Ectopic pregnancy

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Introduction

Advances in medical technology have allowed improvements in both diagnosis and treatment of ectopic pregnancy, which occurs in approximately 2% of all reported pregnancies. Tools such as enzyme-linked immunoassays and radioimmunoassays for β-hCG as well as transvaginal ultrasound have allowed for more rapid diagnosis of ectopic pregnancy; increased competence in laparoscopy and widespread usage of methotrexate have improved the outcomes of maternal morbidity, mortality, and future fertility. However, despite these medical and surgical advances, ectopic pregnancy remains a leading cause of death in the first trimester. In 1992, approximately 109,000 ectopic pregnancies occurred, accounting for 9% of pregnancy related deaths (Ectopic pregnancy U.S., 1995).

Etiology/risk factors

Tubal infection

Any process which causes tubal damage or impairs transtubal movement may be associated with increased risk for ectopic pregnancy. The tubal inflammation, adhesions, and obstruction of pelvic inflammatory disease (PID) are well known risk factors for ectopic pregnancy. Tubal gestation has been demonstrated to occur in approximately 6% of pregnancies after the first episode of PID, compared to 1% of controls (Westrom 1985). In addition, tubal obstruction has been shown to increase with successive episodes of PID (Westrom et al 1981).

Prior ectopic pregnancy

Prior tubal pregnancy is perhaps the greatest risk factor for future ectopic pregnancy (see Reproductive Outcomes, below). The demonstration of tubal obstruction by hysterosalpingogram seems to correlate with future ectopic pregnancy rates, but both appear to be independent of the initial treatment. In two studies of expectant management of stable ectopic pregnancies, tubal patency by hysterosalpingogram ranges from 74-93%, and the recurrent ectopic pregnancy rate 4-12% (Rantala and Makinen 1997, Shalev et al 1995). However, most studies have looked at medically and surgically managed tubal pregnancies. These suggest that the risk of recurrent ectopic gestation ranges from 10-15% after either laparotomy or laparoscopy, and 6-9% after treatment with methotrexate (Yao and Tulandi, 1997).

Sterilization

Tubal sterilization is the most effective form of birth control; however, when pregnancy does occur, one-third are ectopic gestations (Peterson et al 1997). According to a large, multicenter, retrospective cohort study of 10, 685

women enrolled in the U.S. Collaborative Review of Sterilization, the 10-year cumulative probability of ectopic pregnancy for all methods of tubal sterilization was 7.3 per 1000. Specifically, bipolar coagulation was associated with the highest rate of future ectopic pregnancy (17/1000 procedures) and postpartum salpingectomy the lowest (1.5/1000). In addition, women sterilized under the age of 30 by any method had an increased risk of ectopic pregnancy; the use of bipolar coagulation prior to the age of 30 had the highest 10-year cumulative probability of ectopic pregnancy of 32/1000 (Peterson et al 1997).

Infertility surgery

Surgery for tubal causes of infertility is associated with a risk of ectopic pregnancy of 2-15%. Even prior to surgery, the fallopian tube is morphologically damaged and or otherwise abnormal, with an inherent increased risk for tubal gestation should pregnancy occur. This is true for both tubal reconstruction after sterilization as well as tubal repair for postsalpingitis adhesions or obstruction (Lavy et al 1987, Lennox et al 1987, Hulka and Halme 1988).

Contraception

Failure of contraception is an important risk factor for ectopic pregnancy. If correctly used, all forms of birth control prevent both intrauterine and ectopic gestation; however, should pregnancy occur, some methods do have an increased risk of tubal pregnancy. The progesterone IUD (more so than the copper devices), progesterone only "mini-pills," and especially Norplant have been associated with ectopic pregnancy rates of 4-30%. Only women using combination oral contraceptive pills or barrier methods such as condoms and diaphragms do not have increased rates of ectopic pregnancy (Ory 1981, Sivin 1991, Franks et al 1990, Shoupe et al 1991).

Other

Other factors associated with increased risk for ectopic pregnancy include DES exposure in utero (Barnes et al 1980, Herbst et al 1980), smoking (Caste et al 1991), tubal and nontubal causes of infertility, and infertility treatment, particularly in vitro fertilization (Chow et al 1987, Dor et al 1991, Guillaume 1995).

Diagnosis

History

The diagnosis of ectopic pregnancy is based on both clinical and laboratory findings. The patient usually presents with some combination of complaints including amenorrhea, irregular vaginal bleeding, and pain. The pain may be variously described as mild or severe, sharp or cramping, unilateral or bilateral, and not infrequently associated with nausea, vomiting, syncope, or shoulder pain due to diaphragmatic irritation of blood from the ruptured viscus.

