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# Ectopic Pregnancy: Diagnosis, Prevention and Management

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## Abstract

An ectopic pregnancy (EP) falls within the area of the gynecological emergency and/or reproductive management of women, which is the implantation of fertilized ovum outside the endometrial cavity. The etiology of EP concentrated mainly on factor causes delayed transport of the fertilized ovum through the fallopian tube (favors implantation in tubal mucosa), thus giving rise to EP. This chapter describes the causes, diagnosis, prevention and the guidelines to improve the management of women who may have an EP, a major gynecological emergency that is a cause of morbidity or even mortality of women in first trimester. Three types of EP are diagnosed: tubal, cervical and ovarian; tubal is the main type. Identification of the signs and symptoms of acute and chronic EP in women, involving classical clinical trials or other symptoms common to early pregnancy, as well as evaluating the most important congenital and acquired factors related with EP, were discussed. Explanation of the most accurate methods used to diagnose the pregnancy including serum beta hCG and progesterone levels, medical history, ultrasonography, pregnancy tests and laparoscopy was also clarified. The evaluation of the most effective management tools of EP, including methotrexate administration and surgery (laparotomy and laparoscopy), was obviously explained.

**Keywords:** ectopic pregnancy, diagnosis, prevention, management, women

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## 1. Introduction

Ectopic pregnancy (EP) is the result of implantation and maturation of the conceptus outside the endometrial cavity, which ultimately ends in the death of the fetus. Without timely diagnosis and treatment, EP can become a life-threatening situation [1]. It is accepted from the Greek word “ektopos,” meaning out of place [2], referring to the blastocyst implantation outside the endometrial cavity with over 95.5% implanting in the Fallopian tube [3–7], where the fetus or

embryo is absent or stops growing. The EP presents a major health problem for women of child-bearing age, constituting 1.2–1.4% of all reported pregnancies. Most specified risk factors are of maternal origin: pelvic inflammatory disease, *Chlamydia trachomatis* infection, smoking, tubal surgery, induced conception cycle as well as endometriosis [8]. During the past 40 years, its incidence has been steadily increasing concomitant with increased sexually transmitted disease (STD) rates and associated salpingitis (inflammation of the Fallopian tubes). The most common site of ectopic implantation is the Fallopian tube. Other sites such as the abdomen, ovary or cervix are far less common but are associated with higher mortality. This higher mortality is due to greater detection difficulty and to massive bleeding that can result if rupture occurs at these sites [9].

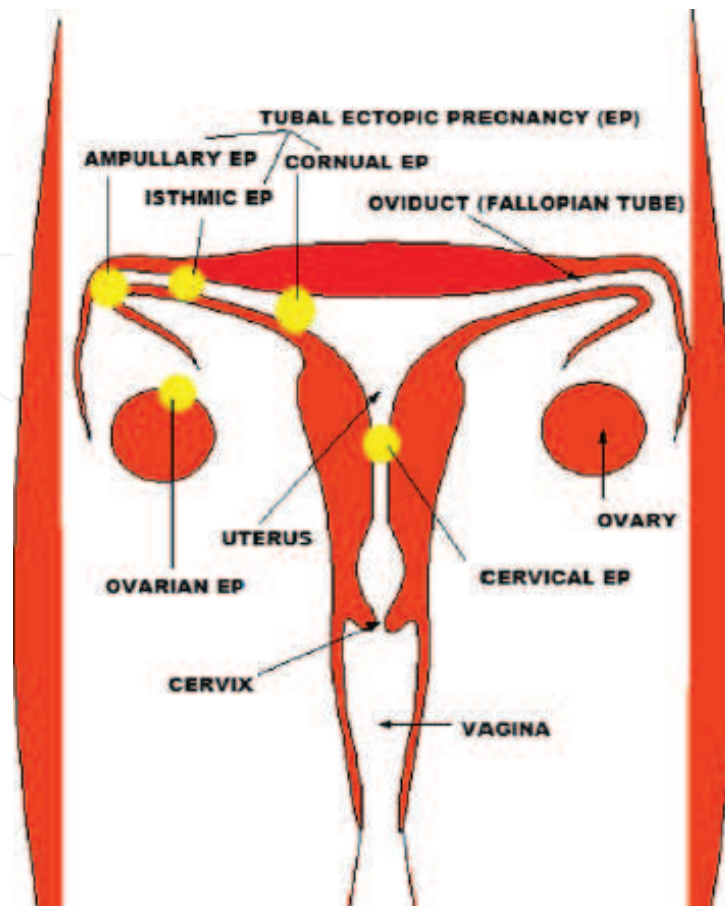
The annual incidence of EP has obviously augmented over the past 34 years [10]. In the western world, 4–10% of pregnancy-associated death has been noticed [11, 12], while it has increased exponentially in developing countries [13]. Notwithstanding the progress in diagnostic methods allowed for earlier diagnosis, it still remains a life-threatening issue. Al-Turki [14] reported that there is an increasing rate of EP in Arabian countries like the Kingdom of Saudi Arabia. Simultaneously, Calderon et al. [15] noticed an EP rate of 11.2 per 1000 pregnancies in California during 1999–2000. The most recent figure for the rate of EP in Ireland is 14.8 per 1000 pregnancies [16]. In Ireland, as in most of the developed world, there has been a reduction in mortality from EP reflecting a success story of modern management. A life-threatening surgical emergency in a woman with a positive pregnancy test and hemodynamic shock has been converted to a non-urgent medical condition in many cases. The major improvement in mortality came as a result of earlier and more accurate diagnosis, made possible by development of high-resolution ultrasonography and radioimmunoassay for human chorionic gonadotropin (hCG) and also the widespread availability of laparoscopy [17].

