Clinical Reviews

Ectopic Pregnancy

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Ectopic pregnancy continues to be a major clinical problem and is the leading cause of death in the first trimester of pregnancy. Diagnosis can be elusive. A thorough knowledge of the clinical spectrum of this disease, as well as the diagnostic tools available to the primary care clinician, provides the opportunity for making an early diagnosis. This is essential if the morbidity and mortality of ectopic pregnancy are to be reduced.

Ectopic pregnancy continues to be a major problem in medical practice and its incidence appears to be increasing.[1,2] It is estimated to account for 10 to 15 percent of maternal deaths in the United States,[1,3] and it is the major cause of death in the first trimester of pregnancy. Delays in establishing the correct diagnosis and instituting treatment are the primary reasons for this high mortality. The difficulty in making the diagnosis is demonstrated in a recent study which found that 50 percent of patients with ectopic pregnancy had obtained medical consultation (and were sent home) at least once 24 hours prior to the time of diagnosis. Eleven percent of these women were sent home twice.[3]

Ectopic pregnancy has been called the "great imitator" and the "disease of diagnostic surprises."[4,5] It represents a major diagnostic challenge to the family physician providing care to women of reproductive age. This paper will review the clinical features of ectopic pregnancy, with emphasis on the various diagnostic tools available for making this often elusive diagnosis.

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Incidence

Ectopic pregnancy is a major public health problem in the United States and its incidence is increasing. During the past decade there has been recorded a dramatic rise in the national incidence of ectopic pregnancy. Between 1970 and 1977, the number of ectopic gestations per year rose from 17,900 to 41,000 cases.[6,7] Although the ratio of ectopic to normal intrauterine gestations is considered by most authors to be approximately 1 to 200, ratios as low as 1 to 357 and as high as 1 to 60 have been reported.[1,8,9]

Epidemiology

Numerous epidemiological factors have been associated with ectopic pregnancy. The pathogenesis may involve structural or functional abnormalities of the fallopian tubes or the embryo, which impedes the normal passage of the fertilized egg into the intrauterine cavity. DeCherney and Kase have attributed the rising incidence of ec-

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topic gestations to (1) the increase in the rate of pelvic infection and its early treatment, (2) the impact of the intrauterine contraceptive device, and (3) the increase in surgical procedures for sterilization and infertility problems.[10]

Age. The highest incidence of ectopic pregnancy occurs in the 20- to 30-year age group,[2,11,12] although the diagnosis must be considered in all women of child bearing age.

Parity. The data regarding parity are somewhat conflicting, with some authors describing a direct relationship[13,14] and others an inverse relationship.[1,2,9,15]

Race. Nonwhite groups are generally felt to be at increased risk for extrauterine pregnancy.[2,6,9,11,13,14]

Socioeconomic Status. Ectopic pregnancy is felt to be more common in low socioeconomic groups.[13,14]

Pelvic Inflammatory Disease

The epidemic of pelvic inflammatory disease in the United States closely parallels the rise in ectopic gestations and is considered to be the most important factor predisposing to it.[2,6,16] Ectopic pregnancies are associated with pathologic changes of pelvic inflammatory disease in 42 to 53 percent of cases,[2] and a prior history of it is elicited in 16 to 31 percent of patients.[1-3] It has been estimated that one episode of pelvic inflammatory disease raises a woman's chances of having an ectopic pregnancy sixfold.[17]

Intrauterine Contraceptive Device

Although a strong relationship between the intrauterine device and the pathogenesis of pelvic inflammatory disease is well established,[18,19] its true role in the etiology of extrauterine pregnancy is still unresolved. The absolute risk of ectopic pregnancy in intrauterine device users has been estimated at 1.2 per 1,000 women per annum.[20] A causal relationship has been postulated,[21] but other authors maintain that the intrauterine device is actually protective against ectopic pregnancy to some extent.[1,6,22] Nevertheless, an intrauterine device is more effective against intrauterine than extrauterine implantation of a fertilized ovum; thus, if an accidental pregnancy occurs, the relative risk of an ectopic gestation is markedly increased. It has been estimated that 1 of 23 pregnancies (4.3 percent) occurring with an intrauterine device in place will be ectopic[9] and that the relative risk is increased 2.5- to 12-fold.[1,9]