Physical examination

Physical exam should take careful note of vital signs. Although a young, otherwise healthy woman may lose significant amounts of blood from a ruptured ectopic without hypotension or tachycardia, often this is the first indication of haemodynamic instability. Some degree of abdominal and adnexal tenderness on exam is usually present and an adnexal mass is frequently palpated; however, if peritoneal signs are present, physical exam may prove very difficult due to patient discomfort and voluntary or involuntary guarding.

Laboratory evidence

Laboratory evidence can be essential in making the diagnosis. In the setting of a β-hCG of > 1500, an intrauterine pregnancy should be visible on transvaginal ultrasound (see Ultrasound, below). If the hCG is less than 1500 in a stable patient with a desired pregnancy, serial hCGs can be drawn to determine a trend: the serum value will rise (66% over 48 hours in 85% of normal pregnancies (Kadar et al 1981). Slowly rising, plateauing, or decreasing hCG levels are associated with nonviable pregnancies.

Other laboratory values have been studied for their use in the prediction of ectopic pregnancy. Creatine kinase has been proven not to be a helpful diagnostic test

(Korhonen et al 1996, Qasim et al 1996). Single serum progesterone measurements have also been evaluated as a screening tool. Progesterone values less than 5 ng/mL are rarely associated with a viable pregnancy; values greater than 15 are associated with a normal pregnancy in > 84% of the cases. However, progesterone is not able to distinguish ectopic pregnancy from abnormal intrauterine pregnancy with any significant diagnostic accuracy (McCord et al 1996).

Ultrasound

Improvements in both ultrasound technology and in the training of those using this technology have allowed for better visualization of the pelvic organs and their pathology. A gestational sac in the endometrial cavity can be seen as early as 4 weeks by transvaginal ultrasound, although this may be difficult to differentiate from a "pseudosac" associated with an ectopic pregnancy (Bree and Marn 1990, Abramovici et al 1983). In either case the endometrium may appear thickened due to decidualization (the Arias-Stella reaction). An intrauterine yolk sac or fetus is clear evidence of an intrauterine pregnancy; however, with rates of heterotopic pregnancy in stimulated cycles as high as 1%, an intrauterine finding of pregnancy does not always rule out a concomitant ectopic (Dor et al 1991). In addition, although an adnexal mass found at ultrasound may be highly suspicious for an ectopic, only the demonstration of an intratubal gestational sac with a fetal pole, an actual fetus, or cardiac activity is diagnostic.

Other

Dilation & curettage and laparoscopy are more invasive, although usually definitive, methods of obtaining a diagnosis. In the general population, however, an emergency department algorithm protocol using a combination of physical exam, quantitative serum β-hCG, and transvaginal ultrasound (UTZ) diagnoses ectopic pregnancy with a sensitivity of 100% and specificity of 99% (Barnhart et al 1994).

Treatment

Expectant Management

Expectant management is not an unreasonable option for the carefully selected and well informed patient. Clinically stable patients with decreasing β-hCGs and no evidence of cardiac activity or haemoperitoneum on ultrasound may be observed for spontaneous resolution/ resorption of the pregnancy. Recent studies have successfully treated 47-73% of ectopic pregnancies expectantly (Shalev et al 1995, Trio et al 1995). Various hCG titers have been quoted as optimally predicting spontaneous resolution: < 2000 mIU/mL associated with 60% success vs. > 2000 mIU/mL associated with 93% failure in one study (Bree et al 1990); < 1000 mIU/mL identifying 88% of those patients successfully expectantly managed in another series (Trio et al 1995). However, even with very low and/or declining hCG levels, tubal rupture with life threatening consequences can occur (Shalev et al 1995, Tulandi et al 1991).

Surgical management

In most cases, therefore, either surgical or medical treatment is more appropriate than "watchful waiting." Traditional surgical management via laparotomy and salpingectomy is currently reserved for the haemodynamically unstable patient; otherwise, the conservative approach, laparoscopic linear salpingostomy, is preferred. Multiple studies (Vermesh et al 1989, Murphy et al 1992) have shown the benefits of laparoscopy over laparotomy, including decreased blood loss, analgesia requirements, hospital stay, and cost. Many of these have, however, shown an increased rate of persistent ectopic pregnancy: one study of salpingostomy at laparoscopy vs. laparotomy demonstrated a persistent ampullary ectopic rate of 15.5% vs. 1.8% (Seifer et al 1993).

Conservative surgical management has the benefit of relative tubal preservation in a patient desiring future fertility (see Reproductive Outcomes, below). In comparison to salpingectomy, however, the rate of persistent ectopic is significantly higher, up to 20% in one earlier

laparoscopic series (Henderson 1989). Tubal sparing surgery is still preferred in the younger woman, unless excessive bleeding, haemodynamic instability, or technical difficulties make salpingectomy the safest and fastest operation. If salpingostomy is performed, hCG levels should be followed postoperatively to insure that no further treatment is required.

Medical management

Methotrexate, a chemotherapeutic agent that interferes with DNA synthesis, is currently used as an alternative to surgical treatment in clinically stable patients. While oral MTX has not been found to be more effective than placebo (Korhonen et al 1996), IM methotrexate has been found to have a success rate of 85-97% (Stovall et al 1991, Stovall and Ling 1993, Thoen and Creinin 1997, Henry and Gentry 1994, Stovall et al 1991). Although primary work with MTX involved citrovorum "rescue," and multiple alternating doses of both drugs, the treatment has been simplified to single dose injection of MTX alone (50 mg/m^2 or 1 mg/kg body weight) for the majority of patients (Stovall et al 1991, Fernandez et al 1994). With a widely varying range dependent on the study, a percentage of women may require a second injection, from 3.3% (Stovall and Ling 1993) to 26% (Henry and Gentry 1994); some may require eventual surgical intervention, from 0% (Stovall and Ling 1993) to 14.7% (Henry and Gentry 1994).

With a varied rate of persistent ectopic after conservative surgery, medical management with methotrexate has become an important second line therapy. Methotrexate (MTX) successfully treated 97% of reported persistent ectopics in a reviewed series of studies (Yao and Tulandi 1997). Prophylactic methotrexate injection has also been proposed as an adjunct to conservative surgical management, with a relative risk of 0.13 of developing persistent ectopic pregnancy after MTX prophylaxis (Graczykowski and Mishell 1997).

Although life threatening side effects of methotrexate (neutropenia and pneumonitis with respiratory distress, for example) are reportable (Isaacs et al 1996, Horrigan et al 1997), less serious side effects are not rare. Complications such as stomatitis, gastritis, enteritis, liver function test elevations, and evidence of non-life threatening bone marrow suppression have been seen in 0 to 20% of systemically treated patients (Stovall and Ling 1993, Kooi and Kock 1992). Abdominal pain, occasionally requiring hospitalization for observation, can be seen in up to 60% of patients from day 2-7 after treatment (Stovall and Ling 1993.).

Given these findings, local injection of methotrexate, shown to have fewer side effects, has been studied under both ultrasound and laparoscopic guidance. In comparison to consistently high resolution rates with systemic MTX and laparoscopic salpingostomy, intratubal injection has had much more varied success, from 43-100% (Yao and Tulandi 1997). Other treatment options have therefore been explored: tubal injection of hyperosmolar glucose was demonstrated to be 94-98% effective in two small series (Yeko et al 1995, Lang et al 1992), and uterine artery embolization was used in a patient bleeding heavily from a cervical pregnancy 4 days after systemic MTX treatment (Cosin et al 1997).

Reproductive outcome

One of the proposed and controversial benefits of expectant management of ectopic pregnancy is improved future fertility. In one study, after spontaneous resolution, the intrauterine pregnancy rate was 88% and repeat ectopic rate only 4% (Rantala and Makinen 1997). This is optimistic compared to rates of ipsilateral tubal patency of those women successfully managed expectantly and those failing, which were not statistically significantly different at 75 and 60% (Shalev et al 1995). In that study, the rates of future intrauterine pregnancy (75%) and repeat tubal pregnancy (12.5%) in the group expectantly managed are comparable to other's findings below. Combining the outcomes of 30 studies with 811 patients after salpingostomy by laparoscopy and 703 by laparotomy, equivalent rates of intrauterine and recurrent

ectopic pregnancies are seen: approximately 60% intrauterine and 15% tubal gestations (Yao and Tulandi 1997). A similar comparision of treatment with salpingostomy versus salpingectomy revealed comparable rates of intrauterine pregnancy (approximately 50%) but a slightly decreased occurrence of repeat ectopic pregnancy in the conservatively managed group (15 vs. 10%). Use of locally injected or systemic methotrexate has been associated with a risk of recurrent ectopic pregnancy of 6 - 9% (Stovall and Ling 1993, Shalev et al 1995, Zilber et al 1996).

Conclusion

The continuing development in all arenas of medical technology has allowed for easier and faster diagnosis of ectopic pregnancy as well as improvement in quality of both patient treatment and their outcomes. Rare forms of ectopic pregnancy, such as cervical and interstitial pregnancies, which have been associated with very poor maternal outcomes in the past, are now able to be diagnosed earlier and managed more safely. For example, cervical pregnancy, which can be associated with massive haemorrhage, has been difficult and dangerous to manage by traditional surgical methods such as dilation and curettage. Methotrexate has been administered both systemically and locally in these cases, and surgical treatment with hysteroscopic resection has recently been described in a case report, with excellent results (Ash and Farrell 1996, Hsu et al 1995).

Given the multiple treatment options available, the continuing dialogue between patient and physician is just as crucial once the diagnosis is made. The patient's understanding of her diagnosis, the physician's assessment of her compliance, and their ability to make a reasonable choice together is dependent on the communication skills of the physician, which need to develop and improve alongside of the rapidly advancing technology.

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