Disorders of Early Pregnancy

Matthew Kippenhan

Approximately 25% of patients will experience some bleeding in the first trimester of pregnancy, with half of these patients proceeding to miscarriage. Risks for spontaneous abortion include advanced maternal age, previous spontaneous abortion, and prolonged time from ovulation to implantation. Other risk factors are smoking, alcohol, cocaine, caffeine, and use of nonsteroidal antiinflammatory drugs.

**PATHOPHYSIOLOGY**

The etiology of miscarriage can be classified as either intrinsic or extrinsic to the embryo. Intrinsic factors include genetic abnormalities and congenital conditions. Most cases of spontaneous abortion are due to genetic factors, either anembryonic gestations or chromosomal abnormalities. The majority of these defects arise de novo during fertilization and are not inherited. Genetic factors tend to lead to miscarriage early because of abnormal growth and development.

In contrast, later miscarriage is more often a result of extrinsic factors. Extrinsic causes of miscarriage include host factors such as fibroids, intrauterine adhesions, septate uterus, maternal infections, hypercoagulable states, endocrine abnormalities, and teratogen exposure. Although blunt trauma to the abdomen is an unlikely cause of miscarriage because of the well-protected placement of the uterus in the pelvis, traumatic procedures such as chorionic villus sampling and amniocentesis may induce miscarriage.

**KEY POINTS**

- Spontaneous abortion (before 12 weeks) will progress to completion with few complications, and incomplete or missed abortion (without shock, fever, or significant bleeding) can be managed expectantly.
- Rh immune globulin is effective for up to 12 weeks; no repeated dose is required if bleeding recurs in that time.
- Ectopic pregnancy is responsible for the greatest morbidity and mortality in early pregnancy; ruptured ectopic pregnancy remains responsible for 10% of pregnancy-related deaths.
- Women with a previous ectopic pregnancy have a 15% recurrence rate.
- Serum human chorionic gonadotropin (HCG) levels can vary by as much as 15% between laboratories, and an HCG level should be ordered when suspicion is high despite a negative urine HCG.
- Gestational trophoblastic disease (up to 75% of malignant cases) may develop after a nonmolar pregnancy (spontaneous and elective abortion, ectopic pregnancy, and term gestation); these patients have prolonged bleeding after delivery or miscarriage, with subsequent HCG levels that fail to return to undetectable values.

**PRESENTING SIGNS AND SYMPTOMS**

Spontaneous abortion is classified as threatened, inevitable, incomplete, complete, missed, or septic. Table 119.1 lists characteristics of these categories. Symptoms of spontaneous abortion include vaginal bleeding, suprapubic cramping or pain, and passage of tissue. Bleeding can vary from minor spotting to severe hemorrhage.

Threatened abortion is defined by vaginal bleeding with or without mild suprapubic cramping or pain. It is the most common manifestation of spontaneous abortion seen in the emergency department (ED). Examination shows a closed cervix, uterine size that correlates to gestational age, and bleeding varying from scant to heavy. Ultrasound imaging confirms an intrauterine pregnancy and fetal heart tones in appropriate gestational ages. Threatened abortion may resolve with progression to normal pregnancy, or it may progress to other forms of miscarriage.
Before the 12th week of gestation, most spontaneous abortions will progress to completion with few complications. After this time, patients are more likely to have an incomplete abortion and require medical or operative intervention.

A septic abortion occurs when infection develops during any stage of the abortion process. Implicated agents include *Staphylococcus aureus*, gram-negative rods, gram-positive cocci, and anaerobes. Risk factors include elective abortion, cytomegalovirus infection, amniocentesis, and incomplete abortion.

### Table 119.1 Classification of Spontaneous Abortion

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DEFINITION, CLINICAL CHARACTERISTICS</th>
<th>ULTRASONOGRAPHIC FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Bleeding and/or cramping with no passage of tissue, closed os, uterine size appropriate for dates, pregnancy viable</td>
<td>Intrauterine pregnancy (IUP), fetal heart tones (if age appropriate)</td>
</tr>
<tr>
<td>Inevitable</td>
<td>Open os without passage of products, pregnancy nonviable</td>
<td>IUP or products in the cervical canal</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Partial passage of products; open os, uterus not well contracted; variable bleeding; pregnancy nonviable</td>
<td>Persistent gestational tissue in the uterus</td>
</tr>
<tr>
<td>Complete</td>
<td>Products of pregnancy completely passed, closed os, minimal bleeding, uterus well contracted</td>
<td>Empty uterus</td>
</tr>
<tr>
<td>Missed</td>
<td>Intrauterine demise with no spontaneous passage of products, closed os</td>
<td>Absent fetal cardiac activity or anembryonic gestation, absent heart tones with a crown rump length &gt; 5 mm, absent fetal pole with &gt;18-mm mean sac diameter</td>
</tr>
<tr>
<td>Septic</td>
<td>Infection complicating any of the previously described categories</td>
<td>Persistent products of conception or hemorrhage within the uterine cavity</td>
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DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING

As mentioned previously, bleeding in early pregnancy is common. It may represent benign bleeding from implantation or marginal separation of the placenta. Many cases are idiopathic. Pathologic processes in the differential diagnosis include ectopic pregnancy, gestational trophoblastic disease, cervicitis, subchorionic hemorrhage, and cervical or vaginal malignancy. Vaginal lacerations from intercourse or trauma may be to blame. Occasionally, nongynecologic sources such as rectal bleeding or hematuria are mistaken for vaginal bleeding.

Pregnancy should be confirmed by a positive urine HCG test. A speculum examination should be performed to assess the degree of bleeding and cervical dilation, as well as to inspect for expelled products of conception. Bimanual examination can assess uterine size, cervical opening, and any abnormal masses or tenderness.

Laboratory studies include a complete blood count, quantitative HCG, and blood type with Rh status. With significant bleeding or other medical disease, coagulation parameters and typing and crossmatching for blood products should be ordered. Ultrasonography is essential for a full diagnosis and for guiding further management (Fig. 119.1). Even if it appears that the patient has passed the embryo, she should undergo ultrasound imaging to evaluate for any retained products.

### TREATMENT

Many patients with spontaneous abortion often need little or no intervention following accurate diagnosis and exclusion of other pathology. Expectant management is the only option for threatened abortion; education and ensuring adequate follow-up care are essential. The presence of fetal heart tones in women with symptoms of threatened abortion is reassuring; less than 5% of women younger than 36 years will miscarry, but this risk rises to 29% in those older than 40.1

Inevitable abortions may be managed either expectantly or by dilation and curettage. Both methods are generally acceptable. If products of conception are visible in the cervical os, gentle removal with ring forceps may allow the cervix to close and may control the bleeding. A complete abortion requires no further treatment as long as ultrasound scanning confirms that no retained products are present. Any retrieved tissue should be examined for villi, which will have a frondlike appearance.

Incomplete or missed abortions can be managed expectantly as long as shock, fever, or significant ongoing bleeding are absent. The time course for completion of a spontaneous abortion is highly variable, and patients will need education and routine gynecologic care to plan for dilation and curettage if tissue does not pass spontaneously or if the bleeding becomes heavy. Patients should attempt to collect the products of conception for examination and should undergo subsequent ultrasonography to assess whether all products of conception have passed. Studies have proved the safety of this practice.4 Approximately 90% of patients with incomplete and 76% of those with missed abortions require no surgical treatment when managed expectantly for 4 weeks. Complications occur in 1%, less than in those managed medically.7
Prostaglandins such as misoprostol can effectively induce abortion for pregnancy failure of longer than 12 weeks and may help control bleeding in patients with inevitable or incomplete abortions. The dose of misoprostol is 800 mcg administered vaginally or rectally, but this drug should be given only after consultation with a gynecologist. One large study showed an 84% success rate. Misoprostol induces spontaneous abortion, so any possibility of a desired viable pregnancy must be excluded.

Surgical management includes dilation and curettage or dilation and evacuation. Indications are listed in Box 119.1. Risks associated with surgical management are small and include uterine perforation, infection, adhesions, and anesthetic complications.

Women with significant hemorrhage or hemodynamic instability should first receive crystalloid volume replacement. If no response is seen or if the bleeding persists, either type-specific or type O-negative blood should be administered. Patients with septic abortions should be given broad-spectrum antibiotics in addition to dilation and curettage.

**Box 119.1 Indications for Dilation and Curettage in Patients with Spontaneous Abortion**

- Incomplete abortion
- Significant hemorrhage
- Signs of septic abortion
- Documented fetal demise or blighted ovum with no spontaneous passage (after a period of observation)
- Patient unwilling or unable to comply with expectant management

**RHo IMMUNE GLOBULIN**

Rh0 immune globulin (Rh0 IG) should be administered to any Rh-negative woman with signs of spontaneous abortion unless the father is also known to be Rh negative. It is administered in a dose of 50 mcg before the twelfth week of gestation and
in a dose of 300 mcg after 12 weeks. It is estimated that 50 mcg will neutralize 2.5 mL of fetal blood and that a 300-mcg dose will neutralize 15 mL. A 12-week-old fetus has approximately 4.8 mL of blood, and a 16-week-old fetus has about 30 mL of blood. It is unlikely that significant amounts of fetal blood will transfer to the maternal circulation during a first-term miscarriage, so the single, appropriate dose of immune globulin will be fully sufficient to prevent maternal antibody formation against the Rh antigen.

