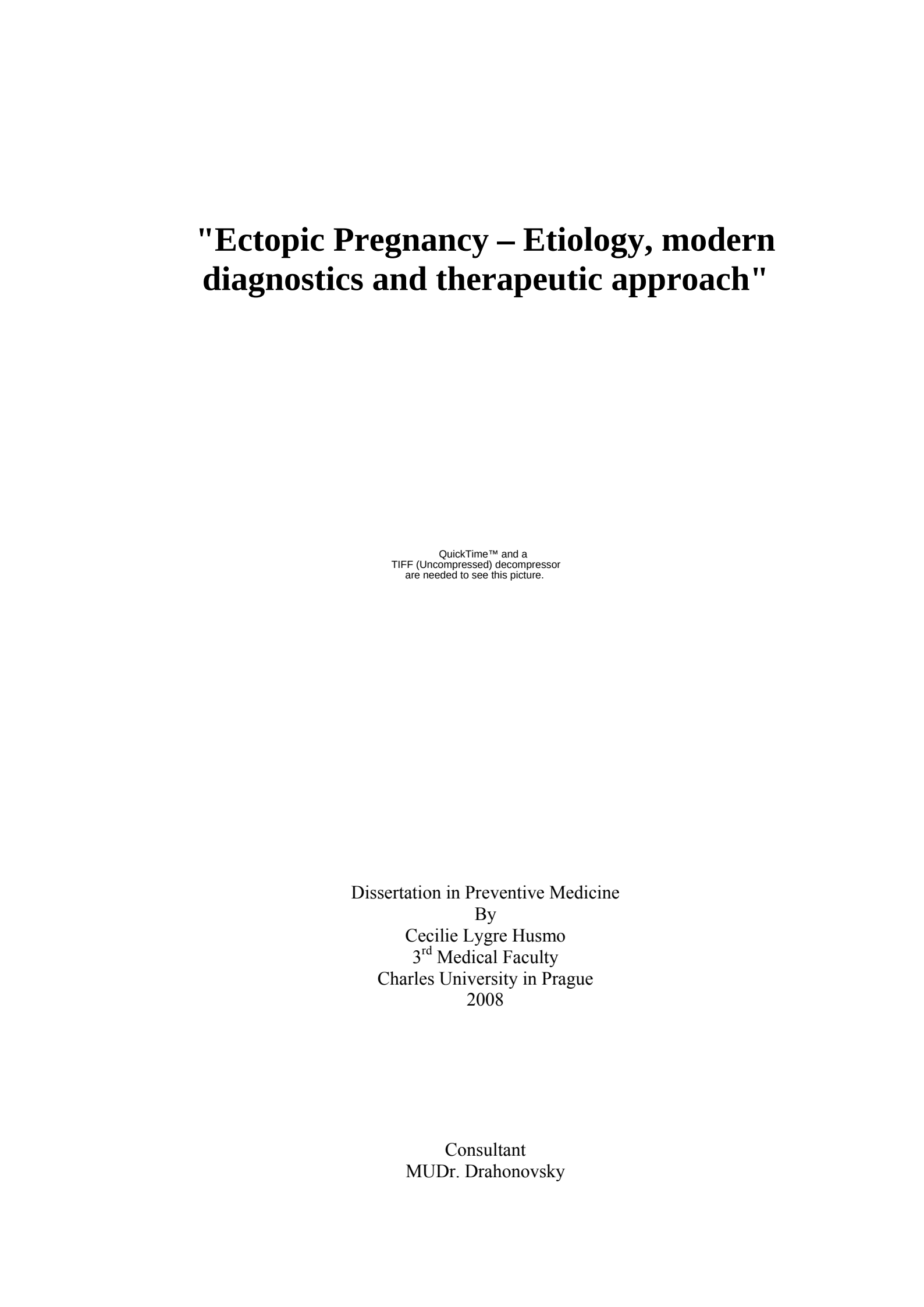
"Ectopic Pregnancy – Etiology, modern diagnostics and therapeutic approach"



Dissertation in Preventive Medicine

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Contents

ABSTRACT

Ectopic pregnancy causes major maternal morbidity and mortality, with pregnancy loss, and its incidence is increasing worldwide. It is still the most common cause of maternal deaths in the first trimester. An ectopic pregnancy in the fallopian tube, if not treated, can cause tubal rupture and/or intra abdominal bleeding. Treatment options for tubal ectopic pregnancy are surgery, medical treatment, and expectant management. Most fatal cases result from delayed diagnosis and inappropriate investigation and treatment despite the management of women with suspected ectopic pregnancy improving considerably because of improved tools for diagnosis and management. Prompt diagnosis and treatment thus is a very important measure to prevent the potential life-threatening complications of ectopic pregnancies.

INTRODUCTION

Ectopic pregnancy is defined as a pregnancy that occurs outside the uterine cavity[2]. Approximately 1% of fertilized eggs implant outside the uterine cavity and develop into extra uterine pregnancies known as ectopic pregnancies. Ectopic pregnancies can occur anywhere along the reproductive tract with the most common site being the fallopian tube. The ectopic pregnancies can be classified by location Table 1 and Figure 1.

Table 1 - Location and Incidence of Ectopic Pregnancies[2].

Location	Incidence
Fallopian tube	97%
Ampulla	55%
Isthmus	25%
Fimbria	15%
Ovary	3%
Cervix	3%
Interstitial	3%
Intra-abdominal	3%

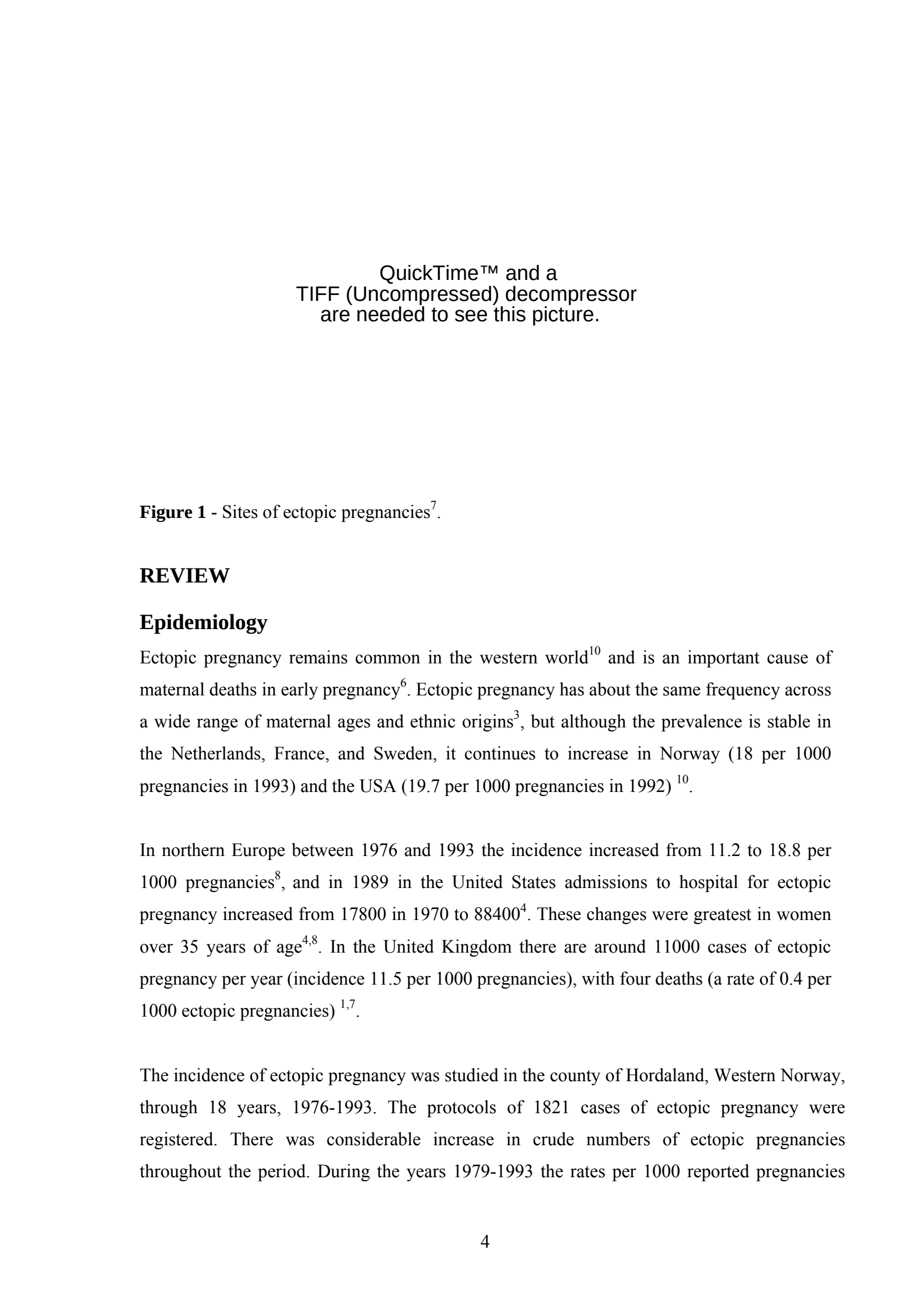

Figure 1 - Sites of ectopic pregnancies[7].