Prior Ectopic Pregnancy

The woman who has had a previous ectopic pregnancy is at definite risk for a subsequent one. Once a patient has had an ectopic pregnancy, her risk of having another is increased 30- to 50-fold.[1] It is generally stated that 10 percent of women with one ectopic pregnancy will have a subsequent one,[9] although figures as low as 1.1 percent and as high as 25 percent have been reported.[1,23]

History of Abdominal-Pelvic Surgery

Brenner et al found that 26 percent of their patients with extrauterine pregnancies had a history of abdominal-pelvic surgery, including some with tubal sterilization procedures.[3] As with the intrauterine device, tubal sterilization procedures are more effective against intrauterine than extrauterine implantation, and thus the overall incidence of ectopic pregnancies among failures by these methods is increased. For sterilization procedures involving transection, ligation, or coagulation of the fallopian tubes, 150 ectopic pregnancies will occur for each 1,000 accidental pregnancies. Tubal occlusion with compression clips is associated with an incidence of 44 ectopic pregnancies per 1,000 pregnancies.[13]

Others

Other factors that have been reported as being associated with ectopic pregnancies include progestin-only oral contraceptives, uterine leiomyomata, and induction of ovulation with clomiphene citrate.[1,13-15]

History

The historical aspects of ectopic pregnancy are shown in Table 1. Only the minority of patients present with the classical triad of amenorrhea, vaginal bleeding, and lower abdominal pain.[4] The most frequent symptom present in women with extrauterine pregnancy is abdominal pain, found

Table 1. Historical Aspects of Ectopic Pregnancy (%)

Indications	Kitchin[1] (n = 191)	Helvancioglu[2] (n = 313)	Brenner[3] (n = 300)	Breen[11] (n = 654)	Tancer[15] (n = 556)
Abdominal pain	99	96	99	100	98
Vaginal bleeding	69	55	74	80	64
Amenorrhea	80	93	68	84	76
Prior pelvic inflammatory disease	16	25	26	—	—
Prior surgery	—	17.6	26	—	—

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Table 2. Physical Finding in Ectopic Pregnancy (%)

Findings	Kitchin[1] (n = 191)	Helvancioglu[2] (n = 313)	Brenner[3] (n = 300)	Breen[11] (n = 654)	Tancer[15] (n = 556)
Adnexal tenderness	94	72	96	75	—
Unilateral	66	37	—	—	—
Bilateral	33	59	—	—	—
Adnexal mass/fullness	61	66	53	49	76
Enlarged uterus	14	26	30	—	—
Cervical tenderness	—	43	—	89	78
Fever	6.8	1.8	3	50	9
Shock	17.3	9.4	—	48	14

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in 96 to 100 percent of cases.[1-3,11] Abnormal vaginal bleeding is a less constant feature and may be absent in 26 to 45 percent of cases. Similarly, a history of amenorrhea or delayed menses may be absent in 17 to 32 percent of cases.[1,2,11]

Physical Examination

Common physical findings in ectopic pregnancy are shown in Table 2. The most common finding on physical examination is adnexal tenderness, which is present in 72 to 96 percent of cases[1-3] and is bilateral in distribution in 33 percent.[1] A palpable adnexal mass or fullness is found in only 49 to 76 percent of patients, and an enlarged uterus in only 14 to 30 percent.[1-3,11,24] Fever has been reported in as few as 1.8 percent and as high as 50 percent of cases, although a temperature above 38 C is generally more consistent with an infectious process. The presence or absence of clinical shock is dependent on how early in its course the diagnosis of ectopic pregnancy is made and has been found in as few as 9.4 percent and as high as 48 percent of cases.[2,11]