Rh₀ IG is effective for up to 12 weeks after administration, so patients with recurrent bleeding who already received immunization within that time frame do not need a repeated dose. If significant hemorrhage occurs later in pregnancy, especially in the setting of trauma, additional doses are necessary. Ideally, Rh₀ IG is administered within 72 hours of the event leading to fetal-maternal hemorrhage (Box 119.2).

**NEXT STEPS IN CARE AND FOLLOW-UP**

Emergency gynecologic consultation is needed for patients with significant hemorrhage or signs of infection. Others may be managed expectantly or with close follow-up as long as adequate outpatient care is ensured. Patients with missed abortions may ultimately need surgical management if they do not spontaneously pass tissue.

Patients should be instructed to contact their physician or return to the ED if heavy bleeding, severe pain, or fever develops. Bleeding should resolve over the course of a few weeks, and menses will generally resume within 6 weeks. Pelvic rest (no vaginal intercourse, tampons, or douching) for 2 weeks is often recommended because of the theoretic risk for infection, although no studies support this risk. Patients are often advised to not become pregnant for 2 to 3 months, but again no studies show worse outcomes if another pregnancy is achieved during this interval.

Psychosocial issues surrounding miscarriage are common, including feelings of guilt and sadness. Reassuring women that most miscarriages are due to genetic abnormalities and are not the result of their actions is essential. Women with substance abuse leading to abortion should be counseled appropriately. Referral for grief counseling may be appropriate. Patients with recurrent miscarriages should be offered referral for fertility treatment and genetics counseling.

**ECTOPIC PREGNANCY**

**EPIDEMIOLOGY**

Ectopic pregnancy, in which the developing embryo implants outside the uterine cavity, is responsible for the greatest morbidity and mortality in early pregnancy. The incidence of ectopic pregnancy in the United States has increased over the past 30 years, and it now accounts for 2% of all pregnancies.³ This increase has been attributed to rising rates of pelvic inflammatory disease, as well as the advent of assisted reproductive technologies.

At the same time there has been a decrease in the morbidity and mortality associated with ectopic pregnancy because of more widespread use of ultrasound and methotrexate. Despite advances in diagnosis and management, ruptured ectopic pregnancy remains responsible for 10% of pregnancy-related deaths.

**PATHOPHYSIOLOGY**

Risk factors for ectopic pregnancy are outlined in Box 119.3. Tubal pathology, the most significant risk factor, leads to abnormal transport and implantation of the embryo. The majority of cases arise in women with a history of pelvic inflammatory disease, and women with a previous ectopic pregnancy have a 15% recurrence rate. However, up to 50% of patients with an ectopic pregnancy have no identifiable risk factor.⁴

Genetic abnormalities in the embryo have not been found to be a risk factor for abnormal implantation. Although women using an intrauterine device or those who have undergone a sterilization procedure are at decreased overall risk for pregnancy, the incidence of ectopic pregnancy is increased in those who do become pregnant. For example, the pregnancy rate after tubal ligation is 0.1% to 0.8%, but as many as one third of these pregnancies are ectopic.

The most common location for ectopic implantation is the fallopian tube, which accounts for 95% of all ectopic
Approximately one half of patients are asymptomatic before tubal rupture. Of those with rupture, 99% have abdominal pain, 74% have amenorrhea, and 56% have vaginal bleeding.

An interstitial, or cornual, pregnancy occurs when the embryo is implanted in the proximal portion of the tube that is embedded in the muscle of the uterus. The tube at this location is more distensible, so the embryo may grow undetected for a longer period. It may not be discovered until 12 weeks or later. Ultrasonography demonstrates an asymmetric uterine thickness surrounding the gestational sac. However, a skilled ultrasonographer is required, and in the early stages it may be mistaken for a normal intrauterine pregnancy. Cornual pregnancy is associated with a 2% to 2.5% maternal mortality rate and is more likely than other tubal pregnancies to require hysterectomy.

A heterotopic pregnancy occurs when an intrauterine pregnancy is present simultaneously with an ectopic gestation. Its incidence was at one time estimated to be 1 in 30,000, but the true incidence is unknown. Thus an ectopic gestation can essentially be excluded if an intrauterine pregnancy is demonstrated by ultrasonography. Patients using assisted reproductive techniques have up to a 1% incidence of ectopic pregnancy, highest in patients with transfer of multiple embryos. In these patients, an ectopic gestation should not be excluded solely on the basis of the presence of an intrauterine pregnancy.⁹

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The differential diagnosis of ectopic pregnancy is listed in Box 119.4. Because of the high potential for morbidity, any patient with abnormal vaginal bleeding or abdominal or pelvic pain should be considered to have an ectopic pregnancy until proved otherwise (see Fig. 119.1).

