An embryo with a crown rump length (CRL) ≥7 mm that does not have cardiac activity.

After a pelvic ultrasound showed a gestational sac without a yolk sac, absence of an embryo with a heartbeat in ≥2 weeks.

After a pelvic ultrasound showed a gestational sac with a yolk sac, absence of an embryo with a heartbeat in ≥11 days.
Findings that are suspicious for, but not diagnostic of, pregnancy loss include:

- CRL <7 mm and no heartbeat.
- Mean sac diameter of 16 to 24 mm and no embryo.
- Absence of embryo with a heartbeat 7 to 13 days after a scan that showed a gestational sac without a yolk sac.
- Absence of embryo with a heartbeat 7 to 10 days after a scan that showed a gestational sac with a yolk sac.
- Absence of embryo ≥6 weeks after last menstrual period.
- Empty amnion (amnion seen adjacent to yolk sac with no visible embryo).
- Enlarged yolk sac (>7 mm).
- Small gestational sac in relation to the size of the embryo (<5 mm difference between mean sac diameter and CRL).
EARLY SECOND-TRIMESTER PREGNANCY LOSS

Early second-trimester pregnancy loss, or fetal death, occurs in approximately 2 to 3 percent of pregnancies. Conventionally, this is defined as fetal death between 13 and 20 weeks, and losses after 20 weeks gestation are defined as stillbirth, but this cutoff does not have a biological basis.

Known and suspected etiologies of second-trimester pregnancy loss include:

- Infection, including chorioamnionitis and maternal viral infection
- Chronic stressors, including contributions from racial/ethnic, financial or other disparities, chronic food or housing insecurity, and other long-term life stressors \[13\]
- Uterine malformation
- Cervical insufficiency
- Fetal malformation or syndromes such as anencephaly, trisomies, renal agenesis, or hydrops
- Thrombophilies
- Abruption
- Premature preterm rupture of membranes
- Preterm labor
Infection appears to often be either a primary or secondary factor.

In one study, 77 percent of losses had histologic evidence of chorioamnionitis, compared with a control group undergoing induction pregnancy termination.

This is much higher than the 15 percent incidence of infection with EPL at less than 12 weeks gestation.

Racial disparities in loss are also more pronounced between 10 and 20 weeks, with self-reported black race conferring nearly double the adjusted hazard ratio as compared with white race.

Signs and symptoms of second-trimester pregnancy loss include bleeding, signs of chorioamnionitis, cramping/pain, or labor.

Diagnosis of second-trimester pregnancy loss includes ultrasound documentation of fetal death or spontaneous delivery.

All pregnancies prior to 20 weeks are previable, and if a woman in the early second trimester experiences significant, life-threatening hemorrhage or intrauterine infection, intervention should be undertaken for maternal health and safety, even prior to the loss of fetal heart tones.
Ectopic pregnancy: Clinical manifestations and diagnosis

- An ectopic pregnancy is an extrauterine pregnancy.
- The majority of ectopic pregnancies occur in the fallopian tube (96 percent)
- Other possible sites include: cervical, interstitial (also referred to as cornual; a pregnancy located in the proximal segment of the fallopian tube that is embedded within the muscular wall of the uterus), hysterotomy (cesarean) scar, intramural, ovarian, or abdominal.
- In addition, in rare cases, a multiple gestation may be heterotopic (include both a uterine and extrauterine pregnancy).
- The diagnosis of ectopic pregnancy is based upon a combination of measurement of the serum quantitative human chorionic gonadotropin and findings on transvaginal ultrasonography.
Differential diagnosis and management

Ectopic pregnancy

- All women with early pregnancy bleeding and pain are assumed to have ectopic pregnancy until this diagnosis has been excluded by laboratory and imaging studies.
- Women with a history of ectopic pregnancy or other risk factors for the disorder are at highest risk, but many women with ectopic pregnancy have no risk factors.
- The discriminatory zone is the serum hCG level above which a gestational sac should be visualized by transvaginal ultrasound if an intrauterine pregnancy is present.
- In the hands of an experienced ultrasonographer, absence of an intrauterine pregnancy on transvaginal ultrasound examination when the hCG concentration is greater than 2000 IU/L (greater than 6000 IU/L for transabdominal ultrasound) strongly suggests ectopic pregnancy.
- An adnexal mass may or may not be seen.
- The presence of hemodynamic instability and a tender abdomen suggest the ectopic pregnancy has ruptured.
- Management of ectopic pregnancy is generally medical or surgical.
- Expectant management can be dangerous for the mother, but may be possible in rare cases.
- Even if an intrauterine pregnancy is diagnosed, the possibility of heterotopic pregnancy should be kept in mind, even though rare (1 in 30,000 pregnancies). This is particularly important in women who conceived via an assisted reproductive technique (ART) since these patients are at increased risk of this pregnancy complication (1.5 per 1000 ART pregnancies).
Uncommon sites of ectopic pregnancy