## 2. Types of ectopic pregnancy

The Fallopian tube is the common site in most cases of tubal EP [18]. 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 [19]. The tubal EP can be diagnosed by a transvaginal ultrasound scan (TVS) and implies an intact Fallopian tube with a pregnancy that is likely to be growing and visualized as an inhomogeneous mass that might well be a collapsed sac, which contains trophoblastic tissue [20].

Cervical EP is rare and represents only 0.15% of all EPs [21]. It can be defined as the implantation of the blastocyst in the endocervix, blowing the internal orifice. It is associated with a high morbidity and mortality potential. Timely intervention is required to preserve fertility and avoid the need for a hysterectomy [22]. It can be diagnosed by ultrasonography according to the criteria described by Hofmann and Timor-Tritsch. In true EP, Doppler investigations observed characteristic patterns of trophoblast with high flow velocity and low impedance [23].

Ovarian EP is one of the rarest variants, and incidence is estimated to be 0.15–3% of all diagnosed EPs [24, 25]. One of the important risk factors for ovarian pregnancy is in the use of intrauterine devices (IUDs). IUD is one of the contraceptive methods that prevent intrauterine



**Figure 1.** Different sites of ectopic pregnancy [8].

implantation in 99.5%; if implant occurs with IUD, it is tubal implantation in 95% of cases, and it is very rare in other places such as ovary [26]. One in every nine ectopic pregnancies among intrauterine device (IUD) users is an ovarian pregnancy [27, 28]. The diagnosis is intricate and based on surgical and histopathological observations [29]. Early diagnosis is necessary to avoid more serious complications and emergency invasive procedures [30]. However, Panda et al. [31] noticed that its preoperative diagnosis remains a challenge, and it cannot be diagnosed early. **Figure 1** shows the different sites of EP.

### 3. Symptoms of acute and chronic ectopic pregnancy

The symptoms of EP could be acute, like short period of amenorrhea (5–8 weeks), intermittent scanty vaginal bleeding of dark blood (spotting) and abdominal and shoulder-tip pain. The chronic symptoms including those recovered from previous attack of acute pain, amenorrhea, dull aching lower abdominal pain, vaginal bleeding, dysuria, frequency of micturition or retention of urine and rectal tenesmus.

Acute EP is a common clinical problem, diagnosed by a combination of clinical, sonographic and laboratory findings. Chronic EP is a more usual situation and is thought to result from minor repeated ruptures of tubal pregnancy that develop into a hematocele containing blood, clots and

trophoblastic tissue that can be active or inactive [32]. The hematocele is surrounded by adhesion and induces an inflammatory response. Other findings [33] reported that women who presented acutely or chronically had similar presenting medical and surgical histories. In particular, the two groups did not differ in terms of the putative risk factors for EP; they had similar history of pelvic surgeries, tubal ligation, sexually transmitted diseases or pelvic infection.