**QUANTITATIVE HUMAN CHORIONIC GONADOTROPIN TESTING**

Urinary HCG testing is essential for any woman of childbearing age with abdominal pain. Commercially available kits detect as low as 20 mIU/mL, although there have been case reports of ectopic pregnancy with an undetectable urine HCG.

**BOX 119.4 Differential Diagnosis of Ectopic Pregnancy**

- Spontaneous abortion
- Benign bleeding from implantation
- Hemorrhage, rupture, or torsion of a corpus luteum cyst
- Molar pregnancy
- Pelvic inflammatory disease
- Endometriosis
- Appendicitis
- Diverticulitis
- Urinary tract infection
- Nephrolithiasis

**BOX 119.3 Risk Factors for Ectopic Pregnancy**

**High Risk**
- History of pelvic inflammatory disease
- Tubal surgery
- Previous ectopic pregnancy
- Tumor or congenital tubal abnormality
- In utero diethylstilbestrol exposure

**Moderate Risk**
- Previous genital infection, especially if recurrent
- Infertility
- More than one lifetime sexual partner

**Low Risk**
- Smoking
- Douching
- First intercourse when younger than 18 years
- Age older than 35 years
- In vitro fertilization
- Tubal ligation

**Fig. 119.2 Sites and rate of occurrence at each site of ectopic implantation.**
In normal pregnancy, HCG production begins shortly after fertilization with a peak of about 100,000 mIU/mL at approximately 41 days’ gestational age. In the early weeks of normal pregnancy, HCG levels are expected to double roughly every 48 hours, with a range of 1.4 to 2.1 days. In contrast, HCG levels generally rise more slowly with ectopic and nonviable intrauterine pregnancies. However, in some normal pregnancies, HCG levels may increase as little as 66% over a 48-hour period, and up to 17% of ectopic pregnancies have normal doubling times. Patients should have serial measurements done by the same laboratory because interassay variability may be as high as 15%.

**ULTRASONOGRAPHY**

Transvaginal ultrasonography is essential for making the diagnosis. A visible extraterine gestational sac with a yolk sac or embryo confirms the diagnosis of ectopic pregnancy, but this is seen in less than half of cases. Highly suggestive findings include a complex adnexal mass or free fluid in the pelvis in conjunction with an empty uterus.

**Ultrasonographic Findings Plus Human Chorionic Gonadotropin**

To obtain the full benefit of transvaginal ultrasonography, serum HCG levels must be taken into consideration.

The earliest ultrasonographic confirmation of intrauterine pregnancy is a true gestational sac seen within the uterine cavity. The sac is routinely visualized when HCG levels reach 1500 to 2000 mIU/mL, but it can be detected with levels as low as 800 mIU/mL. The discriminatory zone refers to the level of HCG at which a true gestational sac can be seen. Lack of an intrauterine pregnancy with an HCG level above the discriminatory zone raises concern for ectopic pregnancy or a failed intrauterine gestation. The discriminatory zone is generally accepted to be in the range of 1500 mIU/mL but is dependent on equipment quality and operator skill.

Transvaginal sonograms are more likely to be nondiagnostic in women with very low HCG levels, but they may still be useful. Given its safety, transvaginal ultrasonography should be performed on all women with a suspected ectopic pregnancy, even those with HCG levels below the discriminatory zone. In a study by Kaplan et al., 19% of patients with HCG levels higher than 1000 mIU/mL at the time of evaluation had transvaginal sonograms diagnostic of an ectopic pregnancy. The specificity of the ultrasonography findings was 100%.

As discussed previously, ectopic pregnancy is visualized by ultrasonography only half of the time; therefore, women with serum HCG levels below the discriminatory zone and nondiagnostic ultrasonographic findings present a clinical challenge. These findings may represent an ectopic pregnancy or a nonviable early intrauterine pregnancy. In these cases, HCG testing and ultrasonography should be repeated at 48 to 72 hours. HCG levels increasing normally at 48 to 72 hours should be monitored until the intrauterine pregnancy can be seen on the sonogram. A decreasing HCG level is most consistent with a failed pregnancy or spontaneously resolving ectopic pregnancy. In these cases, serial measurements should be monitored until HCG reaches nondetectable levels.

Patients with HCG levels that plateau or rise by less than double in 72 hours are likely to have either a nonviable intrauterine or an ectopic pregnancy. Repeated transvaginal ultrasonography may be helpful to distinguish the two. Failure to visualize an intrauterine gestation with HCG levels higher than 2000 mIU/mL excludes the possibility of a viable pregnancy. These patients have a high likelihood of having an ectopic gestation and should be treated accordingly. Patients with HCG levels higher than 1500 mIU/mL may undergo dilution and curettage to obtain tissue for examination. Confirmation of villi in the curettage specimen confirms the diagnosis of a failed intrauterine pregnancy, whereas their absence suggests an ectopic pregnancy. Laparoscopy may then be used to provide a definitive diagnosis and guide treatment.