Laboratory Aids

Complete Blood Count

The complete blood count is not a sensitive or specific test in diagnosing ectopic pregnancy. Thirty-eight percent of patients may have hematocrit readings above 35 percent and only 28 percent may have values less than 30 percent.[1,3] The white blood cell count is also nonspecific and may be greater than 15,000/mm^3 in 15 percent.[3]

Pregnancy Testing

Urinary Agglutination-Inhibition Tests

Traditional slide and tube tests are not very useful in the diagnosis of ectopic pregnancies because they lack sensitivity. The two-minute latex slide tests with a sensitivity for human chorionic gonadotropin (HCG) ranging from 2,500 ± 1,000 mIU/ml have an estimated 50 percent false-negative rate for ectopic pregnancy. The standard tube tests (requiring 90 to 120 minutes to perform) with sensitivities ranging from 500 to 1200 mIU/ml have a 15 to 35 percent false-negative rate.[25] Thus, a negative test by either of these two methods by no means rules out the possibility of ectopic pregnancy, which often has a low titer.

Radioreceptor Assay for HCG

The most recent improvement in pregnancy testing is the radio-receptor assay (RRA) for human chorionic gonadotropin.[26,27] This serum assay, which requires approximately one hour to perform, is based on the binding of HCG or luteinizing hormone to protein receptor sites on plasma membranes. The sensitivity of the commercially available Biocept-G test* has been set at 200 mIU/ml to avoid false positive results secondary to the midcycle luteinizing hormone surge. Berry et al demonstrated 94 percent sensitivity for ectopic pregnancy, with only a 6 percent false-positive rate in patients suspected clinically of having an ectopic pregnancy but found later at surgery not to have this condition.[26] Pelosi found the test positive in all 15 of his surgically proved tubal pregnancies.[28]

*Wampole Laboratories, Carter-Wallace Inc, Cranbury, NJ

Beta-Subunit of HCG Radioimmunoassay (RIA)

The radioimmunoassay for detection of the serum beta-subunit of human chorionic gonadotropin (beta-HCG) is the most sensitive of the pregnancy tests, with a sensitivity of 5 ImU/ml. It is able to detect pregnancies from 9 to 12 days after conception.[27] The sensitivity of this assay for ectopic pregnancy is 100 percent;[24,29] thus, a negative assay all but rules out the diagnosis of ectopic pregnancy. However, it is obviously not specific for extrauterine pregnancies and is elevated in any condition associated with HCG production, including viable intrauterine pregnancies, spontaneous abortions, gestational trophoblastic disease, and recent voluntary abortions. A positive result, therefore, still requires localization of the tissue responsible for the HCG production. In addition, the expensive reagents and laboratory equipment required to perform this test have precluded its widespread usage.[27]

Adjunctive Diagnostic Studies

Culdocentesis

Culdocentesis is a rapid, safe, and valuable procedure for diagnosing hemoperitoneum and has been used for decades in the diagnosis of ectopic pregnancy.[30] It is considered positive if nonclotting blood is aspirated from the cul-de-sac, negative if straw colored peritoneal fluid is obtained, and nondiagnostic if clotting blood or no fluid is obtained. It is generally felt to be positive in 82 percent of ectopic pregnancies.[2,26] Berry et al found that 97 percent of their patients with ectopic pregnancy had a positive Biocept-G radioreceptor assay and/or a positive culdocentesis.[26]

Pelvic Ultrasound

The value of pelvic ultrasound in the diagnostic evaluation of acute pelvic pain has recently been demonstrated.[31,32] With respect to ectopic pregnancy, ultrasound is felt to be a fairly sensitive (77 percent), although not particularly specific, diagnostic test. The classical ultrasound appearance of an ectopic pregnancy is an extrauterine gestation sac, but this is seen in only 15 percent of cases.[33] Ultrasound is often more helpful in excluding ec-

topic pregnancy by identifying a normal intrauterine pregnancy. This virtually excludes ectopic pregnancy, as intrauterine and tubal pregnancy coexist very infrequently (approximately once in 30,000 cases).[34] An intrauterine pregnancy is confirmed by identifying a "gestation sac" or "ring" within the uterus that first appears approximately five to six weeks after the last menstrual period,[35] although the phenomenon of a "pseudogestation sac" must be kept in mind.[36] Decidual casts can be mistaken for true gestation sacs by even the best ultrasonographers. As ultrasound technique, interpretation, and availability improve, the diagnostic potential of this procedure will be increasingly used.

