19

Prior pelvic inflammatory disease, endometriosis and ectopic pregnancy

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The aim of pre-pregnancy counseling is to address issues regarding women's concerns about their ability to fall pregnant and to give birth to a healthy baby at the end of pregnancy.

Pelvic inflammatory disease (PID)[1] and endometriosis[2] are both risk factors associated with subfertility and thus could potentially lead to failure to become pregnant. In the event of a successful conception, tubal damage secondary to these pre-existing disease processes increases the risk of an ectopic pregnancy. Of great importance, a prior history of an ectopic pregnancy is a possible indicator of existing tubal damage and hence a strong risk factor for reoccurrence[3]. Such an event will not only be associated with an unsuccessful pregnancy, but also with maternal morbidity at the very least, if not mortality. Even in the presence of first-world medical facilities, ectopic pregnancy still remains the leading cause of maternal mortality in the first trimester, with three women dying in the UK[4] and 45 in USA every year[5].

With the development of early pregnancy assessment units, screening for risk of ectopic pregnancy, one of WHO's primary objectives[6], not only is possible, but also has been shown to be cost effective[7]. It is therefore imperative to use the opportunity, when meeting a potential mother to be, to identify risk factors for ectopic pregnancy and to decide upon a management plan in advance for possible complications that may arise.

PRIOR 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[1]. The majority of cases in young women are associated with sexually transmitted infections (STIs), the most prevalent being *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. These organisms often initiate an inflammatory process and then are replaced by opportunistic bacteria including aerobes, anaerobes and *Mycoplasma* sp[8]. Special consideration should be given to tuberculosis which is discussed separately in this book.

The Department of Health and Human Services in the USA[9] and the Department of Health in the UK[10] have expressed concerns that with changes in lifestyle, STIs represent a growing problem with nearly 333 million curable cases occurring worldwide annually[9]. This concern is not only based on increasing numbers of new STIs diagnosed in genitourinary clinics, but also on the fact that these rates are highest in women who are young and in the reproductive age range. Young women aged 16–25 years account for nearly half of all STIs diagnosed in genitourinary clinics, and it is this same group that will potentially be considering a pregnancy post-infection. Of further concern is the

fact that 15% of women rarely or never use a condom with a new sexual partner[9].

Prior infection (symptomatic or asymptomatic) is a risk factor for current infection, which may be associated with vaginal discharge, irregular vaginal bleeding or pelvic pain, all of which direct women to seek medical advice. Unfortunately, such infections can also be asymptomatic and thus undetected at the time of consultation in the absence of routine screening procedures. Pre-pregnancy counseling sessions may provide one of the few times that an otherwise healthy woman voluntarily accesses medical attention, and, as such, becomes an ideal chance to opportunistically screen for STIs.

For women with no prior history of infection, the current UK national antenatal care guidelines published by the National Institute of Clinical Excellence (NICE)[11] state that there is no good evidence to suggest that routine antenatal screening for STIs (other than HIV, syphilis and hepatitis B) is indicated. Previously, however, with the advent of the National Chlamydia Screening Programme[12], NICE had envisaged that based on current expert opinion, women who are pregnant or seeking pre-pregnancy counseling at the age of 25 years or younger, should be advised on the availability of the screening program and that screening could be undertaken as part of this program. In the USA routine antenatal screening is recommended for chlamydia along with gonorrhea, the latter if the pregnant woman comes from an area of high prevalence[13]. Referral screening programs also have the additional benefit of contact tracing.

Chlamydia

Chlamydia trachomatis is currently the most common curable STI in the western world. In current screening programs, 8.5% of women below 25 years of age test positive for chlamydia[14]. The clinical implications of chlamydia infection in pregnancy are identical to those outside pregnancy, with development of repeat PID, increased risks of subfertility and ectopic pregnancy. Approximately 70% of pregnant and non-pregnant women infected with chlamydia are asymptomatic; a small proportion may present with non-specific symptoms including vaginal discharge, dysuria, lower abdominal pain, postcoital bleeding or arthritis. The vaginal discharge may be mild, irritating, usually yellow, and often goes unnoticed. Therefore, in the presence of these symptoms, women in the clinic should be offered a test to exclude the possibility, with appropriate treatment and counseling if the result proves positive.

Asymptomatic chlamydia infection during pregnancy is associated with adverse pregnancy outcomes (low birth weight, preterm delivery and preterm rupture of membranes) as well as with postpartum endometritis and neonatal morbidity, including respiratory tract infection and conjunctivitis[15]. Up to two-thirds of women affected with chlamydia during labor may transmit the organism to the infant during vaginal delivery. The infection clearly is treatable and therefore is not an indication for cesarean section; no evidence links chlamydia with chorioamnionitis.

