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Incidence, diagnosis and management of ectopic pregnancies: A review

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Abstract
Background: Ectopic pregnancy; the conceptus implanting outside the uterine cavity, arises in 1.3–2.4% of all pregnancies which put the lives of many young women in peril. It causes major maternal morbidity and mortality and its incidence is increasing worldwide. Though the set medical practices to address the grave situation are improved, it still remains worrying to note in third world countries.
Methods: We review the incidence, causes, diagnosis, and management of ectopic pregnancy. The evidence presented is from a combination of selected published papers identified from Medline and a reflection of clinical practice in our unit.
Results: Diagnosis involves a combination of clinical symptoms, serology, and ultrasound. Medical management with methotrexate is an effective option in most clinically stable patients. Patients, who have failed medical management or presented with ruptured ectopic pregnancy are most frequently managed with excision by laparoscopy or, less commonly, laparotomy. Following tubal ectopic pregnancy, the rate of subsequent intrauterine pregnancy is high and independent of treatment modality.
Conclusion: This review describes the incidence, risk factors, diagnosis, and management of tubal and non-tubal ectopic pregnancies, and reviews the existing data regarding recurrence and future fertility.

Keywords: Ectopic pregnancy, diagnosis, intervention, prevention

Introduction
Ectopic pregnancy (EP) involves the implantation of a fertilized ovum outside the endometrial cavity and is reported to have an approximate incidence of 1.5–2.0% in all pregnancies [1]. A potentially life-threatening disease, still, it remains a predicament in contemporary gynecological practice [2]. Though the set medical practices are improved over time, EP still remains as an important cause of morbidity and mortality in women.
Though improved diagnostic and therapeutic methods have made maternal death from EP rare an occurrence (0.05%), the quality of diagnosis and treatment of this condition is yet not standardized [3]. In spite of the availability of minimally invasive surgical methods, delayed diagnoses and inaccuracies in treatment still make ruptured ectopic pregnancy a gynecological emergency. The etiology of EP is put down to mainly on factor that causes delayed transport of the fertilized ovum through the fallopian tube [4, 5]. Here in this review we focus on the types, causes, diagnosis, intervention and prevention of ectopic pregnancy.

Types of ectopic pregnancy
The archetypal presentation of ectopic implantation is in the Fallopian tube. About 75–80% of EPs occur in ampullary portion, 10–15% in isthmic portion, and about 5% in the fimbrial end of the Fallopian tube [6]. EPs on other sites such as the abdomen, ovary or cervix are infrequent but are considered fatal [7]. Cervical EP is rare and represents only 0.15% of all EPs [8]. Ovarian EP is out of ordinary, and incidence is estimated to be 0.15–3% of all diagnosed EPs [9]. The higher mortality of other site EPs is attributed to the difficulty in detection as well due to the massive bleeding that can result if rupture occurs at these sites [10].

Risk factors
Albeit a proportion of women with ectopic pregnancy have no known causative factors, in general, there exists risk of EP due to multiple factors. History of Infertilty, and infertility treatment, prior ectopic pregnancy, tubal damage from infection or surgery, increased age, and smoking are all considered risk factors [11, 13].

It has also been reported that the incidence of EP has been continually increasing concomitant with increased sexually transmitted disease (STD) rates and associated salpingitis [14]. Untreated pelvic inflammatory disease (PID) causes scar tissue to develop in the fallopian tubes which prevents the fertilized egg from making its way through the fallopian tube to implant in the uterus. This applies relevant to Chlamydia trachomatis, the main cause of PID and it has been reported comprehensive treatment strategies to prevent chlamydia not only decrease the incidence of C trachomatis infections but also the prevalence of ectopic pregnancies [15].

With respect to maternal cigarette smoking, studies have reported that cotinine; an active metabolite of nicotine, increases the expression of prokineticin PROKR1 in the Fallopian tube, leading to distortions in the tubal microenvironment that could make prone the subjects to develop EP [16]. Increased maternal age is considered the uttermost risk of EP and is contemplated that maternal age especially over 35 years bear a significant risk factor [17].

Progestin only contraceptives, delayed ovulation, transmigration of the ovum to the opposite tube, prenatal exposure to diethylstilbestrol, and spastic tubes are among other proposed casual factors of ectopic pregnancy [18].