These ectopic pregnancy sites are uncommon:

- Cervical
- Hysterotomy scar
- Rudimentary uterine horn
- Interstitial
- Ovarian, and abdominal pregnancy.

Regardless of the location, the endometrium often responds to ovarian and placental production of pregnancy-related hormones, so vaginal bleeding is a common symptom.

Cervical pregnancy is estimated to occur in 1/2500 to 1/18,000 pregnancies and accounts for 1 percent of ectopic pregnancies.

Interstitial pregnancy accounts for up to 1 to 3 percent of ectopic pregnancies.

Ovarian pregnancy occurs in 1/2100 to 1/60,000 pregnancies and accounts for 1 to 3 percent of ectopic pregnancies.

Abdominal pregnancy accounts for up to 1.4 percent of ectopic pregnancies. These pregnancies can go undetected until an advanced age and often result in severe hemorrhage. Rates of maternal mortality have been reported as high as 20 percent.

Intramural pregnancy refers to pregnancy implanted within the myometrium of the uterus. This type of pregnancy is extremely rare with less than 50 reported cases in the literature.

Cesarean scar pregnancy (CSP) is estimated to occur in 1 per 2226 pregnancies and 6 per 100 ectopic pregnancies after cesarean deliveries. In CSP, the embryo is implanted in the cesarean scar.
Ovarian pregnancy
Sonographic diagnosis of an ovarian pregnancy is difficult.

- The diagnosis of ovarian pregnancy is typically made at the time of surgery, but differentiation from a hemorrhagic ovarian cyst or pregnancy in the distal fallopian tube can be difficult.
- Ultrasound may suggest the diagnosis preoperatively.
- Strict histopathological criteria are used to distinguish ovarian pregnancies from those originating in the fallopian tube. The exact diagnosis is not clinically important, as these pregnancies are usually treated by surgical excision of the involved organs. Methotrexate.
- treatment has been successful in case reports.

Interstitial pregnancy

- The interstitial portion of the fallopian tube is the proximal segment that is embedded within the muscular wall of the uterus. A pregnancy implanted at this site is called an interstitial pregnancy.
- the term cornual pregnancy is also widely used to describe a pregnancy at this location.
- Originally, the term cornual pregnancy referred only to pregnancies implanted in either the horn of a bicornuate uterus, a rudimentary horn of a unicornuate uterus, or in one side of a septated or partially septated uterus.
Ectopic pregnancy may also be asymptomatic.

The most common clinical presentation of ectopic pregnancy is first-trimester vaginal bleeding and/or abdominal pain. Clinical manifestations of ectopic pregnancy typically appear six to eight weeks after the last normal menstrual period, but may occur later, especially if the pregnancy is at an extrauterine site other than the fallopian tube.

Normal pregnancy discomforts (e.g., breast tenderness, frequent urination, nausea) are sometimes present in addition to the symptoms specifically associated with ectopic pregnancy.

There may be a lower likelihood of early pregnancy symptoms in women with ectopic pregnancy because progesterone, estradiol, and human chorionic gonadotropin may be lower in ectopic pregnancy than in normal pregnancy.

An ectopic pregnancy may be unruptured or ruptured at the time of presentation to medical care.

Tubal rupture (or rupture of other structures in which an ectopic pregnancy is implanted) can result in life-threatening hemorrhage. Any symptoms suggestive of rupture should be noted. These include severe or persistent abdominal pain or symptoms suggestive of ongoing blood loss (e.g., feeling faint or loss of consciousness).