**TREATMENT**

Ruptured ectopic pregnancy may have dramatic findings, with the patient in hemorrhagic shock. Rapid stabilization with intravenous fluids and packed red blood cells is essential. Unstable patients may require O-negative blood until a full crossmatch is performed. Laboratory studies include a complete blood count, quantitative HCG, and coagulation studies. The gynecology department should be consulted for operative management. Rh-negative patients should receive RhIg.

In stable patients, treatment of confirmed unruptured ectopic pregnancy may be medical, surgical, or expectant.

**METHOTREXATE THERAPY**

The medical treatment of choice is methotrexate, a folate antagonist that inhibits DNA synthesis in rapidly dividing cells such as embryonic tissue. This action leads to medically induced abortion of the embryo. Despite limitations, use of methotrexate allows noninvasive management and has proved successful in properly selected patients. Methotrexate protocols vary by institution, but single-dose treatment consisting of an intramuscular injection of 50 mg/m² of body surface area is widely used.

The ideal candidate for methotrexate therapy is relatively asymptomatic with no significant pain or bleeding. A minority of patients will fail treatment or progress to rupture, and the patient must be made aware of these possibilities. Criteria predicting success include diameter less than 3.5 cm, absence of cardiac activity on ultrasonography, and HCG level lower than 5000 mIU/mL. Patients with lower HCG levels tend to have fewer treatment failures.

Patients should be counseled on the risks and benefits of methotrexate therapy. They must be willing to comply with follow-up visits and have ready access to care. The patient should be aware of the possibility of treatment failure.

Relative contraindications include a high HCG level (>6000 mIU/mL), visible cardiac activity, and a large ectopic mass. Although visible cardiac activity is generally considered a contraindication, one study showed good results despite this finding. Absolute contraindications to the use of methotrexate include hemodynamic instability, as well as the factors listed in Box 119.5.

Side effects of methotrexate include stomatitis, conjunctivitis, enteritis, pleuritis, bone marrow suppression, and elevated liver function test results. Thirty percent of patients are affected, but most symptoms are mild and self-limited. The
the monitoring associated with methotrexate therapy, and patients with poor access to emergency care.

Resection of the ectopic mass with preservation of normal anatomy is ideal. Consequently, salpingostomy is preferred over salpingectomy. Laparoscopic resection is the standard approach, although laparotomy is occasionally required. After surgery, patients should be monitored with weekly HCG testing given the slight possibility of persistent ectopic tissue following resection.

A recent review showed the highest success rates with salpingostomy, although single-dose methotrexate therapy had the lowest financial cost and the least impact on quality of life. Methotrexate therapy was less costly in patients with HCG levels lower than 1500 mIU/mL. The cost of medical therapy increases in patients with higher HCG levels because of the increased risk for failure, the requirement for multiple doses, and the need for extended monitoring.

Stable patients with nondiagnostic HCG and ultrasound findings are designated as having a pregnancy of unknown location. Expectant management relies on the fact that the spontaneous resolution rate of pregnancies of unknown location is 70%. These patients are monitored with serial HCG levels and ultrasonography until a definitive diagnosis can be made. Expectant management is most successful in patients with HCG levels lower than 200 mIU/mL; increased complications occur in those with HCG levels higher than 1500 mIU/mL. However, the complication of tubal rupture can develop in as many as 30%, and it may occur even with decreasing HCG levels, so patients must be aware that treatment failures do occur.

**Next Steps in Care and Follow-Up**

In consultation with the patient’s gynecologist, patients with a confirmed ectopic pregnancy should receive methotrexate or be transferred for operative management. Low-risk patients with an indeterminate work-up who are clinically stable may be discharged with appropriate follow-up in 48 to 72 hours for repeated HCG testing and ultrasonography. Patients without access to follow-up may be admitted for observation. Patients with a pregnancy of unknown location should be counseled about the possibility of an ectopic pregnancy.

**Surgical Treatment**

Surgical treatment is the only option for unstable patients with ectopic pregnancy. It is also indicated for patients with large ectopic masses, patients unable or unwilling to comply with the monitoring associated with methotrexate therapy, and patients with poor access to emergency care.

In contrast to the pain from rupture, this pain is milder, and patients do not have hemodynamic instability or signs of a surgical abdomen. Although only 20% of patients with abdominal pain following methotrexate administration will ultimately need laparoscopy to evaluate for rupture, this subset can be difficult to identify. Transvaginal ultrasonography should be performed in these patients to evaluate for rupture. It is normal for HCG levels to increase for as long as 4 days following methotrexate administration. Patients typically have HCG testing repeated between days 4 and 7. By day 7, if the serum HCG level has not decreased by 25%, a second dose of methotrexate is given (required in 15% to 20% of patients), and HCG values are monitored weekly until levels decrease to less than 10 to 15 mIU/mL. Success rates with methotrexate range from 86% to 94%.