Presentation

The classic clinical presentation of ectopic pregnancy is abdominal pain, amenorrhea and vaginal bleeding between 6 and 10 weeks' gestation. The pain can be persistent, severe and is often unilateral and abdominal tenderness is reported in up to 75% cases [19]. Cervical motion tenderness has been reported in up to 67% of cases, and a palpable adnexal mass in about 50% [20]. In recent times, it has also been reported that one third of women with ectopic pregnancy have no clinical signs and 9% have no symptoms [21].

A ruptured ectopic pregnancy should be strongly suspected if a woman has a positive pregnancy test and presents with syncope and signs of shock including tachycardia, pallor and collapse. There may be abdominal distension and marked tenderness. Shoulder tip pain, syncope and shock occur in up to 20% of women [22].

Unfortunately, atypical presentation is also relatively common. Ectopic pregnancy may mimic other gynecological disorders and gastrointestinal or urinary tract disease [23]. For these reasons, clinicians should be mindful that women of reproductive ages who presents with abdominal or pelvic symptoms shall also be considered for a possible ectopic pregnancy.

Diagnosis of ectopic pregnancy

Physical findings, like symptoms, vary markedly and frequently depend on the acuteness of the patient's condition. A bimanual vaginal examination is used to detect masses and localize discomfort. Adnexal tenderness is the most frequently noted finding on pelvic examination in patients with an ectopic pregnancy and an adnexal mass may be palpable.

The measurement of serum markers along with transvaginal sonography could be a promising method for earlier and more accurate differential diagnosis of EP [24, 25]. The serum marker hCG plays an important role alongside ultrasonography in the diagnostic evaluation of pregnancy of unknown location [26]. Ectopic pregnancy is generally associated with a rise in hCG by no more than 66%, or a fall by no more than 13% from the baseline level, in 48 hours. A ratio lying within this range, along with an absolute hCG value above 1500 IU/L in the absence of any visualizable intrauterine pregnancy, can be taken as evidence for a probable ectopic pregnancy. This combined criterion is 92% sensitive and 84% specific [27]. Dissimilar to β-hCG concentrations, serum progesterone levels are stable for the initial 8–10 weeks of gestation. Earlier studies described that progesterone concentrations are higher in normal IUP and hence for this reason, serum progesterone levels may be helpful for evaluation of suspected EP if it is very low in concentration [28-29]. Previous studies have also demonstrated that placental protein levels are markedly reduced in EP when compared to normal IUP at the same gestational age [30].

Likewise it is previously reported that serum values of VEGF is a potential marker for EP. Its concentrations in women with EP are higher than in those with normal and arrested intra uterine pregnancy (IUP). With a cut-off concentration of 200 pg/ml, serum VEGF could distinguish normal IUP from EP with a sensitivity of 88% [31]. In-addition, an earlier report suggest that women with EP have significantly greater Serum creatine kinase (CK) activity as compared to the women with normal pregnancies, suggesting that CK could be a crucial predictive marker for EP [32]. However, a few previous studies have demonstrated poor sensitivity and positive predictive values for this marker, suggesting that it alone, is insufficient for use in clinical practice [33].

Transvaginal sonography (TVS) is the imaging modality of choice for the diagnosis of EP of sensitivity less than 90% [34]. A diagnosis of EP should be established only on the basis of the positive visualization of an extrauterine pregnancy [7]. In cases where an ectopic pregnancy is suspected and ultrasound is inconclusive, a diagnostic laparoscopy may be required and this is believed by many to be the 'gold standard' investigation in ectopic pregnancy [35].

Medical management of ectopic pregnancy

The treatment option of EP involves surgical treatment by laparotomy or laparoscopy, and medical treatment is usually systemic or through local route, or by expectant treatment [36].

Expectant treatment

Some ectopic pregnancies resolve spontaneously, and expectant management is possible in selected cases. This is not related to the size of the ectopic pregnancy on an ultrasonogram, but the initial serum titre of human chorionic gonadotrophin, and the trend in titres are independent predictors of success. Hence it is important to serially monitor serum titres of human chorionic gonadotrophin in patients who are being managed expectantly. The higher the serum concentration the more likely expectant management will fail. Overall, if the initial serum concentration of human chorionic gonadotrophin is less than 1000 IU/l, expectant management is successful in up to 88% of patients. It is recently recommended that an initial serum beta HCG cut off level of 2500 IU/l for expectant management can be used for asymptomatic patients with suspected ectopic pregnancy [37-38]. However the available evidence is scant and hence expectant management cannot be considered a reliable therapeutic option.