Microbiological detection is by vaginal, urine or blood tests (Tables 1 and 2). Nucleic acid amplification tests (NAAT) have a higher sensitivity (90–95%) than enzyme immunoassays (40–70%) and therefore are the recommended laboratory test for diagnosing chlamydia infection from endocervical and vulvovaginal swabs[16]. The vulvovaginal swabs have a sensitivity similar to endocervical swabs (90–95%) and can be taken by either the patient or health-care worker. Variable sensitivities (65–100%) have been reported using the first catch urine (FCU) specimen. Cell culture can be used on all specimen types, but has low sensitivity (60–80%); because it requires expertise and is costly, it is not recommended for routine purposes. On the other hand, the

Table 1 Tests in asymptomatic women. (Modified from UK National Screening and Testing Guidelines, 2006[16])

Site or specimen	*Gonorrhea*	*Chlamydia*	*Syphilis*	*HIV*
Urethra				
Cervix	Culture	NAAT		
Vagina		NAAT		
Rectum				
Oropharynx				
Urine		NAAT		
Blood			EIA/TPPA/TPHA+VDRL	EIA

NAAT, nucleic acid amplification test; EIA, enzyme immunoassay; TPPA, *Treponema pallidum* particle assay; TPHA, *Treponema pallidum* hemagglutination assay; VDRL, Venereal Disease Research Laboratory

Table 2 Tests in symptomatic women. (Modified from UK National Screening and Testing Guidelines, 2006[16])

Site or specimen	*Gonorrhea*	*Chlamydia*	*Syphilis*	*HIV*
Urethra	M+C		DGM	
Cervix	M+C	NAAT		
Vagina	NAAT	NAAT		
Rectum	Culture	Tissue culture		
Oropharynx	Culture	Tissue culture	PCR	
Urine		NAAT		
Blood			EIA IgM	EIA/LIA

M+C, microscopy + culture; DGM, dark ground microscopy; PCR, polymerase chain reaction; EIA, enzyme immunoassay; LIA, line immunoassay

direct fluorescent antibody test is applicable to all specimens, including rectal and pharyngeal swabs, but its widespread use is hampered by a low sensitivity (80%) and the need for technical expertise; it is therefore not recommended for routine diagnosis.

Diagnosis may also be made at surgical inspection of the pelvic and abdominal cavities with the demonstration of classical peritubular adhesions (Figure 1a) as compared to the central midline adhesive disease more commonly associated with endometriosis (Figure 1b).

The tubal fimbrial ends are often damaged, giving rise to distal occlusion with clubbing and mild hydrosalpinx. Such hydrosalpinges can be identified on transvaginal ultrasonography appearing as elongated paraovarian cysts containing multiple partial septae and an irregular inner luminal wall giving an appearance described as 'cog wheeling'. The cog wheels are a result of aggregation of the tubal luminal cilia (Figure 2). The fallopian tubes are usually bilaterally affected. At laparoscopy, the pathognomonic feature of prior chlamydial pelvic infection is that of perihepatic adhesions named Fitz-Hugh-Curtis syndrome which is also seen with prior gonorrheal infection and less commonly with tuberculosis associated PID.

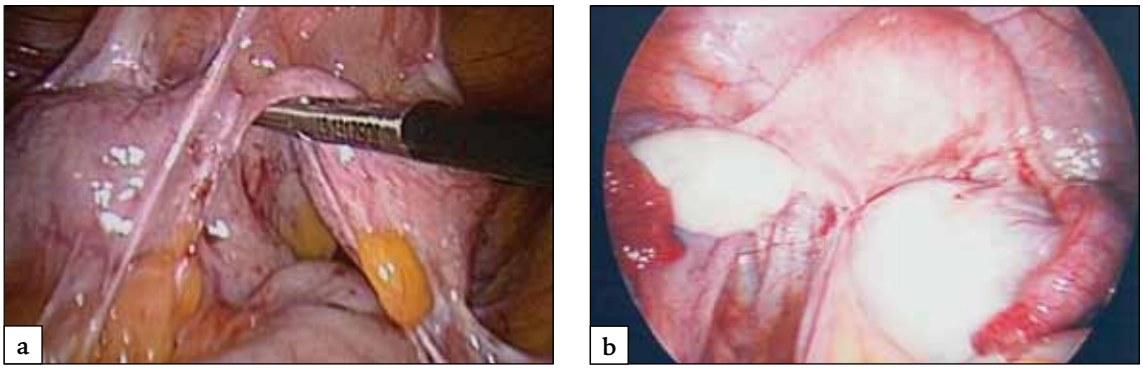

Figure 1 (a) Fine filmy peritubular adhesions associated with pelvic inflammatory disease. (b) Dense central adhesions of the posterior cul de sac associated with endometriosis (note the tubal sparing)

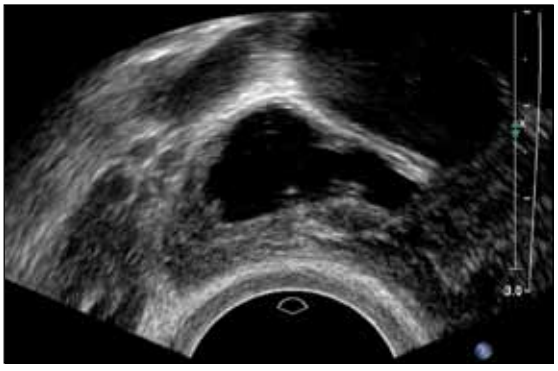

Figure 2 Hydrosalpinx on transvaginal ultrasound (cog wheel)

The recommended antibiotic therapy for genital chlamydia infection (Table 3) in non-pregnant women is doxycycline (100 mg twice daily for 7 days) or azithromycin (1 g single dose). Alternative agents are erythromycin (500 mg four times a day for 7 days) or ofloxacin (200 mg twice daily for 7 days). Doxycycline and ofloxacin are contraindicated in pregnancy. The safety of azithromycin in pregnancy and lactating mothers has not yet been fully assessed, although available data indicate that it is safe[17]. Recommended therapeutic alternatives in pregnancy and breastfeeding are erythromycin or possibly amoxicillin (500 mg three times a day for 7 days). A test of cure is not routinely recommended but should be performed in pregnancy or if non-compliance or re-exposure is suspected. It should be deferred for 5 weeks (6 weeks if azithromycin is given) after treatment is completed in order to avoid false positive results[16].