#### 4. Risk factors affecting the incidence of ectopic pregnancy

The main risk factors of ectopic pregnancy are different in various countries due to different cultural and social characteristics. Determination of main risk factors of ectopic pregnancy leads to a rapid diagnosis and an improvement in strategies for its prevention. Various risk factors for ectopic pregnancy have been identified, including previous ectopic pregnancy, previous pelvic surgery, induction of ovulation, intrauterine device (IUD) usage, history of pelvic inflammatory disease (PID) and smoking at the time of conception [34–37].

Women having EP may have their future fertility affected, and it increases their risk of having another EP. When EP grows in a Fallopian tube, it can damage the surrounding tubal tissue. This may make it more likely that an egg will get stuck there in the future. But early detection and treatment can minimize the damaging effects of EP. The chance of having another EP will be affected by the combination of other risk factors. These can include smoking, the use of assisted reproductive technologies (ARTs) to get pregnant and the extent of the Fallopian tube damage.

Previous pelvic operation may increase the risk of EP [38]. Previous surgery in the pelvic area or on the tubes can cause adhesions. Adhesions form in the majority of women after gynecologic pelvic surgery. Studies have shown that adhesions formed in 55–100% of patients who had reproductive pelvic surgery, whether open or laparoscopic. For example, myomectomy (surgery to remove fibroids), tubal surgery (to remove EP), surgery on the ovary (to remove cysts) and surgery for endometriosis can cause adhesions.

EP must always be considered particularly after the induction of ovulation by clomiphene citrate (100 mg/day starting on day 5 of the cycle) or assisted reproductive technology (ART). The incidence of EP rises significantly after ART and varies from 2 to 11 [39]. Every clinician treating women of reproductive age should keep this diagnosis in mind. Ovulation induction using eight injections of FSH and hCG hormonal protocol caused left tubal EP and started growing earlier than the right one causing pain and bleeding [40]. Gynecologists, primary care physicians, sonologists and emergency room physicians should have a high suspicion of heterotopic pregnancy in women conceived after using ovulation-inducing agents [41].

Intrauterine contraception is the most commonly used method of long-acting reversible contraception because of its high efficacy and safety, ease of use and low cost. IUD is the most commonly used method of reversible contraception worldwide and is used by an average of 23% of women contraceptive users, with a range of <2 to >40% depending on the country [42]. Pregnancy with an IUD in situ is more often an ectopic one than a pregnancy with no IUD. Past IUD use could mildly elevate the risk of ectopic pregnancy (pooled OR: 1.40, 95% CI: 1.23–1.59)



[43]. The increasing number of EP among IUD users was believed to be associated with several factors. First, the irritation of the fallopian tubes caused by the presence of the IUD in the uterine cavity may prevent the egg from going into the uterus. Second, the IUD can only prevent intrauterine pregnancy, not EP. Third, bacteria brought in through IUD insertion may cause Fallopian tube infection, which increases the risk of EP. This risk among IUD users is 2.94–4.5 times that in nonusers [44].

Pelvic inflammatory disease (PID) is defined as an infection of the endometrium, Fallopian tubes and/or contiguous structures caused by the ascent of microorganisms from the lower genital tract [45]. Most girls with PID develop it after getting a sexually transmitted disease (STD), such as chlamydia or gonorrhea. There is a global rise in the incidence of EP, which is mainly attributed to the increasing incidence of PID [46]. In the UK, around 11,000 cases are diagnosed per year (incidence 11.5 per 1000 maternities) [47], while in the USA, 108,800 cases (incidence 19.7 per 1000 maternities) are noticed annually.