**TIPS AND TRICKS**

**Methotrexate**

- Relative contraindications to methotrexate include an HCG level higher than 6000 mIU/mL, visible cardiac activity, and a large ectopic mass because of a high rate of treatment failure.
- It is normal for HCG to increase for as long as 4 days after treatment.
- On day 7, if HCG has not decreased by 25%, a second dose is needed (15% to 25% of patients).
- Most patients will have some abdominal pain 2 to 3 days after administration; this pain is milder than that with rupture. Twenty percent of these patients will need laparoscopy to exclude rupture, however.

**SURGICAL TREATMENT**

Surgical treatment is the only option for unstable patients with ectopic pregnancy. It is also indicated for patients with large ectopic masses, patients unable or unwilling to comply with
Gestational Trophoblastic Disease

Epidemiology

The incidence of gestational trophoblastic disease (GTD) varies from 1 per 1000 pregnancies in the United States to 2 per 1000 pregnancies in Japan. Well-established risk factors include nulliparity, personal history of GTD, and maternal age younger than 20 or older than 35 years. Heavy smoking, oral contraceptive use, infertility, and maternal blood types AB or B are also risk factors. Although the disease carried significant morbidity in the past, earlier diagnosis with ultrasonography and more sensitive HCG measurements have led to more successful treatment in recent years.

Pathophysiology

GTD is a disorder of abnormal proliferation of trophoblastic tissue. The benign form is a hydatidiform mole, whereas the malignant forms are grouped as gestational trophoblastic neoplasia, which includes choriocarcinoma, placental site trophoblastic tumor, and persistent or invasive GTD. Although GTD is classically associated with molar pregnancy, it may result from any gestational event, such as spontaneous abortion or term pregnancy.

The most common form of GTD is a hydatidiform mole, either partial or complete. A partial mole contains fetal tissue and arises from fertilization of a haploid ovum by two sperm or by a single sperm that then duplicates. In contrast, a complete mole has no fetal tissue or maternal DNA and results from fertilization of an enucleate egg. Up to 15% of complete moles result in malignancy, whereas malignant transformation of a partial mole is less common. Table 119.2 lists the typical characteristics of molar pregnancies.

The abnormal trophoblastic tissue in GTD secretes HCG, thereby resulting in quantitative serum levels much higher than predicted in normal pregnancy. Patients with GTD have an increased incidence of hyperemesis gravidarum and early preeclampsia. Hyperthyroidism may result because of the structural similarity of HCG and thyroid-stimulating hormone. Theca lutein cysts seen in patients with GTD are bilateral, multiloculated ovarian cysts that are present in 15% to 25% of patients with complete moles.

Trophoblastic hyperplasia causes uterine enlargement abnormal for the stage of pregnancy. Deeper uterine invasion may result and lead to severe hemorrhage from destruction of the myometrium or uterine vasculature. Malignant forms of GTD may spread into the pelvis or be manifested as distant metastases, most commonly to the liver, lungs, vagina, and brain.

Presenting Signs and Symptoms

The most common complaint with molar pregnancy is first trimester vaginal bleeding. Patients may also complain of pelvic pain or pressure, and there may be passage of hydropic vesicles from the vagina.

Complete moles have a more striking clinical manifestation, with uterine size larger than expected at the stage of pregnancy, absent fetal heart tones, and markedly elevated HCG levels. Vaginal bleeding may be heavy. Medical complications include pregnancy-induced hypertension, early preeclampsia, hyperthyroidism, anemia, and hyperemesis gravidarum.

In contrast, the manifestation of a partial mole is subtle. Symptoms are similar to those of spontaneous abortion, with mild to moderate bleeding and cramping. Patients typically do not have significant uterine enlargement, and the diagnosis is made only when the abnormal placental tissue is visualized on ultrasonography. Patients with partial moles are less likely to develop serious complications.
to have the medical complications associated with complete moles because HCG levels are lower.

As mentioned earlier, GTD may also develop after a non-molar pregnancy, such as spontaneous and elective abortion, ectopic pregnancy, and term gestation. These patients have prolonged bleeding after delivery or miscarriage, with subsequent HCG levels that fail to return to undetectable measurements. Up to 75% of cases of malignant GTD occur after nonmolar pregnancies. Because placental site trophoblastic tumors may occur years after pregnancy, GTD should be considered in a woman with metastatic disease from an unknown primary site.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

Molar pregnancy should be included in the differential diagnosis of any patient with first trimester bleeding (see Box 119.4). Abnormally elevated quantitative HCG levels suggest the diagnosis, although there is no absolute level that identifies molar pregnancy. Pelvic ultrasonography is diagnostic in almost all cases. Tissue obtained from uterine evacuation provides histologic confirmation.