Pre-pregnancy treatment of the tubal damage is by surgery to divide adhesions and possibly open up the distal blocked end of the fallopian tube by a cuff salpingostomy. An anti-adhesive barrier may be employed as recurrence of disease and tubal re-occlusion is high (25–50%)[18], forcing couples to later resort to *in vitro* fertilization (IVF) therapies.

The evidence is limited regarding treatment of chlamydia around pregnancy as well as its effectiveness in reducing the incidence of preterm rupture of membranes, preterm delivery and low birth weight babies. Current studies are of poor quality[19–23]. Cohen *et al.*[20] compared the clinical outcomes in pregnant women with proven cervical chlamydia infection successfully treated with erythromycin 500 mg four times a day for 7 days ($n = 244$) against those who remained chlamydia positive throughout pregnancy ($n = 79$) and chlamydia-free matched controls ($n = 244$) in a low-income indigenous urban pregnant population considered at high risk. The successfully treated group had a significantly lower frequency of preterm rupture of membranes (7.4% versus 20.3%), preterm contractions (4.1% versus 24.1%) and small for gestational age babies (13.1% versus 25.3%) when compared with

Table 3 Treatment and follow-up. (Modified from UK National Screening and Testing Guidelines, 2006[16])

	Treatment in non-pregnant patient	*Treatment in pregnancy*	*Test of cure*	*Follow-up period*
Chlamydia	Doxycycline 100 mg oral twice daily for 7 days; or azithromycin 1 g single oral dose	Erythromycin 500 mg oral four times a day for 7 days	In pregnancy only: 5 weeks after completing therapy	Asymptomatic: 6 months; Symptomatic: 4 weeks
Gonorrhea	Single dose: ceftriaxone 250 mg IM; or cefixime 400 mg oral; or spectinomycin 2 g IM	Same as non-pregnant		3 months
Syphilis	Early: single dose of benzathine penicillin G 2.4 MU IM; Late: 3x weekly doses	First and second trimester: Single dose of benzathine penicillin G; Third trimester: 2x weekly doses	Early: 1, 2, 3, 6, 12 months then 6 monthly until serofast; Late: 3 monthly until serofast	
Bacterial vaginosis	Metronidazole 400–500 mg oral twice daily for 5–7 days; or 2 g single oral dose	Same as non-pregnant		

the chlamydia persistent group. There was no such difference, however, when the successfully treated group outcomes were compared to the chlamydia negative group. The frequency of preterm birth was lower in the treated group compared to both the untreated group (2.9% versus 13.9%) and matched controls (2.9% versus 11.9%). There was no difference between the three groups regarding other pregnancy outcomes, including frequency of vaginal deliveries, cesarean section, postpartum endometritis, antepartum hemorrhage or stillbirth. These authors concluded that in a high risk group for chlamydia infection there are potential benefits with repeated prenatal chlamydia testing plus successful erythromycin treatment. However, three large studies in the general female pregnant population in 1985[21], 1990[22] and 1997[23], screened by rapid immunoassay antigen detection and treated with erythromycin failed to show any effect on pregnancy outcome, except when carried out in the third trimester.

The evidence remains difficult to evaluate in terms of neonatal effects. In situations where the link is obvious, such as in vertical infection transmission, rapid identification and proper management of the neonate is considered a clinical and cost effective alternative to screening. This is still considered an area of debate and research, especially for studies looking into treatment effects that reduce the potential harms of preterm birth and neonatal complications. If, however, the patient is symptomatic, then the outlook is altered in favor of treatment.

Gonorrhea

Genital infection with *Chlamydia trachomatis* accompanies genital gonococcal infection in up to 40% of women[24]. Undetected, untreated or inadequately treated gonorrhea is another important cause of upper genital tract infection in addition to facilitating the transmission

of HIV. Not unlike chlamydia, infection of the endocervix is often asymptomatic (in up to 50%). Symptomatic infection may present with altered vaginal discharge, lower abdominal pain, dysuria, menorrhagia or intermenstrual bleeding. Hematogenous dissemination may cause skin lesions, arthralgia, arthritis and tenosynovitis. Diagnosis is based upon identification of Gram-negative *Neisseria gonorrhoeae* by culture of specimen obtained from the endocervix and urethra (Tables 1 and 2). Culture offers a readily available, specific, sensitive and cheap diagnostic test that allows confirmatory identification and antimicrobial susceptibility testing. It is currently the method of first choice for use in genitourinary medicine clinics. Treatment comprises a trio of simultaneous activities: patient treatment, contact finding and treatment, and avoidance of unprotected sexual intercourse until both partners have completed treatment. Recommended antibiotics (Table 3) include ceftriaxone (250 mg IM single dose), cefixime (400 mg oral single dose) and spectinomycin (2 g IM single dose). Pregnant women should not be treated with quinolone or tetracycline antimicrobials. A microbiological test of cure is not routinely necessary. Pregnancy does not diminish treatment efficacy. There is no evidence base to support widespread unselected or selective community screening for gonorrhea in the USA[25] and UK[26].