Maternal cigarette smoking at the time of conception was associated with an increased risk of ectopic pregnancy with a dose-response relationship (adjusted odds ratios: 1.30–2.49) [48]. Studies reported that cotinine (an active metabolite of nicotine) increases the expression of prokineticin PROKR1 in the Fallopian tube, a regulator of smooth muscle contractility and a gene thought to be important for intrauterine implantation [49]. Smoking was associated with decreased levels of proapoptotic gene (BAD) transcript ( $P < 0.01$ ) and increased levels of BCL2 transcript ( $P < 0.05$ ) in Fallopian tube biopsies. BAD- and BCL2-specific immunolabeling was localized to Fallopian tube epithelium. So, smoking may alter tubal epithelial cell turnover and is associated with structural, as well as functional, changes that may contribute to the development of EP [50]. Moreover, cigarette smoking increases transcription of prokineticin receptor 1 (PROKR1), a G-protein-coupled receptor [49]. The PROKRs are receptors for PROK1, a molecule known for its angiogenic properties, control for smooth muscle contractility and regulation of genes important for intrauterine implantation [51].

Age is the utmost risk of EP that increases with advancing maternal age, with age over 35 years being a significant risk factor [1]. The incidence of EP showed a steady increase with the increase in maternal age at conception from 1.4% of all pregnancies in women aged 21 years to 6.9% of pregnancies in women aged 44 years or more due to chromosomal abnormalities in the trophoblastic tissue [52].

## 5. Diagnosis of ectopic pregnancy

In the past, EP was diagnosed on clinical symptoms such as vaginal bleeding and lower abdominal pain, but it imposed constraints on early detection [53]. It is worthy to mention that the initial diagnosis of first-trimester hemorrhage presents a crucial challenge. Recently, detection of EP is possible through serum beta-human chorionic gonadotropin ( $\beta$ -hCG) and progesterone levels as well as vaginal ultrasonography techniques [54, 55]. Blood test alone cannot tell where the pregnancy is developing, but it can help doctors monitor patients who might have a growing EP.

### 5.1. Serum $\beta$ -hCG concentration

In early pregnancy, the level of  $\beta$ -hCG should double roughly every 48 hours. After a miscarriage, it drops quite quickly. If it rises slowly, or stays around the same level over this time, this can mean a pregnancy is failing or EP. A single serum measurement of  $\beta$ -hCG concentration may not show the location of gestational sac [56, 57]. Demonstration of normal doubling of serum levels over 48 hours supports a diagnosis of fetal viability but does not rule out EP. Failing levels on raising the level of  $\beta$ -hCG concentration to reach 50% confirm nonviability suggesting occurrence of EP [58]. Moreover, it was noticed that  $\beta$ -hCG cutoff values on day 12 after embryo transfer are useful to predict the final type of clinical pregnancy. Cutoff values were found at 91 IU/L for EP (sensitivity 82.7%, specificity 71.1%) [59]. In a study of 287 patients with pain or bleeding, the minimum rise in  $\beta$ -hCG for a viable IUP was 24% at 24 hours and 53% at 48 hours [60]. Seeber et al. [61] produced data with a 99% CI that suggested a more conservative minimum rise of 35% over 2 days. In current practice, most units use a minimum value of between 50 and 66% for the acceptable 48-hour increase in  $\beta$ -hCG in a normal pregnancy [62].

### 5.2. Serum progesterone concentration

Patients with normal intrauterine pregnancies had serum progesterone levels greater than 20 ng/ml (mean = 30.9 ng/ml), while all patients with ectopic pregnancies had progesterone levels less than 15 ng/ml (mean = 5.7 ng/ml) [63]. In contrast to  $\beta$ -hCG concentrations, serum progesterone levels are stable for first 8–10 weeks of gestation [6]. Elson et al. [64] demonstrated that patients that have serum progesterone concentration below 10 ng/ml (31.8 nmol/L) and  $\beta$ -hCG levels below 1500 mIU/L are more likely to have a spontaneous EP. Similarly, Williams et al. [65] reported that the mean progesterone for normal pregnancies was  $32.8 \pm 4.25$  ng/ml ( $n = 49$ ), for ectopic pregnancies  $7.8 \pm 0.79$  ng/ml ( $n = 51$ ), and pregnancies that spontaneously aborted  $8.1 \pm 0.91$  ng/ml ( $n = 74$ ). This test may be useful in selected patients when the diagnosis is unsure after  $\beta$ -hCG and transvaginal ultrasound have been performed.