Based upon the concern about the risk of rupture at the time or after presentation, clinicians should consider ectopic pregnancy as a diagnosis in any woman of reproductive age with vaginal bleeding and/or abdominal pain who has the following characteristics:

- pregnant, but does not have a confirmed intrauterine pregnancy;
- pregnancy status uncertain, particularly if amenorrhea of >4 weeks preceded the current vaginal bleeding;
- in rare cases, a woman who presents with hemodynamic instability and an acute abdomen that is not explained by another diagnosis.
Vaginal bleeding
- The volume and pattern of vaginal bleeding vary, and there is no bleeding pattern that is pathognomonic for ectopic pregnancy.
- Bleeding may range from scant brown staining to hemorrhage.
- Bleeding is typically intermittent, but may occur as a single episode or continuously.
- The vaginal bleeding associated with ectopic pregnancy is typically preceded by amenorrhea.

Abdominal pain
- The pain associated with ectopic pregnancy is usually located in the pelvic area.
- It may be diffuse or localized to one side.
- In cases in which there is intraperitoneal blood that reaches the upper abdomen or in rare cases of abdominal pregnancy, the pain may be in the middle or upper abdomen.
- If there is sufficient intraabdominal bleeding to reach the diaphragm, there may be referred pain that is felt in the shoulder. Blood pooling in the posterior cul-de-sac (pouch of Douglas) may cause an urge to defecate.
- The timing, character, and severity of abdominal pain vary, and there is no pain pattern that is pathognomonic for ectopic pregnancy.
- The onset of the pain may be abrupt or slow, and the pain may be continuous or intermittent.
- The pain may be dull or sharp; it is generally not crampy.
- The pain may be mild or severe. Tubal rupture may be associated with an abrupt onset of severe pain, but rupture may also present with mild or intermittent pain.
DIAGNOSTIC EVALUATION OF ECTOPIC PREGNANCY

- Confirm that the patient is pregnant.
- Evaluate the patient for hemodynamic instability.
- Determine whether the pregnancy is intrauterine or ectopic.
- Determine the site of the ectopic pregnancy.
- Perform additional testing to guide further management.

Confirm pregnancy and ectopic pregnancy symptoms

- **History** — A menstrual history should be taken and the estimated gestational age should be calculated. Risk factors for ectopic pregnancy should be elicited, including:
  - prior ectopic pregnancy,
  - current use of an intrauterine device,
  - prior tubal ligation,
  - and in vitro fertilization (IVF)
Human chorionic gonadotropin

- Measurement of hCG is performed initially to diagnose pregnancy and then followed serially to assess for ectopic pregnancy.
- In some cases, the diagnosis of ectopic pregnancy can be made after a single measurement of hCG in combination with transvaginal ultrasound.

In pregnant women, hCG can be detected in serum and urine as early as eight days after the luteinizing hormone surge (approximately 21 to 22 days after the first day of the last menstrual period in women with 28-day cycles).
Step two: Evaluate hemodynamic stability

- Women with ectopic pregnancy may become hemodynamically unstable if there is a rupture of and hemorrhage from the structure in which the pregnancy is implanted, usually the fallopian tube.

Physical examination

- Vital signs should be measured and hemodynamic stability assessed. The abdominal examination is often unremarkable or may reveal lower abdominal tenderness. If rupture has occurred, the abdomen may be distended and diffuse, or localized tenderness to palpation and/or rebound tenderness may be found on examination.
- A complete pelvic examination should be performed.
- A bimanual pelvic examination is performed; the examination is often unremarkable in a woman with a small, unruptured ectopic pregnancy.
- Palpation of the adnexa should be performed with only a small degree of pressure, since excessive pressure may rupture an ectopic pregnancy.
- Findings on examination may include cervical motion, adnexal, and/or abdominal tenderness. An extraovarian adnexal mass is noted in some women.
- The uterus may be somewhat enlarged, but will likely be smaller than appropriate for gestational age. Uterine enlargement in women with ectopic pregnancy may be due to endocrine changes of pregnancy, rare cases of heterotopic pregnancy, or incidental uterine pathology (most commonly, uterine fibroids).
INVESTIGATION

- Complete blood count
- Blood type and screen – An Rh(D)
- crossmatching for potential transfusion.
- Pretreatment laboratory tests – Women with a suspected ectopic pregnancy may require treatment with methotrexate, methotrexate pretreatment blood tests are complete blood count and renal and liver function tests.
The tests used to diagnose an ectopic pregnancy are a combination of serum quantitative hCG level and transvaginal ultrasound (TVUS).