Syphilis

This is caused by infection with *Treponema pallidum* and is an uncommon cause of pelvic infection *per se*, but in pregnancy the causative agent can cross the placenta to infect the fetus, thus resulting in congenital disease. Untreated babies can display physical deformities (saddle nose, frontal bossing, dental deformities, bowed legs), delays in development and seizures, along with many other problems. Of equal importance, maternal syphilis can also lead to serious adverse outcomes of pregnancy (80%) including spontaneous miscarriage, low birth weight babies, stillbirth and an increased risk of perinatal death[27].

Based on the recent increase in cases of infectious syphilis in the UK and USA, screening is recommended for all asymptomatic patients attending genitourinary clinics. Attendance at a pre-pregnancy clinic also provides an excellent screening opportunity. Furthermore, screening for syphilis should be offered to all pregnant women at an early stage in antenatal care because treatment of syphilis is beneficial to the mother and baby[9,11].

The diagnosis is based upon serological tests and direct detection of *Treponema pallidum* by dark ground microscopy in primary and secondary syphilis (Tables 1 and 2). *Treponema pallidum* enzyme immunoassays (EIA) that detect both IgG and IgM tend to be more sensitive in primary infection. The *Treponema pallidum* particle assay (TPPA) is recommended in preference to the *Treponema pallidum* hemagglutination assay (TPHA). TPHA can be used in combination with a cardiolipin antigen/reagin test, such as Venereal Disease Research Laboratory (VDRL) or rapid plasma regain (RPR), to maximize the detection of primary infection on screening[28].

The first line of treatment for infected individuals is benzathine penicillin G 2.4 MU intramuscularly. A single dose is adequate for early syphilis, whereas three weekly doses are recommended for late syphilis. In pregnancy, a single dose is optimum treatment in the first and second trimester, but two weekly doses are required in third trimester. Alternative treatment agents include azithromycin, ceftriaxone and doxycycline. Follow-up is essential to monitor cases of re-infection or relapse (Table 3). As is the case with most STIs, contact tracing and treatment is imperative not only for prevention of reinfection, but also for the health of the general population.

Bacterial vaginosis

The etiology of bacterial vaginosis is unknown. It commonly causes asymptomatic disease which can increase the risk of PID as well as adverse pregnancy outcomes including preterm rupture of membranes, preterm delivery and low birth weight babies[29]. It has been suggested that bacterial vaginosis is also linked to increased risk of acquisition of HIV, but further studies are required for accurate evaluation[30].

Diagnosis is based on the appearance of a Gram-stained smear according to the modified Ison-Hay scoring system. There is insufficient evidence regarding routine screening or treatment of asymptomatic pregnant and non-pregnant women to improve outcome. The recommended antibiotic for treatment in symptomatic bacterial vaginosis is oral metronidazole 400–500 mg twice daily for 5–7 days or 2 g single dose[31] (Table 3).

A past history of unexplained late miscarriage and/or preterm birth has been linked to bacterial vaginosis in early pregnancy[32], and hence may be considered as an indicator for screening in subsequent pregnancies[33].

Serological screening for hepatitis B virus and HIV infection should be offered to all pregnant women early in antenatal care because appropriate antenatal interventions can reduce mother-to-child transmission of infection[9,11]. This is discussed elsewhere in this book.

PRIOR ENDOMETRIOSIS

Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity, the presence of which induces a chronic inflammatory reaction[2]. Common locations for such tissue include the ovaries, uterosacral ligaments and posterior cul de sac peritoneum.

Although endometriosis is a chronic condition thought to be potentially present at least from the time of menarche, it also has been identified in the female embryo[34]. This latter finding is recent and, if verified, may be important to future research efforts to understand the etiology of the condition. At present, the most popular theory, that is, retrograde menstruation and implantation[35], originally proposed over a century ago by John Albertson Sampson, tends to be repeated in textbooks, albeit with very little evidence, as it fails to account for the presence of distal metastasis except for implantation at operative scar sites after cesarean section, a well described but rare complication of this mode of delivery. Another theory with growing popularity is that of tissue metaplasia[36], but this is yet to be confirmed.

Endometriosis is said to involve 5% of the female population[37], with higher incidence found at laparoscopy when investigating for causes of subfertility (25–40%)[38] or pelvic pain (45–50%)[39]. Except in severe forms where resultant adhesions cause tubal damage, the causal link with subfertility is not well defined. It is thought that endometrial deposits may secrete cytokines within the pelvic cavity that may be cytotoxic to sperm and/or the embryo immediately or shortly after fertilization. The possibility of subfertility is the main concern in a pre-pregnancy clinic. During pregnancy there are few issues, and rarely endometriosis may be associated with worsening of pain due to adhesion stretching. More commonly, pregnancy leads to an improvement of endometriosis associated pelvic pain[40], and pregnancy was advised as a therapeutic methodology in the era before modern treatment modes. Having said this, becoming pregnant should not be considered as a long-term treatment option, as the effects usually are short term and confined to the length of the associated amenorrhea[41].