### 5.3. Serum vascular endothelial growth factor (VEGF) concentration

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that acts as a modulator of vascular growth, remodeling and permeability in the endometrium, decidua and trophoblast, as well as during vascular development in the embryo, all of which are crucial processes related to the normal implantation and placentation [66]. Serum values of VEGF were increased in EP. Daponte et al. [54] described greater serum VEGF concentrations in women with EP (227.2 pg/ml) than with abnormal intrauterine pregnancy (107.2 pg/ml). They subsequently concluded that VEGF serum concentrations might be a good marker for EP and suggested 174 pg/ml as the cutoff value for EP diagnosis.

### 5.4. Serum creatine kinase (CK) concentration

Obvious evidence suggests elevated creatine kinase (CK) as a tool for diagnosis of EP. The trophoblast usually invades the muscle layer and maternal blood vessels are eroded, allowing

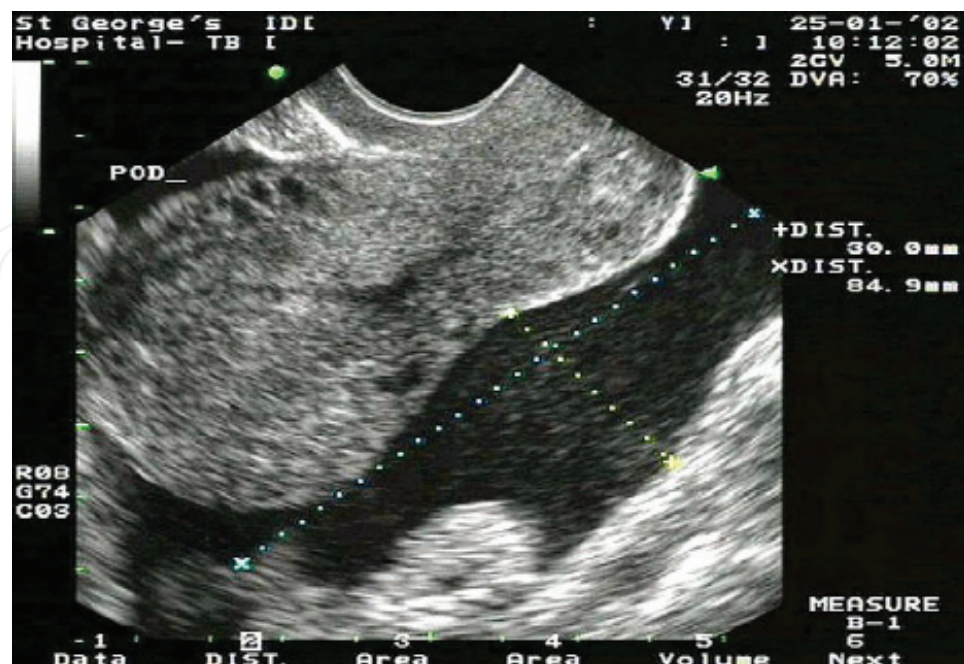
muscle cell products such as CK to enter the circulation [67]. Consequently, increased serum CK activity is normal during EP [67]. Saha et al. [68] carried out a study involving 40 women, and the total serum CK activity was found to be greater in the EP group compared to the controls, suggesting that this test might be an indicator for EP. Similarly, Katsikis et al. [69] studied 40 women with EP cases and concluded that women with EP had significantly greater CK activity as compared to the women with intrauterine abortive pregnancies and controls, suggesting that CK could be a crucial predictive tool for EP.

### 5.5. Transvaginal sonography

Transvaginal sonography (TVS) is the imaging modality of choice for the diagnosis of EP of sensitivity less than 90%. Diagnosis is based on the visualization of an ectopic mass rather than the inability to visualize an intrauterine pregnancy. A diagnosis of EP should be made on the basis of the positive visualization of an extrauterine pregnancy. If neither extrauterine nor intrauterine pregnancy is visualized on TVS, the woman should be classified as having a “pregnancy of unknown location” and then followed up until the final pregnancy outcome is known [70].