- **Transvaginal ultrasound**: TVUS is the most useful imaging test for determining the location of a pregnancy.

- TVUS alone (without measurement of hCG) can exclude or diagnose an ectopic pregnancy **only** if one of the following findings is present:
  - Findings diagnostic of an IUP (i.e., gestational sac with a yolk sac or embryo). However, in women who conceived with ovulation induction or in vitro fertilization, a heterotopic pregnancy may rarely occur.
  - Findings diagnostic of a pregnancy at an ectopic site (gestational sac with a yolk sac or embryo).
  - In some ectopic gestations, a pseudosac is formed, that is merely fluid/blood in the endometrial cavity that may appear to be a gestational sac.

- TVUS can also detect findings that are suggestive, but not diagnostic, of ectopic pregnancy. An extraovarian adnexal mass is the most common ultrasound finding in ectopic pregnancy and is present in 89 percent or more of cases.

- If TVUS is nondiagnostic, it may be because the gestation is too early to be visualized on ultrasound. If so, serial measurements of the serum hCG concentration should be taken until the hCG discriminatory zone is reached.
A finding of echogenic fluid (consistent with blood) in the pelvic cul-de-sac and/or abdomen is consistent with rupture.

However, a small amount of fluid is present in many women and a small amount of blood may be present in other conditions (eg, spontaneous abortion).

A ruptured ovarian cyst is another condition that is common in pregnant women and may result in a small or large amount of blood. Rupture is indicated by ultrasound findings of free fluid (blood) in the abdominal cavity.
hCG discriminatory zone

- It is the serum hCG level above which a gestational sac should be visualized by TVUS if an IUP is present. In most institutions, the discriminatory zone is a serum hCG level of 2000 international units/L. However, results and discriminatory zone vary by laboratory and institution, and some data suggest that an IUP may not be visible until a higher level is reached (3500 international units/L).

- Setting the discriminatory zone at 3500 international units/L minimizes the risk of interfering with a viable IUP, if present, but increases the risk of delaying diagnosis of an ectopic pregnancy. However, it is important to emphasize that a patient should not be treated for an ectopic pregnancy based upon a single assessment with ultrasound and hCG. If an IUP has not been confirmed, the hCG is between 2000 and 3500, the patient is stable, and the pregnancy is desired, the patient may be followed with close surveillance until the hCG is at least 3500 iu/L.

- The discriminatory zone is higher for transabdominal ultrasound (approximately 6500 iu/L), but TVUS is the standard modality used to evaluate ectopic pregnancy.

- The reported sensitivity and specificity of TVUS for the detection of an ectopic pregnancy at a serum hCG of >1500 iu/L.
Step four: Follow with hCG and ultrasound to confirm or exclude ectopic pregnancy

Serial hCG

Measurement of serum quantitative hCG is performed initially to diagnose pregnancy and then followed to assess for ectopic pregnancy. For follow-up, hCG is measured serially (every 48 to 72 hours) to determine whether the increase is consistent with an abnormal pregnancy. A single hCG measurement alone cannot confirm the diagnosis of ectopic or normal pregnancy.

Normal pattern of hCG in pregnancy

Studies in viable IUPs have reported the following changes in serum hCG

- In a study of 20 patients in the first 40 days of pregnancy, the hCG concentration rose by at least 66 percent every 48 hours in 85 percent of viable IUPs; only 15 percent of viable pregnancies had a rate of rise less than this threshold

- A serum hCG that does not rise appropriately is consistent with an abnormal pregnancy. The hCG concentration rises at a much slower rate in most, but not all, ectopic and nonviable IUPs

- A decreasing hCG concentration is most consistent with a failed pregnancy (e.g., arrested pregnancy, tubal abortion, spontaneously resolving ectopic pregnancy, complete or incomplete abortion).
The clinical protocol for the evaluation for an ectopic pregnancy includes assessment with serum hCG and TVUS:

- **hCG below the discriminatory zone** – A serum hCG concentration <3500 international units/L (or another value, the discriminatory zone for the institution should be used) should be followed by repeated measurement of quantitative hCG to follow the rate of rise.