Evidence to date suggests endometriosis to be a complex trait influenced by both genetic and environmental factors. It has long been considered that endometriosis carries a genetic predisposition in many families, but despite extensive research no specific genes have been identified. Encoding genes for detoxification

enzymes GST (glutathione-S-transferase) and NAT2 (N-acetyltransferase 2) are thought to be responsible, but further studies are required to confirm such an association[42]. Higher levels of dioxin, an exogenous toxin, have been detected in the blood of women with endometriosis[43]. The peritoneal environment promoted by hormones, growth factors and cytokines, along with existing damage to the peritoneal surface by trauma, infection or inflammation, can contribute to an increased risk of disease development. Factors thought to be protective against development of endometriosis include current use of combined oral contraceptive pills, smoking and exercise[44].

The gold standard of diagnosis is surgical inspection[2], at either laparoscopy or laparotomy. Endometriosis is characterized by a variety of appearances which range from superficial transparent sago grain lesions, red or black lesions to deep fibrotic lesions of the peritoneum. Endometriotic cysts of the ovaries, occurring in up to 20% of cases[45], can reliably be diagnosed by community based transvaginal ultrasonography[46]. Using this technique, the positive likelihood ratio ranges from 7.6 to 29.8 and the negative likelihood ratio ranges from 0.1 to 0.4, thus establishing sonography as a good diagnostic test to either confirm or exclude this condition. Endometriotic cysts are colloquially known as chocolate cysts due to their hemoglobin content.

More recently, in highly specialist tertiary clinics, it has been possible to identify peritoneal disease on transvaginal ultrasound[47], transrectal ultrasound[48] and magnetic resonance imaging[49]. These are, however, not widely available in the community and most hospital based practices.

Despite the variable macroscopic appearances of endometriosis, the common linking feature of these lesions is that all display histological features of endometrial glands and stroma.

Expectant management is the first line treatment, as the ability to manage the condition medically and/or surgically is fraught with limitations. In a study by Mahmood and Templeton[50], women with suspected endometriosis underwent a diagnostic laparoscopy and staging. A repeat laparoscopic assessment at a mean interval of 12 months revealed that 27% of women had disease regression, whilst the disease was static in 9%, and 64% had worsening of the disease severity as defined by the rAFS (revised American Fertility Society) score. Treatment is therefore based on current symptomatology and not disease identification or suspicion. Although it may be thought that early stage treatment will protect against future disease progression and thus reduce the risk of future sub- or infertility, no evidence substantiates this theory, as the disease progression rate is unknown (it would require repeated surgical observation assessment), and the limited available data clearly identify spontaneous disease regression. Interventional treatment is not without risks which can result in a reduction in fertility with a risk of peritonitis and adhesion formation[51].

Medical management of this estrogen dependent condition involves estrogen suppression and thus ovulation suppression. Benefits only last for the duration of therapy, are limited by the adverse side-effects of the drugs, and are short lived following cessation of therapy[52]. The main indication for medical therapy, therefore, is pain management rather than subfertility.

Laparoscopic surgical management by excision or ablation is currently considered optimal management with concurrent treatment for subfertility[2,53]. In the presence of severe deep nodular disease careful prior counseling is required, as treatment is not without associated morbidity that can in itself adversely affect and delay pregnancy. In these circumstances, surgical treatment should be carried out by specialist centers of excellence. In the UK currently the British Society for Gynaecological Endoscopy (BSGE) has set out to identify such units (www.bsge.org.uk). In cases of severe

disease with tubal occlusion treatment may be by IVF. However, many IVF specialists require removal of endometriomas of 4 cm or more in diameter prior to treatment to improve ovarian drug response and reduce the complication of peritonitis by inadvertent puncture of the cyst during egg collection[53].

There are no known problems that can affect the fetus once conceived, except the risk of future susceptibility of female offspring if a genetic link is believed, as discussed earlier.

Endometriosis support groups available worldwide (www.endometriosis.org) play a vital role in improving awareness about the disease process and its common sequelae, particularly in relation to future fertility.

PRIOR ECTOPIC PREGNANCY

Ectopic pregnancy is defined as implantation of a fertilized ovum anywhere other than the endometrial lining of the uterus. Extrauterine implantation occurs most commonly in the fallopian tube accounting for 98.3% of all ectopic locations. Tubal implantation can be in the ampular region (79.6% of tubal pregnancies), the isthmic region (12.3%), at the fimbrial end (6.2%) or rarely in the interstitial region (1.9%)[3]. The less common sites of ectopic pregnancy are ovarian, cervical, cesarean scar and intra-abdominal. Heterotopic pregnancy, when an intrauterine and an extrauterine pregnancy occur simultaneously, is a rare condition with an incidence in spontaneous conception cycles of 1:30,000. However, this incidence has been slowly rising in recent years with the advent of assisted reproduction techniques and could range from 1:500 to 1:100 in IVF pregnancies[54].

There is a global rise in the incidence of ectopic pregnancy which is mainly attributed to the increasing incidence of PID[55]. In the UK around 11,000 cases are diagnosed per year (incidence 11.5 per 1000 maternities)[56], while in the USA 108,800 cases (incidence 19.7 per 1000 maternities) are reported annually. In Northern Europe the incidence of ectopic pregnancy is 18.8 per 1000 maternities[55]. In the last triennium (2003–05)[4] in the UK, 14 reported maternal deaths resulted from early pregnancy complications; ruptured ectopic pregnancies and subsequent hemorrhage accounted for ten of these deaths. In the USA ectopic pregnancy accounts for 9% of all pregnancy related deaths each year[55]. This outlines the serious implications of the condition.

Women with a prior ectopic pregnancy or those who are aware of its potential risk, possibly directed by the presence of predisposing risk factors[3] (Table 4), should be alert to its possibility in a future pregnancy and require both counseling and support at any preconception visit.

Classically, ectopic pregnancy presents with a triad of associated symptoms: (1) amenorrhea of 6 weeks, (2) abdominal pain (69.3%) and (3) vaginal bleeding (45.3%)[57]. However,

Table 4 Risk factors for occurrence of an ectopic pregnancy[3]

High risk
Tubal surgery
Sterilization
Previous ectopic pregnancy
In utero DES exposure
Intrauterine device use
Documented tubal pathology
Moderate risk
Infertility
Previous genital infections
Multiple sexual partners
Low risk
Previous pelvic or abdominal surgery
Cigarette smoking
Vaginal douching
Early age of intercourse (<18 years)

DES, diethylstilbestrol

diagnosis can be difficult, as clinical presentation is exceedingly variable, and some women (as many as one-third) are completely asymptomatic with absent risk factors. Hence the only way of ensuring that this potentially lethal diagnosis is never missed is that the clinician should always be aware of the probability and act to exclude the possibility, if there is any suspicion.

Early diagnosis is important to minimize morbidity, allow for different treatment options and maximize scope for future fertility. For these reasons, there exists a valid argument for offering ectopic pregnancy screening to women with known risk factors as soon as conception is confirmed with a positive urine pregnancy test. In view of the unpredictability and significant implications of the condition, it may even be considered that there could be a role for screening the entire pregnant population. In many ways awareness is one of the main objectives of early pregnancy assessment units in the form of secondary screening. However, although routine screening for ectopic pregnancy in the high risk population is not cost effective[58], it is undeniably good practice to offer women with a prior ectopic pregnancy an early pregnancy scan to confirm the location of the gestational sac. *It is axiomatic that ultrasonic findings of an empty uterus in a woman with a positive pregnancy test and clinical signs that might even remotely indicate ectopic pregnancy, receive follow-up by care-givers with sufficient understanding of the potential gravity of the situation to all concerned*. Moreover, the clinician has a duty to inform the woman attending the pre-pregnancy clinic of his/her concerns and the availability (or lack) of such resources locally, so that there is no unnecessary delay when the woman discovers she is pregnant.

Women with a family history of ectopic pregnancy may express concern regarding the chance of their having an ectopic pregnancy. They can be assured that there is no genetic predisposition to occurrence of ectopic pregnancy[59], but should be assessed individually to ascertain the presence of personal risk factors.

The diagnosis of ectopic pregnancy using ultrasonography is often by exclusion with the identification of an intrauterine pregnancy. This can usually be achieved as early as 4 weeks and 3 days of gestation by transvaginal ultrasonography (Figure 3) and a week later by transabdominal ultrasonography. Direct identification of the ectopic pregnancy by ultrasonography has an overall sensitivity of more than 90%[60] (Figure 4); in good units this is now considered the norm.

If the identification of an intrauterine sac is uncertain, the woman should be offered a serial transvaginal ultrasound assessment in 2–3 days, ideally by the same ultrasonographer. At this time the images should become more conclusive with the development of an intrauterine well defined hypoechoic cystic structure within one endometrial leaflet rather than the midline. It should also be spherical in outline and in one-third of cases may have a hyperechoic trophoblastic ring (Figure 3).

In women where a pregnancy cannot be identified, a diagnostic laparoscopy may be proposed if they are clinically compromised. Fortunately, the majority of such women, defined by Banerjee *et al.*[61] as women with

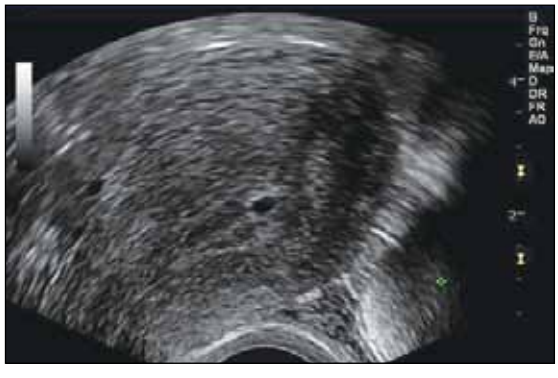

Figure 3 Transvaginal image of the sagittal section through an anteverted uterus along the midline. The hypoechoic cyst seen at the center of the endometrial cavity is consistent with an intrauterine pregnancy of 4–5 weeks' gestation

'pregnancies of unknown location', are clinically stable with minimal symptoms. In such women, serum hormone level estimation of human chorionic gonadotropin (hCG) and progesterone is a useful tool to identify and monitor for spontaneous resolution of the pregnancy, thus allowing attention to focus on those women with a potentially problematic diagnosis of ectopic pregnancy. Subsequent follow-up should be logical and individualized. The authors' current practice is to follow the protocol described in Table 5, which aims to reach a conclusive diagnosis in the safest possible way with minimum number of hospital visits.

If ectopic pregnancy is identified in a woman who is clinically stable and presenting initially for pre-pregnancy counseling, the therapeutic options include expectant, medical and surgical management.

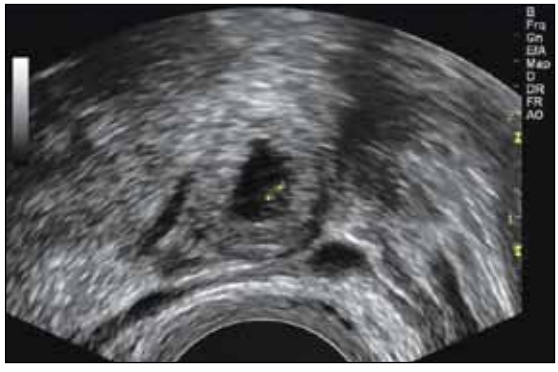

Figure 4 Transvaginal ultrasound image of an ectopic pregnancy

Expectant management has the obvious benefit of avoiding the risks associated with surgery. The success rate for spontaneous resolution varies between 25% and 88%, depending on the initial serum hCG level[62]. The subsequent intrauterine pregnancy rate following expectant management is 89%, whereas the risk of a recurrent ectopic pregnancy is 5%[56]. It is the authors' current practice to consider expectant management with initial serial hCG assays 48 hours apart and then at weekly intervals until serum levels are less than 20 IU/l[63] in women with a pregnancy that is not considered viable on ultrasound (absence of embryonic heart action or features not comparable to menstrual dates). As a predictor of success, one would expect a drop in serial hCG levels of greater than 66% within the first 48 hours and then more than 50% within 7 days, ideally with an initial hCG of less than 1000–1500 IU/l[56]. In a district general hospital setting, approximately 60% of ectopic pregnancies are successfully managed conservatively with no significant morbidity[64].

A reasonable alternative in clinically stable women with an initial hCG of less than 3000 IU/l is medical management. In the western world, this is increasingly becoming

Table 5 Protocol for management of 'pregnancy of unknown location' as defined by the absence of an intrauterine or extrauterine pregnancy on transvaginal ultrasound examination

Progesterone (nmol/l)	*hCG* (IU/l)	*Likely diagnosis*	*Management*
<20	>25	Resolving pregnancy	Repeat urine pregnancy test or serum hCG in 7 days
20–60	>25	Ectopic pregnancy or miscarriage requiring intervention	Repeat serum hCG in 2 days
>60	<1000	Normal intrauterine pregnancy	Repeat scan when hCG expected >1000 IU/l
>60	>1000	Ectopic pregnancy	Repeat scan same day by a senior examiner ± laparoscopy

hCG, human chorionic gonadotropin

an attractive treatment option and has been found to be cost-effective[65].

Medical management of ectopic pregnancy comprises a single dose methotrexate injection (systemic or local) at a dose of 50 mg/m^2. A small group of these women (14%) may require more than one dose of methotrexate, while around 10% will fail treatment, needing subsequent surgical intervention[56]. The success rate (defined as not requiring surgery) varies between 74% and 97% depending on the initial level of serum hCG rather than the size of the ectopic pregnancy[66]. After methotrexate therapy, 62–70% of women have a subsequent intrauterine pregnancy and 8% have recurrent ectopic pregnancy[62]. These values are almost identical to those obtained for expectant management.

In order to offer either non-surgical option, it is essential that the woman fully understands the risks discussed, particularly that of pregnancy rupture leading to hematoperitoneum and the need for emergency surgery. It is essential when offering such treatment regimens that there be appropriate local protocols with a 24/7/365 immediate access for medical reappraisal, should the clinical situation alter. If this is not possible or there is even a doubt about patient compliance, a surgical approach should be adopted as the first line treatment option.

Surgical management of ectopic pregnancy is still widely considered the first line of management in most countries worldwide. Surgery involves laparoscopy or laparotomy (if hemodynamically unstable) to perform either a salpingectomy (Figure 5) or salpingotomy (Figure 6). A meta-analysis of four cohort studies[63] suggested that there might be a higher subsequent intrauterine pregnancy rate associated with salpingotomy (Table 6), but the magnitude of benefit is small. This would need to be taken into consideration with the woman's desire for future fertility, the state of the unaffected contralateral fallopian tube, the additional morbidity associated with salpingotomy (small risk of tubal bleeding in the initial postoperative period), the potential need for further monitoring, and any treatment for persistent trophoblast (10%) as well as a risk of repeat ectopic pregnancy in future. Also under consideration would be the woman's wishes and availability of IVF services. After partial or total salpingectomy the rate of recurrent ectopic pregnancy is 7–10% as compared to 15% after salpingotomy[62].

The results of these studies have prompted the recommendation by the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK[63] to consider laparoscopic salpingotomy as the primary treatment when managing a tubal ectopic pregnancy in the presence of contralateral tubal disease, whilst the evidence is not so clear when the contralateral tube is

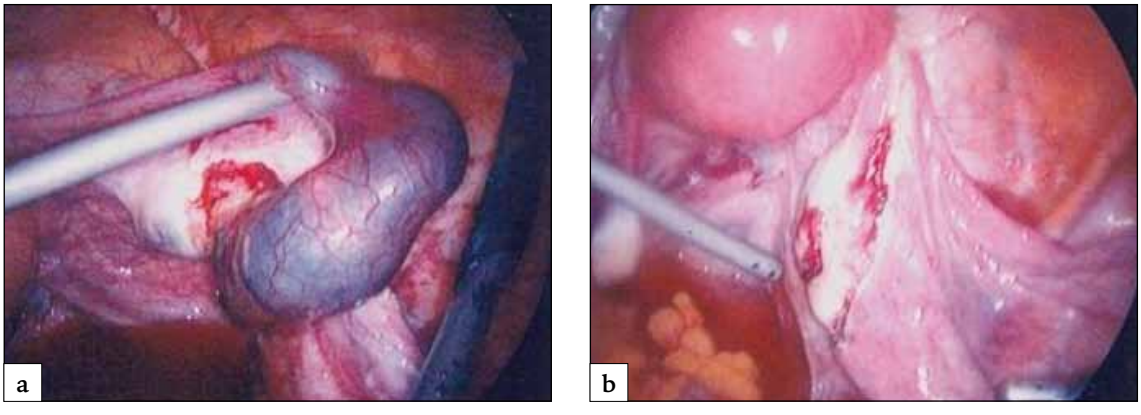

Figure 5 Laparoscopic salpingectomy ((a) before and (b) after)

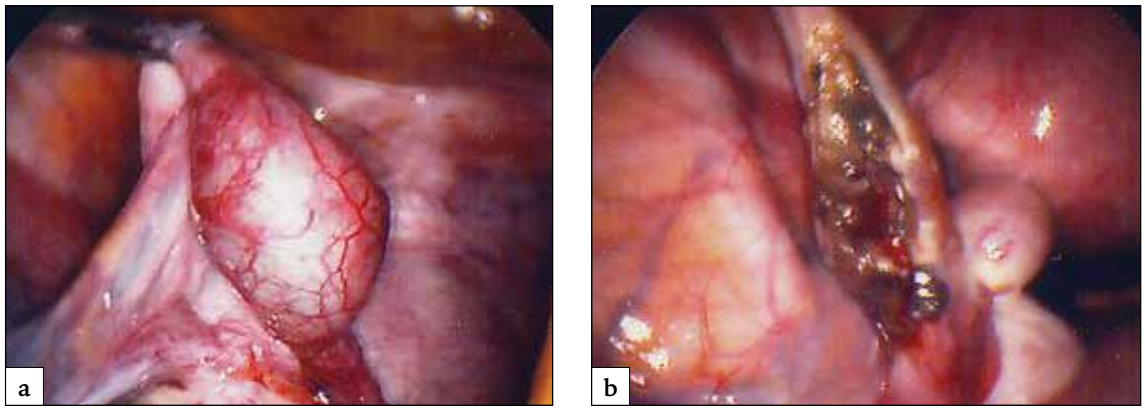

Figure 6 Laparoscopic salpingotomy ((a) before and (b) after)

Table 6 Intrauterine pregnancy rates following surgical treatment of tubal ectopic pregnancy[63]

	Salpingectomy (%)	*Salpingotomy* (%)
Silva *et al*.	54	60
Job-Spira *et al*.	56.3	72.4
Mol *et al*.	38	62
Bangsgaard *et al*.	66	89

healthy and future pregnancy is desired. In the latter circumstance the current accepted practice is towards that of salpingectomy.

Laparoscopy is superior to laparotomy irrespective of the type of tubal surgery, resulting in a higher rate of intrauterine pregnancy (77% versus 66%) and a lower rate of recurrent ectopic pregnancy (7% versus 17%). The cumulative pregnancy rate is also influenced by a history of infertility with an overall conception rate of 77% for all methods of treatment and a recurrence rate of 10%[62].

Age of the woman and prior history of infertility rather than a prior history of ectopic pregnancy should be the determining factor for considering IVF. Referral to an assisted conception unit may be considered in women with a history of recurrent ectopic pregnancies because of the concern of tubal subfertility. Screening for evidence of tubal patency may be performed either radiologically or at laparoscopy. However, patients should be made aware that with IVF there is an increased risk of recurrence of ectopic pregnancy and heterotopic pregnancy and that ovulation induction techniques can also lead to an increased risk of ectopic pregnancy (2.2% from IVF and 1.9% from intracytoplasmic sperm injection)[67]. Prophylactic salpingectomy after salpingotomy could be considered if there is evidence of hydrosalpinx in the affected fallopian tube, as it has been shown to increase the cumulative success rate of IVF[68].

In heterotopic pregnancies, the tubal ectopic is usually managed by salpingectomy as it is impossible to monitor for persistent tubal trophoblast implants with a simultaneous ongoing intrauterine pregnancy. The management of non-tubal ectopic pregnancies is outside the scope of this chapter.

Finally, all non-sensitized women who are rhesus negative with a confirmed or suspected ectopic pregnancy should receive anti-D immunoglobulin if managed medically or

surgically[63]. Furthermore, a previous ectopic pregnancy does not increase the risk of miscarriage (23%)[69] or any other adverse outcome in subsequent intrauterine pregnancies. Women who have had an ectopic pregnancy in the past or are concerned owing to the presence of risk factors may be aided further by the assistance and support of self-help groups (www.miscarriageassociation.org.uk).

SUMMARY

Women who present for pre-pregnancy counseling with a previous history or risk factors for pelvic infection, endometriosis or ectopic pregnancy require careful assessment as to the significance of the problem and its effects on the health of the woman both outside and during a future pregnancy, as well as the health of the potential future progeny. This is crucial even if only to reassure the woman that she is not at significant risk of serious problems. Pre-pregnancy assessment and correct advice will often avoid, if not limit, the potential complications that could arise as a result of these conditions.

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