A number of findings may suggest the presence of EP, but are not diagnostic. There may be anechoic or echogenic-free fluid within the pouch of Douglas. Echogenic fluid within the pouch of Douglas may suggest hemoperitoneum secondary to a ruptured EP or tubal miscarriage, but it may also be noticed with the rupture of hemorrhagic ovarian cyst (**Figure 2**).

The precise relationship between the appearance of tubal EP on TVS, the size of the mass and serum hCG levels is uncertain. In their study on 120 women with EP, Cacciatore [71] found that hCG levels correlated with the size of ectopic gestational sacs but not with the diameter of



**Figure 2.** TVS image of echogenic fluid in the pouch of Douglas, suggestive of hemoperitoneum following rupture of EP [70].



inhomogeneous adnexal mass. They also found that in women with ectopic gestational sacs, the majority of serum hCG levels were high and increasing, while in those with an inhomogeneous mass, the serum hCG levels were significantly lower and most were decreasing.

## 6. 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. Reducing the risk of sexually transmitted infections (STIs), such as gonorrhea or chlamydia, may increase a woman's chances of having an ectopic pregnancy. If a woman reduces her risk of contracting one of these diseases, she may reduce her risk of having an ectopic pregnancy as well [7]. 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. Common symptoms of STIs include abdominal pain, painful urination, vaginal discharge, abnormal vaginal bleeding, vaginal odor and pain during sex. On the other hand, smoking may increase the risk of having EP. Women should quit smoking before trying to conceive in order to reduce the risk [7]. Interestingly, intraperitoneal sperm transmigration occurs approximately half the time in effecting spontaneous human pregnancies. 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 [72].

## 7. 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 [73, 74].

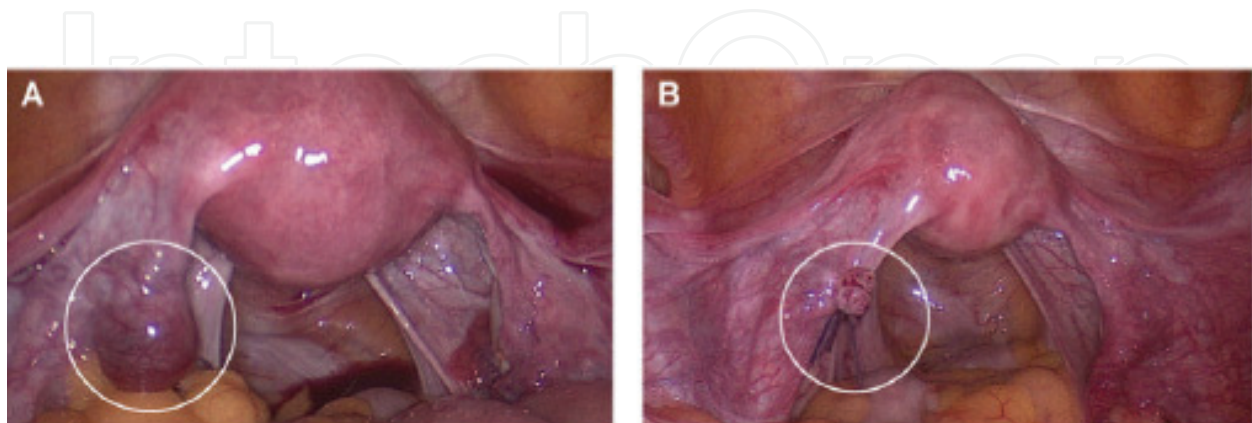
### 7.1. Surgical treatment by laparotomy or laparoscopy

In spite of the various recent advances in the management of ectopic pregnancy, conventional surgical treatment by laparotomy is still the most widely used modality of treatment in our institution. With appropriate and prompt management, maternal mortality due to ectopic pregnancy can be prevented. In a study involving 56 patients, 3 (5.4%) had unruptured tubal pregnancy, 27 (48%) had ruptured ectopic pregnancy and 26 (46.3%) had chronic ectopic pregnancy. With laparotomy, salpingectomy was done in 21 (37.4%) patients, salpingo-oophorectomy in 26 (46.3%), excision of rudimentary uterine horn in 4 (7.1%), resection and end-to-end anastomosis in 1 (1.8%) and total abdominal hysterectomy in 4 (7.1%). There was no maternal mortality [75]. In fact, laparoscopic treatment of ectopic pregnancy reported for the first time was conservative [76]. It was later on that Dubuisson et al. [77] proposed salpingectomy via laparoscopy.