Ultrasonographic findings in a patient with a complete mole include diffuse hydatidiform swelling of chorionic villi (“snowstorm pattern”), bilateral theca lutein cysts, and absence of fetal tissue or amniotic fluid. The ultrasonographic appearance of a partial mole is not as striking and may be misinterpreted by an inexperienced ultrasonographer. There is only focal hydatidiform swelling with absence of theca lutein cysts. Growth-restricted embryonic tissue or amniotic fluid may also be seen.

Laboratory tests should include a complete blood count, blood typing and antibody screen, clotting function analysis, renal and liver studies, and measurement of the serum HCG level. For patients with malignant disease, additional work-up includes chest radiography to search for metastases. Other appropriate studies include computed tomography of the chest and magnetic resonance imaging of the abdomen, pelvis, and brain.

**TIPS AND TRICKS**

**Gestational Trophoblastic Disease**

Molar pregnancy should be in the differential diagnosis of patients with exaggerated symptoms of pregnancy such as hyperemesis and early preeclampsia.

In patients with spontaneous abortion, the products of conception should be sent for pathologic evaluation because of the possibility of incidental molar pregnancy.

The clinician should consider gestational trophoblastic disease in patients with prolonged or abnormal bleeding after delivery or miscarriage.

**TREATMENT**

GTD is likely to be diagnosed only incidentally in the ED during evaluation for spontaneous abortion or ectopic pregnancy. Most patients have few or mild symptoms. Initial ED management includes supportive care for significant hemorrhage, including intravenous fluids and blood products. Rh Ig should be administered to Rh-negative women. Patients with rupture or torsion of theca lutein cysts may require operative management, although rupture is rare.

**NEXT STEPS IN CARE AND FOLLOW-UP**

Any woman with suspected or diagnosed GTD should be referred to a gynecologic oncologist urgently because the disease may progress quickly. Definitive management of molar pregnancy includes dilation and curettage. As long as serial HCG levels decline appropriately, no further treatment is needed. Persistent local disease is usually treated with chemotherapy, although hysterectomy may be performed in women with locally invasive disease who no longer desire fertility.

Posttreatment monitoring for malignant or persistent disease consists of serial HCG measurements. Patients should have frequent pelvic examinations to monitor for local recurrence or vaginal metastases. Patients should be instructed to use contraceptive methods for 12 months because an increase in HCG levels as a result of pregnancy would obscure the monitoring results. Affected patients have an approximately 1% chance for a recurrent mole in future pregnancies, although this risk increases to as high as 28% after two molar pregnancies.

**HYPEREMESIS GRAVIDARUM**

**EPIDEMIOLOGY**

Estimates of the incidence of hyperemesis gravidarum range from 0.3% to 2% of all pregnancies. Risk factors include multiple gestations, GTD, personal or family history of hyperemesis, and female sex of the fetus. Protective factors include advanced maternal age, cigarette smoking, and anosmia. Hyperemesis gravidum is responsible for the highest percentage of hospital admissions during the first half of pregnancy.

**PATHOPHYSIOLOGY**

Up to 85% of pregnant patients experience nausea and vomiting to some degree. Hyperemesis gravidarum has no strict diagnostic criteria, but it is generally defined as nausea and vomiting that results in loss of 5% or more of prepregnancy weight, as well as ketonuria. In addition, the symptoms must not be attributable to another medical condition.

Hormonal factors are believed to be the pathogenesis. Studies have shown that women with higher HCG and estradiol concentrations have an increased incidence of hyperemesis, but the mechanism is unknown. In contrast, no correlation of progesterone levels and symptoms has been shown. Other potential causes such as vitamin deficiencies, gastric motility, and Helicobacter pylori infection have not been consistently
linked to the disease. The belief in the past that psychologic issues were causative has no supporting data.

**PRESENTING SIGNS AND SYMPTOMS**

Hyperemesis classically begins early in the first trimester, with symptoms peaking at 9 to 10 weeks and generally resolving by 16 to 18 weeks. Most patients report more severe symptoms in the morning hours, often made worse by noxious smells. Frequently, multiple ED visits or interactions with a primary care provider occur because of the persistence of symptoms.

Symptoms of abdominal pain and tenderness are usually minimal; such findings suggest another pathology. The physical examination confirms varying levels of dehydration.

Complications include dehydration, weight loss, and vitamin deficiencies. Esophagitis, Mallory-Weiss tears, and Wernicke encephalopathy have been reported in patients with persistent vomiting and malnutrition. Anxiety, as well as depressive symptoms, may occur in response to the illness.

**DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING**

The diagnosis of hyperemesis gravidarum is one of exclusion given the lack of confirmatory testing available. A careful history should confirm that the symptoms began in the first trimester, with review of systems negative for symptoms consistent with coexistent pathology. Physical examination is aimed at identifying these other conditions. **Box 119.6** outlines the differential diagnosis of hyperemesis.

Serum HCG measurements and ultrasonography can determine the time of gestation and rule out a hydatidiform mole. Urinalysis can rule out infection and may reveal ketonuria and high specific gravity. Laboratory evaluation can be helpful in excluding other pathology. Initial testing includes a complete blood count; basic chemistry panel; and liver, amylase, lipase, and thyroid function assays, including thyroid-stimulating hormone and free thyroxin levels.

As many as half of patients with hyperemesis will have mild elevations in transaminases; levels are usually in the low hundreds, with alanine transaminase levels being higher than aspartate transaminase levels. Amylase and lipase may be elevated, but much less so than with pancreatitis. Typical laboratory test results include hemococoncentration, electrolyte abnormalities, and mildly elevated hepatic and pancreatic function via urinalysis. The laboratory test abnormalities generally resolve by the 20th week of gestation, and no treatment is necessary.

**TREATMENT**

After coexistent pathology has been ruled out, treatment consists of rehydration, correction of electrolyte abnormalities, control of nausea, and reinstatement of nutrition. Volume resuscitation is accomplished with normal saline or lactated Ringer solution. Dextrose-containing solutions can then be used for maintenance fluids. Potassium, magnesium, and phosphorus supplements should be added to fluids as needed. Patients with prolonged vomiting should be given thiamine (100 mg/day) and multivitamins intravenously.

Pharmacotherapy is appropriate for significant nausea, although patients may have reservations about using these medications. The combination of pyridoxine (10 mg) and doxylamine (12.5 mg) three to four times a day is considered safe; randomized, placebo-controlled studies have shown a 70% reduction in nausea and vomiting. This combination should be considered first-line therapy.

Various antiemetics (Table 119.3) have been used for hyperemesis with good results and reasonable safety data. Antihistamines have the best safety profiles, but phenothiazines, metoclopramide, and ondansetron are considered safe as well. Gynecologists may prescribe oral corticosteroids for patients with refractory nausea and vomiting. Studies have shown conflicting results of effectiveness, and the incidence of cleft palate appears to be slightly increased in infants whose mothers received methylprednisolone in the first trimester of pregnancy. Steroids should thus be reserved as a last resort.

**Table 119.3 Antiemetics for Hyperemesis Gravidarum**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CLASSIFICATION</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxylamine</td>
<td>A</td>
<td>12.5 mg PO</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>B</td>
<td>50-100 mg PO, PR; 50 mg IV</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>B</td>
<td>5-10 mg PO, IV, IM</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>B</td>
<td>4-8 mg PO, IV, IM</td>
</tr>
<tr>
<td>Promethazine</td>
<td>C</td>
<td>12.5-25 mg IV, IM, PO, PR</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>C</td>
<td>5-10 mg IV, IM, PO; 25 mg PR</td>
</tr>
</tbody>
</table>

IM, intramuscularly; IV, intravenously; PO, orally; PR, parenterally.
Many patients are reluctant to use pharmacotherapy because of a perceived fear of birth defects. These patients may be agreeable to adjunctive therapies such as acupuncture, hypnosis, and powdered ginger. Studies of acupuncture and acupuncture have yielded conflicting results, whereas hypnosis has been shown to decrease vomiting in patients with hyperemesis. Powdered ginger (250 mg to 1 g/day) is as effective as pyridoxine, but its safety is not well established. The ultimate goal of treatment is restoration of nutrition. Many patients are able to tolerate feeding after a short course of rehydration along with gut rest. The Patient Teaching Tips box outlines dietary suggestions.

Patients who cannot maintain their weight despite rehydration and antiemetics are candidates for enteral nutrition. Those who cannot tolerate enteral feedings should be given total parenteral nutrition. This regimen carries the usual risks of infectious and metabolic complications.

Hyperemesis

- Daily multivitamin use at the time of conception may decrease the severity of nausea and vomiting.
- Avoid triggers such as noxious odors, brushing teeth after eating, and iron supplements.
- Eat small, frequent meals rich in protein and carbohydrates and low in fat. Avoid spicy foods.
- Eat as soon as you feel hungry.
- Drink small amounts of liquids often. Cold, clear, carbonated, and sour liquids are best tolerated.
- Aromatic mint tea and teas with lemon or orange flavoring may be helpful.

Patient Teaching Tips

![Patient Teaching Tips]

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES