ECTOPIC PREGNANCY

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Epidemiology

In 1992, ectopic pregnancies accounted for approximately 2% of reported pregnancies, and ectopic pregnancy-related deaths accounted for 9% of all pregnancy-related deaths. The incidence of ectopic pregnancy has been increasing since 1970, when the Centers for Disease Control and Prevention first began collecting data, from 4.5 per 1000 reported pregnancies to 19.7 per 1000 pregnancies in 1992.[1] The increased incidence is thought to be due to two factors: (1) the increased incidence of acute salpingitis, due to increased infection with Chlamydia trachomatis, and (2) improved diagnostic techniques, which enable diagnosis of unruptured ectopic pregnancy to be made earlier and with more precision.[2] Other factors that appear to be associated with an increased risk of ectopic pregnancy include prior ectopic pregnancy, cigarette smoking, prior tubal surgery (especially for distal tubal disease), diethylstilbestrol exposure, increasing age,[3] multiparity,[4] and current IUD use. The 10-year cumulative probability of ectopic pregnancy for all methods of tubal sterilization combined was shown to be 7.3 per 1000 procedures. Of all pregnancies found in that study after tubal sterilization, 32.9% were ectopic.[5] An operative procedure on the oviducts themselves is a cause of ectopic pregnancy. The incidence of ectopic pregnancy after salpingoplasty or salpingostomy procedures to treat distal tubal disease rages from 15-25%. The rate of ectopic pregnancy after reversal of sterilization procedures is about 4%, because the tubes have not been damaged by infection. Women who have had a prior ectopic pregnancy, even if treated by unilateral salpingectomy, are at increased risk for a subsequent ectopic. Of women who conceive after having one ectopic, about 25% of subsequent pregnancies are ectopic.

Definitions and Incidence of Ectopic Location[6]

Abdominal pregnancy (1.37%): pregnancy that develops in any portion of the peritoneal cavity. It usually occurs after secondary implantation of the trophoblast after tubal abortion (secondary abdominal pregnancy). A primary abdominal pregnancy is one that implants directly into the peritoneal cavity.

Cervical pregnancy (0.15%): Ectopic gestational tissue in the cervical canal below the level of the internal os.

Cornual pregnancy (0.61%): pregnancy developing in one horn of a bicornuate uterus.

Ectopic pregnancy: pregnancy that develops after implantation of the blastocyst anywhere other than the endometrium lining the uterine cavity.

Heterotopic pregnancy (1/6579): combined intrauterine and extrauterine pregnancy.

Interstitial pregnancy (1.2%): pregnancy developing in the interstitial portion of the oviduct.

Ovarian pregnancy (0.15%): pregnancy developing in the ovary. For the diagnosis to be made, the tube on the affected side should be intact, the gestational site must occupy the normal position of the ovary, the gestational site must be connected to the uterus by the ovarian ligament, and histologically identified ovarian tissue must be present in the sac wall.

Tubal pregnancy (97%): pregnancy occurring in the oviduct in either the ampulla (75-80%), fimbria (5%), or isthmus (10-15%).

Diagnosis and Treatment

The most common symptoms of ectopic pregnancy are abdominal pain (90-100%), a history of amenorrhea (75-95%), and vaginal bleeding (50-80%). The most common findings in a woman with a symptomatic ectopic pregnancy is abdominal tenderness (80-95%) which together with adnexal tenderness (75-90%) is present in nearly all women with an advanced or ruptured ectopic pregnancy. An adnexal mass is palpable in 50% of the women.[7]

Many of these classical signs and symptoms are associated with an advanced or ruptured ectopic pregnancy and frequently require surgical intervention. In such cases, intravenous access should be attained quickly with volume resuscitation if hemodynamically unstable. In addition, the patient should be cross-matched for at least four units of packed red blood cells. Measurement of urine output can also assist in the assessment of volume status.

In cases where the pregnant patient is hemodynamically stable and presents with abdominal or pelvic pain, a transvaginal ultrasound (TVS) is warranted. The identification of an ectopic gestational sac is obviously diagnostic. The sensitivity and specificity of TVS to detect an ectopic pregnancy are 90.9% and 99.9%, respectively, and positive and negative predictive values of 93.5% and 99.8% when women were diagnosed with an ectopic pregnancy using TVS if any of the following were noted in the adnexal region: 1, an inhomogeneous mass or blob sign adjacent to the ovary and moving separately from the ovary; or 2, a mass with a hyper-echoic ring around the gestational sac or bagel sign; or 3, a gestational sac with a fetal pole with or without cardiac activity.[8] When any adnexal mass other than a simple cyst is used as diagnostic criterion for ectopic pregnancy, the specificity is 98.9%, sensitivity is 84.4%, positive predictive value is 96.3%, and the negative predictive value is 94.8%.[9] If an intrauterine pregnancy cannot be identified, a quantitative β-hCG (according to the First or Second International Reference Preparation) should be ordered. TVS can often detect an intrauterine pregnancy within five weeks if the last menstrual period.[10] An intrauterine gestational sac in a normal uterus can usually be seen with the hCG level is between 1000 to 2000 mIU/mL (1st and 2nd International Reference Preparation).[11]

If the patient is stable, she may return in 48 hours for another quantitative hCG determination. The mean doubling time for hCG in a normal intrauterine pregnancy is 1.4 to 2.1 days. However, in patients with an ectopic pregnancy, the hCG will rise at a much slower rate. Based on studies of doubling time, hCG levels should rise by 66% in 48 hours in 85% of normal pregnancies. That is, 15% of normal intrauterine pregnancies will not have a normal doubling time. However, a rise of less than 50% is associated with an abnormal pregnancy 99.9% of the time.[12]

Single-Dose Methotrexate Protocol

Classically, uterine curettage (D&C) has played an important role in the diagnosis of ectopic pregnancy. The absence of chorionic villi on curettage in the presence of an elevated β-hCG level is evidence of a presumptive diagnosis of ectopic pregnancy. Stovall's protocol employed D&C on day 0 followed by methotrexate 50 mg/m^2 intramuscularly on Day 1 after liver and kidney function was verified to be normal. A repeat hCG level is drawn on days 4 and 7. If the

hCG level falls less than 15% between days 4 and 7, a repeat dose of Methotrexate was given. If the hCG levels fell more than 15%, then hCG titers were followed weekly until undetectable.[13]

Criteria for Receiving Methotrexate[14]

Absolute Indications

- Hemodynamically stable without active bleeding or signs of hemoperitoneum
- Patient desires future fertility
- GETA poses a significant risk
- Patient is reliable and able to return for follow-up care
- Patient has no contraindications to Methotrexate

Relative Indications

- Unruptured mass $\leq$ 3.5 cm in greatest dimension
- No fetal cardiac motion
- β-hCG level does not exceed a predetermined level (Among women with initial hCG concentrations below 15,000 mIU/mL, 93% were successfully treated)[15]

Contraindications to Medical Therapy[16]

Absolute Contraindications

- Breastfeeding
- Evidence of immunodeficiency
- Alcoholism or liver disease
- Preexisting blood dyscrasias
- Hypersensitivity to Methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic dysfunction

Relative Contraindications

- Gestational sac $\geq$ 3.5 cm.
- Fetal cardiac motion

The presence of blood in the pelvis is not considered a contraindication to medical therapy. Approximately 50 to 60% of unruptured ectopic pregnancies will have blood in the pelvis on pelvic ultrasound.

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