A laparoscopic approach is preferable to an open approach in a patient who is hemodynamically stable. Laparoscopic procedures are associated with shorter operative times, less intraoperative blood loss and shorter hospital stays and lower analgesia requirements [78–80]. Laparotomy should be reserved for patients who present with rupture and are in a state of hypovolemic shock and compromise. If the contralateral tube is healthy, the preferred option is salpingectomy, where the entire Fallopian tube, or the affected segment containing the ectopic gestation, is removed (**Figure 3**). A salpingostomy is the removal of the ectopic pregnancy, by dissecting it out of the tube, leaving the Fallopian tube in situ in an attempt to preserve fertility on that side [7].

The success rate of salpingostomy is 92% and failure cases can be managed with methotrexate (MTX) [81]. Serial  $\beta$ -hCG measurements should be taken until undetectable to be certain that there is no persistence of trophoblastic tissue. Sometimes a prophylactic dose of MTX is given with salpingostomy [82]. Persistent EP occurs as a result of incomplete removal of trophoblastic tissue [83], the most common complication of laparoscopic salpingostomy, and occurs at a frequency of 5–20% [84, 85]. It is diagnosed during follow-up when  $\beta$ -hCG concentrations measured once a week plateau or rise [8]. NICE [86] recommended that women undergoing salpingostomy have a serum  $\beta$ -hCG level taken 7 days after surgery and then weekly until a negative result is obtained. In one randomized controlled trial of laparoscopic surgery, prophylactic MTX lowered the rate of persistent ectopic pregnancy from 14.5 to 1.9%. The major benefit was in the shorter duration of postoperative monitoring [85].

Evidence strongly suggests that there is no difference in terms of health benefits between laparoscopy and laparotomy, including the key outcome of subsequent successful pregnancy [87]. Thus, over the years, the trend has increasingly changed, and currently laparotomy for ectopic pregnancy is reserved for complicated cases where the patient is unstable hemodynamically and in complex cases where there are coexisting pelvic and abdominal masses, in which the practitioner feels that achieving pneumoperitoneum would likely be unsuccessful and a waste of time. Thus, if you are a senior specialist trainee, currently, you will have to justify to your consultant why the patient had laparotomy instead of laparoscopy [88].



**Figure 3.** (A) Left tubal ectopic pregnancy at laparoscopy and (B) tubal ectopic pregnancy has been removed by salpingectomy [7].

## 7.2. Medical management

Medical treatment is useful for patients with an unruptured tubal ectopic pregnancy who are hemodynamically stable and have minimal symptoms and a low volume of free intraperitoneal fluid on ultrasound scan [89]. Medical treatment of EP is quite less expensive than surgery [90]. Many different agents have been used to treat ectopic pregnancies including systemic and local MTX, local potassium chloride, hyperosmolar glucose, prostaglandins, danazol, etoposide and mifepristone (RU486) [91, 92]. Intramuscular methotrexate is the most widely used and successful medical therapy for ectopic pregnancy and is generally administered in a single-dose protocol. MTX is a folic acid antagonist that targets rapidly dividing cells and arrests mitosis. MTX was first used in diagnosed EP in the 1960 to aid safe surgical removal of the placenta from its abdominal implantation sites in second- and third-trimester cases [93]. In ectopic pregnancy, the drug prevents the proliferation of cytotrophoblast cells, reducing cell viability and  $\beta$ -hCG secretion and thus progesterone support for the pregnancy. This facilitates the resolution of the ectopic pregnancy and tissue remodeling [7].

Two common regimens are available for MTX: multidose (MTX 1.0 mg/kg IM daily; days 0, 2, 4 and 6 alternated with folinic acid 0.1 mg/kg orally on days 1, 3, 5 and 7) and single dose (MTX 0.4–1.0 mg/kg or 50 mg/m<sup>2</sup> IM without folinic acid) [93]. The multidose regimen alternates an every other day dose of intramuscular MTX 1.0 mg/kg with an every other day dose of intramuscular leucovorin calcium 0.1 mg/kg, a folic acid antagonist antidote, up to four doses of each until the  $\beta$ -hCG level decreases by 15% on two consecutive days [8]. Approximately 14–20% of patients receiving single-dose treatment will require a repeat dose, usually decided on following a fall of the  $\beta$ -hCG concentration of less than 15% from day 4 to 7 after treatment. This timescale is used as MTX can cause a transient rise in serum  $\beta$ -hCG after initial treatment [7]. MTX treatment is very successful for small stable ectopic pregnancies. A meta-analysis of nonrandomized studies showed success rates of 93% (95% CI 89–96%) for multidose protocols and 88% (95% CI 86–90%) for single-dose therapy [94]. The smaller the increase in  $\beta$ -hCG level prior to administration of MTX, the higher the chance of a successful medical management. A serum  $\beta$ -hCG increase of up to 11–20% over 48 hours prior to the administration of MTX has been associated with higher rates of success [95, 96]. Barnhart et al. [97] investigated in their meta-analysis both regimens (multidose and single dose) and concluded that the multidose regimen was more effective than the single-dose regimen, with success rate reported as 93% for the multidose regimen and 88% for the single-dose regimen.

Many side effects associated with MTX treatment are nausea and vomiting, stomatitis, diarrhea, abdominal discomfort, pneumonitis, photosensitivity skin reaction, impaired liver function, reversible, severe neutropenia (rare) and reversible alopecia (rare) [98]. Moreover, side effects of MTX high dose (MTX-HD) may be life-threatening; however, those of various doses of oral MTX are variable because of the interindividual variability of gastrointestinal absorption of this drug. Bone marrow, gastrointestinal mucosa and hair are particularly vulnerable to the effects of MTX, secondary to their high rate of cellular turnover, and because MTX concentration is inversely proportional to renal clearance [99], renal toxicity is frequent with MTX-HD.

## 7.3. Expectant management

Expectant management means that we expect EP to resolve naturally without any intervention. It will be closely monitored by the hospital instead of having immediate treatment.

Expectant treatment can be applied in a selected subset of patients with self-limiting ectopic pregnancy; the proportion overtreated must be accepted until a marker that identifies this subgroup of patients is found [100, 101]. Studies evaluating expectant management of ectopic pregnancy are primarily based on this concept of trophoblast in regression and therefore exposed to the uncertainties of definite primary EP, which are diagnosis [98].

A suitable candidate for expectant management must have an ectopic pregnancy with no evidence of rupture, be clinically stable and asymptomatic and have consistently declining  $\beta$ -hCG concentrations [7]. Low serum progesterone is also a possible marker of suitability for the expectant approach. Follow-up should be between one and three times weekly with  $\beta$ -hCG measurement and ultrasonography as required. Expectant management is reported to be most useful when the initial  $\beta$ -hCG is  $<1000$  IU/L [102]. Other most recent guideline, published by the American College of Obstetricians and Gynecologists, is that there may be a role for expectant management when the  $\beta$ -hCG level is 200 mIU/ml and which is further in decline phase [8]. Another analysis has noticed that the favorable prognostic signs for successful expectant management of EP are the following minimal clinical symptoms with no evidence of hemodynamic compromise: evidence of ectopic resolution by declining  $\beta$ -hCG levels preceding expectant treatment can be used for such dilation; low initial serum  $\beta$ -hCG: successful expectant management occurs in 98% of cases for hCG 200 IU/L, in 73% for  $\beta$ -hCG 500 IU/L and in 25% for  $\beta$ -hCG 2000 IU/L. Overall, if initial serum  $\beta$ -hCG levels are 1000 IU/L, then successful expectant management might occur in most patients (88%) with an ectopic pregnancy size of 4 cm, without a fetal heart beat on transvaginal sonography, followed by hemoperitoneum 50 ml. Evidence of ectopic resolution on scan is another way to diagnosis [8, 98]. Success rates between 47 and 82% are reported, depending on the patient's initial status [7].

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