  - The most common protocol is to measure the hCG every two days. Thus, the protocol is as follows:
    - hCG is rising normally (increasing by ≥35 percent in 48 hours OR doubling in 72 hours) – The patient should be evaluated with TVUS when the hCG reaches 3500 international units/L. At that time, an IUP or ectopic pregnancy can be diagnosed by TVUS.
    - hCG is rising, but NOT normally – The lack of a normal rise in hCG across three measurements (the initial serum quantitative hCG and two additional serial measurements) is consistent with an abnormal pregnancy. The hCG level may be rising slowly or may plateau at or very close to the previous level. The clinician can be reasonably certain that a normal IUP is not present. The number of serial measurements to use to make the diagnosis has not been well studied. Some data suggest that use of three serial measurements is more effective than two measurements.
    - In patients with an abnormal rise in hCG, the TVUS should be repeated or diagnostic uterine aspiration performed. If there are findings that confirm an IUP, an ectopic pregnancy is excluded and the patient should be managed as a failed pregnancy. If an extraovarian adnexal mass is consistent with an ectopic pregnancy is visualized, then medical or surgical treatment is administered for a presumed ectopic pregnancy. If an extraovarian adnexal mass is not visualized, some clinicians administer methotrexate and others perform aspiration to exclude an IUP and thereby avoid medical therapy of nonviable IUP [33]. (See ‘Aspiration’ below.)

  - hCG is decreasing – A decreasing hCG is most consistent with a failed pregnancy (eg, spontaneous abortion, tubal abortion, spontaneously resolving ectopic pregnancy). To follow up with these patients, weekly hCG concentrations should be measured until the result is undetectable.

  - Patients who are being followed for suspected ectopic pregnancy should be counseled about the risk of rupture and should be advised to call if symptoms associated with rupture occur. These include the new onset of or a significant worsening of abdominal pain, vaginal hemorrhage, or feeling faint. In addition, women with a suspected ectopic pregnancy should be counseled about possible outcomes of the evaluation, including viable IUP or the end of a pregnancy with treatment for ectopic pregnancy.

- **hCG above the discriminatory zone** – For women with a quantitative serum hCG above the discriminatory zone, the results of TVUS guide management. If TVUS does not reveal an IUP and shows a complex extraovarian adnexal mass, an extrauterine pregnancy is almost certain. Treatment of ectopic pregnancy should be instituted. If the serum hCG level is ≥3500 milli-international units/mL and no IUP is visible on TVUS, it is almost certain that the pregnancy is extrauterine.

  - The diagnosis of ectopic pregnancy is less certain if no complex extraovarian adnexal mass can be visualized, since there is variability in the level of expertise among ultrasonographers. Furthermore, a serum hCG ≥2000 international units/L without visualization of intrauterine or extrauterine pathology may represent a multiple gestation, since there is no proven discriminatory level for multiple gestations. For these reasons, our next step in this clinical scenario is to repeat the TVUS examination and hCG concentration two days later. If an IUP is still not observed on TVUS, then the pregnancy is abnormal.
Ruptured versus nonruptured ectopic pregnancy

- Diagnosis of rupture of the structure within which the ectopic gestation is implanted (usually the fallopian tube) is a clinical diagnosis.
- The typical findings of rupture are abdominal pain, shoulder pain due to diaphragmatic irritation by blood in the peritoneal cavity, and, eventually, hypotension and shock.
- Abdominal examination findings include tenderness and possible peritoneal signs. The typical finding on TVUS is free blood in the peritoneal cavity.
- However, the presence or absence of peritoneal free fluid is not a reliable indicator of whether an ectopic pregnancy has ruptured.
- For women who undergo surgery, the diagnosis of rupture can be made by direct visualization.
Multiple gestation

- In women with an intrauterine multiple pregnancy, the serum human chorionic gonadotropin (hCG) level could be higher than 1500 milli-international units/mL and yet ultrasound examination will not reveal an intrauterine pregnancy (IUP).
- Levels of over 9000 international units/L have been described for intrauterine triplet pregnancies unobserved by transvaginal ultrasound (TVUS).

Heterotopic pregnancy

- The investigation for ectopic pregnancy can be terminated, under most circumstances, if a transvaginal sonogram reveals an IUP.
- Heterotopic pregnancy (combined intrauterine and extrauterine pregnancy) is rare, except among women conceiving through in vitro fertilization (IVF).
- The extrauterine pregnancy is usually in the fallopian tube, but can be at another location, such as the cervix.
NATURAL HISTORY

If left untreated, an ectopic pregnancy in the fallopian tube can progress to a tubal abortion or tubal rupture, or it may regress spontaneously.

- **Rupture** – Tubal rupture is usually associated with profound hemorrhage, which can be fatal if surgery is not performed expeditiously to remove the ectopic gestation. Salpingectomy is the most common surgical approach when the tube has ruptured. Ruptured ectopic pregnancy is the major cause of pregnancy-related maternal mortality in the first trimester [66]. Most of these deaths occur prior to hospitalization or proximate to the woman’s arrival in the emergency department.

- **Abortion** – Tubal abortion refers to expulsion of the products of conception through the fimbria. This can be followed by resorption of the tissue or by reimplantation of the trophoblasts in the abdominal cavity (i.e., abdominal pregnancy) or on the ovary (i.e., ovarian pregnancy). Tubal abortion may be accompanied by severe intra-abdominal bleeding, necessitating surgical intervention, or by minimal bleeding, not requiring further treatment.

- **Spontaneous resolution** – The incidence of spontaneous resolution of an ectopic pregnancy is unknown. In one older (1955) series of 119 hospitalized patients with typical ectopic pregnancy symptoms, 57 were safely managed expectantly, without surgical or medical intervention (except opiates). It is difficult to predict which patients will experience uncomplicated spontaneous resolution. Potential candidates are hemodynamically stable women with an initial human chorionic gonadotropin concentration less than 2000 international units/L that is declining.

- Gestational products left in the fallopian tube may resorb completely or, less commonly, may cause tubal obstruction. Alternatively, a tubal abortion may occur.
Three consecutive pregnancy losses, before 12 weeks gestation

RPL can be further divided into primary or secondary processes

Primary RPL refers to pregnancy loss in women who have never carried to viability.

In contrast, secondary RPL refers to pregnancy loss in a woman who has had a previous live birth. The prognosis for successful pregnancy is better with secondary RPL.

There is no specific term for describing women who have had multiple spontaneous miscarriages interspersed with normal pregnancies (ie, nonconsecutive pregnancy losses).
Approximately 15 percent of pregnant women experience sporadic loss of a clinically recognized pregnancy.

Just 2 percent of pregnant women experience two consecutive pregnancy losses.

Only 0.4 to 1 percent have three consecutive pregnancy losses.
RISK FACTORS AND ETIOLOGY

- Although RPL is an important problem in women's health, there are many unsolved questions regarding etiology, evaluation, and management.

- Unfortunately, the cause of RPL can be determined in only 50 percent of patients.

- General etiological categories of RPL include anatomic, immunological, genetic, endocrine, infectious, thrombophilic, and environmental factors.

- **Previous pregnancy loss**
  
  In a first pregnancy, the risk of miscarriage is 11 to 13 percent. After one miscarriage, this rate rises slightly to 14 to 21 percent. After two or three miscarriages, the rate is 24 to 29 percent and 31 to 33 percent, respectively. However, several factors influence these rates:
Uterine factors

- Acquired and congenital uterine abnormalities are responsible for 10 to 50 percent of RPL.

Anomalies

- Congenital uterine anomalies are present in 10 to 15 percent of women with RPL versus 7 percent of all women. Pregnancy loss may be related to impaired uterine distention or abnormal implantation due to decreased vascularity in a septum, increased inflammation, or reduction in sensitivity to steroid hormones.
- The septate uterus is the uterine anomaly associated with the poorest reproductive outcome and the most common uterine abnormality associated with RPL.

Leiomyoma

- Submucous leiomyomas that protrude into the endometrial cavity can impede normal implantation as a result of their position, poor endometrial receptivity of the decidua overlying the myoma, or degeneration with increasing cytokine production.

Endometrial polyps
Intrauterine adhesions
Intrauterine adhesions or synechiae lead to pregnancy loss because there is insufficient endometrium to support fetoplacental growth. The main cause of intrauterine adhesions is curettage for pregnancy complications.

Cervical insufficiency
Cervical insufficiency is a cause of recurrent midtrimester, but not early, pregnancy loss.

Defective endometrial receptivity
Estrogen and progesterone prepare the endometrium for pregnancy. Normal endometrial receptivity allows embryo attachment, implantation, invasion, and development of the placenta. These processes are likely to be disturbed when endometrial receptivity is defective, resulting in unexplained infertility and RPL. Causes of defective endometrial receptivity and biomarkers for evaluation of endometrial receptivity are under investigation.

Immunologic factors
Both autoimmune and alloimmune mechanisms have been proposed. Since the mechanisms that allow a mother to tolerate her semi-allogeneic conceptus are not well defined, it is difficult to assess the role of aberrant immunologic factors in reproductive failure.

Antiphospholipid syndrome
Several autoimmune diseases have been linked to poor obstetric outcome, but antiphospholipid syndrome (APS) is the only immune condition in which pregnancy loss is a diagnostic criteria for the disease. Five to 15 percent of patients with RPL may have APS.
Other immunological factors

- Allogeneic factors may cause RPL by a mechanism similar to that of graft rejection in transplant recipients. If the blastocyst is developmentally normal and intact, the embryo should be entirely protected by trophoblast cells.

- However, in some pregnancies, the blastocyst is genetically deformed and not fully intact. As a result, paternally-derived antigens are exposed to the maternal immune system, which leads to a graft rejection response. A secondary immune response would be expected to cause early rejection in cases of recurrent spontaneous abortion.

Endocrine factors

- Endocrine factors may account for 15 to 60 percent of RPL.
1. **Diabetes mellitus**
   - to increased frequencies of miscarriage and congenital malformations

2. **Polycystic ovary syndrome**
   - The miscarriage rate in women with polycystic ovary syndrome (PCOS) may be as high as 20 to 40 percent, which is higher than the baseline rate in the general obstetric population (10 to 20 percent)

3. **Thyroid antibodies and disease**
   - Some studies have reported an increased rate of fetal loss in women with high serum thyroid antibody concentrations (thyroid peroxidase or thyroglobulin), including those who are euthyroid. Poorly controlled thyroid disease (hypo- or hyper-thyroidism) is associated with infertility and pregnancy loss. Excess thyroid hormone increases the risk of miscarriage independent of maternal metabolic dysfunction

4. **Hyperprolactinemia**
   - Normal circulating levels of prolactin may play an important role in maintaining early pregnancy. Treatment to lower prolactin concentration was associated with a higher rate of successful pregnancy (86 versus 52 percent). Prolactin levels during early pregnancy were significantly greater in women who miscarried

5. **Luteal phase defect**
   - Progesterone is required for successful implantation and maintenance of pregnancy; therefore, disorders related to impaired progesterone production or action are likely to affect pregnancy success. Abnormal luteal-phase progesterone production may occur as the result of medical conditions such as elevated prolactin or abnormal thyroid function; women suspected to have one of these disorders are evaluated and treated for the underlying condition
5. Genetic factors

- Abnormalities of chromosome number or structure are the most common cause of sporadic early pregnancy loss, accounting for at least 50 percent of such losses in multiple studies.

- A significant proportion of RPL may also be associated with structural or numerical chromosomal abnormalities (e.g., aneuploidy, mosaicism, translocation, inversion, deletion, fragile sites). Single-gene, X-linked, or polygenic/multifactorial disorders can also result in sporadic or recurrent miscarriage.

6. Aneuploidy

- The risk of aneuploidy increases as the number of previous miscarriages increases.

- The relationship between the karyotype of the abortus and risk of RPL requires further study to better define which abnormalities are likely to be recurrent.
7. Thrombophilia and fibrinolytic factors

- Thrombosis of spiral arteries and the intervillous space on the maternal side of the placenta can impair adequate placental perfusion.
- The resulting abnormalities of the uteroplacental circulation may cause late fetal loss, intrauterine growth restriction, placental abruption, or preeclampsia.
- A relationship to early pregnancy loss is less clear and may be restricted to specific thrombophilic defects that have not been completely defined, or the presence of multiple defects.
- There is a large and contradictory literature on the association between maternal inherited thrombophilia and RPL occurring in the first trimester.

8. Environmental chemicals and stress

- Chemicals that have been associated with sporadic spontaneous pregnancy loss include anesthetic gases (nitrous oxide), arsenic, aniline dyes, benzene, ethylene oxide, formaldehyde, pesticides, lead, mercury, and cadmium.
Risk factors for ectopic
Some surgical instruments

Dilator
To open the cervix enough to get the baby out

Tenaculum
To grab the cervix

Curette
For cutting and scraping

Tools of Mass Destruction

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