Medical treatment

Methotrexate, a folic acid antagonist, is used for medical management in patients before tubal rupture and is also haemodynamically stable [39]. It can be given intramuscularly or injected into the ectopic pregnancy, a route that delivers high concentrations locally with smaller systemic distribution. Close follow up with serial measurements of serum concentrations of human chorionic gonadotrophin is mandated. A second course of treatment may be necessitated in a few cases. Though

methotrexate treatment may produce mild temporary side effects, it has a good success rate for treating small ectopic pregnancies and it offers the best chance of maintaining fertility after treatment [40].

Surgical

Surgical treatments may be radical (salpingectomy) or conservative (usually salpingostomy), and they may be performed by laparoscopy or laparotomy [41]. Salpingectomy is the treatment of choice if the fallopian tube is extensively diseased or damaged as there is a high risk of recurrent ectopic pregnancy in that tube. Salpingostomy harbours a risk of developing persistent trophoblast and ergo follow up with serial measurements of serum concentrations of human chorionic gonadotrophin is necessitated [42]. Since no single postoperative concentration of human chorionic gonadotrophin is predictive, follow up until complete resolution is necessary. The need for a second laparoscopy should be based on symptoms rather than changes in concentrations of human chorionic gonadotrophin. In a randomised controlled trial, methotrexate together with laparoscopic salpingostomy was found effective in reducing the complication of persistent trophoblast [43].

Fertility after treatment

Some studies have shown that tubal patency and future reproductive outcomes are significantly improved in women managed expectantly compared with those who underwent surgery. Rates of intrauterine pregnancy after expectant management varied between 80% and 88%, and rates for recurrent ectopic pregnancy varied between 4.2% and 5%. Subfertility, tubal pathology and age will influence on fertility outcome following ectopic pregnancy. Despite tubal preservation in around 90% of patients and patency in 55%-59%, neither systemic treatment with methotrexate nor laparoscopic salpingostomy improved subsequent pregnancy performance. Radical or conservative surgery does not have influence on future pregnancy outcome and treatment should therefore be directed at therapeutic need [44].

Prevention of ectopic pregnancy

In general, women cannot prevent EP, but they can prevent serious complications with early diagnosis and treatment. If they have one or more risk factors for EP, women and their physician can closely monitor the first weeks of a pregnancy [12, 13]. Reducing the risk of sexually transmitted infections (STIs), such as gonorrhea or chlamydia, may increase a woman's chances of having an ectopic pregnancy. Moreover, if women do get STIs, it is important to get treatment right away. The sooner those women are treated, the less likely they will develop inflammation that may damage the reproductive system and increase the risk of developing EP [14, 15]. As it is previously established that smoking increases the risk of having EP, those habituated, shall quit smoking before trying to conceive. To minimize the risk of ectopic tubal pregnancy in woman with unilaterally damaged Fallopian tubes, salpingectomy should be the preferred surgical treatment, rather than attempting tubal salvage and repair [41, 45].

Conclusion

The major advancement in EP management came as a result of timely and precise diagnosis, made possible by high-resolution ultrasonography and radioimmunoassay for human chorionic gonadotropin (hCG) and also the widespread availability of laparoscopy. Though infrequent in the community, all sexually active women in their reproductive ages, with a history of lower abdominal pain and vaginal bleeding should be referred for early ultrasonography and, if necessary, the values of predictive serum markers shall be assessed. Women with a previous episode of ectopic pregnancy should have early access to ultrasonography to verify a viable intrauterine pregnancy in their subsequent pregnancies. Diagnostic laparoscopy is necessary if the clinical situation cannot be clarified or if the patient's condition deteriorates. Expectant and medical management of ectopic pregnancy are effective options in some cases as long as adequate facilities for monitoring are available. Medical therapy of ectopic pregnancy is appealing over surgical options owing to the difficulties of the procedure itself as well the aftermath. In addition, medical therapy is advantageous that it involves potentially less tubal damage and is more economical. If surgery is necessary, the laparoscopic route is better preferred due to minimal invasion, but it is not clinically indicated that there is an advantage for salpingostomy over salpingectomy. The decision should therefore be made on an individual basis on case complexity. It is also suggestive that ectopic pregnancy can be prevented by decreasing the incidence of pelvic inflammatory disease and improving treatment for the same.

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