Examination of Endometrial Tissue

The examination of endometrial tissue in patients with suspected ectopic pregnancy is generally impractical and contraindicated if the possibility of a desired intrauterine pregnancy exists. However, tissue obtained from curettage for presumed incomplete spontaneous abortions or from the rising number of voluntary therapeutic abortions in the United States[37] is available for gross and histological examination. If evaluation reveals the presence of a decidual or Arias-Stella reaction in the absence of chorionic villi, the diagnosis of ectopic pregnancy must be entertained and further diagnostic workup instituted.[5,14,15,38]

Laparoscopy

The value of laparoscopy in the diagnosis of acute pelvic pain has been well established, often negating the need for exploratory laparotomy.[5,39-41] It offers the advantage of accurate diagnosis of ectopic pregnancy with little increase in risk to the patient. By allowing the diagnosis of ectopic pregnancy to be made earlier and possibly prior to rupture, the risk of intraperitoneal hemorrhage can be averted and more conservative surgery can be attempted. Therefore, a suspected ectopic pregnancy is a clear indication for laparoscopy.

Treatment

Once the diagnosis of ectopic pregnancy is established, laparotomy with removal of the products of conception and control of bleeding is indicated following stabilization of the patient's vital signs.[5] Even in the ambulatory patient with relatively mild symptoms, surgery should be done as soon as possible because of the ever present risk of life-threatening hemorrhage.

The surgical procedure performed is dependent on numerous factors, including the size and extent of tubal damage produced.[4] Conservative procedures include linear salpingostomy, partial salpingectomy, and simple manual expression of the ectopic pregnancy from the fallopian tube. Radical, more ablative procedures include salpingectomy, salpingo-oophorectomy, and hysterectomy with salpingectomy. Advocates of the more conservative procedures feel that they may improve the patient's outlook for future fertility,[1,9,10,42] whereas opponents feel that conservative surgery exposes the patient to an increased risk of ectopic pregnancy in the involved tube. Although this area is still controversial and will require further study, it can generally be said that the surgical procedure used should be individualized according to the findings at operation as well as the patient's desire for childbearing.[9,10]

Postoperatively, if the patient is Rh negative and lacks anti-D antibody, she should receive anti-Rh immunoglobulin to prevent sensitization.[4]

Prognosis

Although the absolute number of maternal deaths due to ectopic pregnancy has decreased, the reduction is not so great as the reduction of maternal deaths from other causes, making ectopic pregnancy the number one cause of death in the first trimester of pregnancy.[3,15] The case fatality rate is frequently cited as 1 per 800 ectopic pregnancies,[9] although Helvancioglu et al recently reported a case fatality figure of 9.5 per 1000.[2]

The effect of an ectopic pregnancy on the patient's reproductive capacity is dramatic. An estimated 38 to 70 percent of patients will be involuntarily sterile following an ectopic pregnancy[23] and only 33 percent can be expected to ever deliver a normal child.[9] It is hoped that through earlier diagnosis prior to rupture of the ectopic gestation, the use of more conservative, less ablative surgical procedures, and the use of currently avail-

able improved techniques for tubal reconstructive surgery, these grim figures can be improved.

Conclusion

In any woman with reproductive capabilities, pelvic pain alone must arouse the suspicion of ectopic pregnancy. Vaginal bleeding and amennorrhea will be absent in a significant number of cases. While knowledge of a past medical history of pelvic surgery, pelvic inflammatory disease, ectopic pregnancy, or intrauterine contraceptive device use is helpful in the diagnosis, the family physician should have a low threshold for invocation of recently improved diagnostic tools. An active effort must be made to confirm or rule out the diagnosis. Only then can appropriate therapy be instituted and the morbidity and mortality of ectopic pregnancy be reduced.

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