REVIEW

Epidemiology

Ectopic pregnancy remains common in the western world[10] and is an important cause of maternal deaths in early pregnancy[6]. Ectopic pregnancy has about the same frequency across a wide range of maternal ages and ethnic origins[3], but although the prevalence is stable in the Netherlands, France, and Sweden, it continues to increase in Norway (18 per 1000 pregnancies in 1993) and the USA (19.7 per 1000 pregnancies in 1992) [10].

In northern Europe between 1976 and 1993 the incidence increased from 11.2 to 18.8 per 1000 pregnancies[8], and in 1989 in the United States admissions to hospital for ectopic pregnancy increased from 17800 in 1970 to 88400[4]. These changes were greatest in women over 35 years of age[4,8]. In the United Kingdom there are around 11000 cases of ectopic pregnancy per year (incidence 11.5 per 1000 pregnancies), with four deaths (a rate of 0.4 per 1000 ectopic pregnancies) [1,7].

The incidence of ectopic pregnancy was studied in the county of Hordaland, Western Norway, through 18 years, 1976-1993. The protocols of 1821 cases of ectopic pregnancy were registered. There was considerable increase in crude numbers of ectopic pregnancies throughout the period. During the years 1979-1993 the rates per 1000 reported pregnancies

increased by 25%, from 9.4 to 11.8 in age groups below 30 years, while the rates for women over 35 years increased by 98%, from 20.7 to 40.9. The rates of ectopic pregnancy increased in age groups older than 20 years during 1976-93, moderately in younger age groups, but considerably in older age groups, who also contributed with higher total rates of pregnancy. More older women, with presumably accumulated risk factors getting pregnant, thus explain part of the increased rates of this disease[8].

In the United States, the reported number of hospitalizations for ectopic pregnancy increased from 17,800 in 1970 to 88,400 in 1989[9]. In the United Kingdom nine deaths were registered in 1991-3 and 12 in 1994-6. This raises the death rate from 0.3 to 0.4 per 1000 estimated ectopic pregnancies[6].

Pathogenesis and Risk factors

Ectopic pregnancy commonly occurs in women with impaired tubal function. The most important risk factors, identified in two recent meta-analyses[56,57], are shown in Table 2. Surgically visualised tubal pathology, commonly the result of pelvic infection, endometriosis, or previous surgery is the strongest risk factor. Pelvic infections, including gonorrhoea, serologically confirmed Chlamydia infection, and pelvic inflammatory disease are, surprisingly, less significant[56,58]. Tubal ligation effectively prevents pregnancy. If pregnancy does occur, however, an ectopic location should be strongly suspected. The risk is increased in women who have had ectopic pregnancy previously, and increases further in proportion to the number of previous ectopic pregnancies. Risk of recurrence decreases with subsequent intrauterine pregnancies after the initial ectopic pregnancy[10]. Women exposed to diethylstilboestrol in utero, with absent or minimal fimbriae, a small os, and fallopian tubes that are shorter and thinner than normal[10], are at higher risk of ectopic pregnancy. Use of intrauterine devices (IUDs) increases risk. If pregnancy occurs, there is a strong probability that it will be ectopic. Several other factors have a moderate influence on risk. Infertility puts women at increased risk[56], particularly for pregnancies that occur during infertility treatment. Among women undergoing in-vitro fertilisation, 4–5% of resultant pregnancies are ectopic, a rate 2–3% higher than that in the general population[59,60]. Multiple sexual partners, early age at first sexual intercourse, cigarette smoking, and vaginal douching increase risk of ectopic pregnancy occurring[56].

Table 2: Risk factors for ectopic pregnancy[10]

Risk factor	Odds ratio*
High risk	
Tubal surgery	21.0
Sterilisation	9.3
Previous ectopic pregnancy	8.3
In-utero exposure to diethylstilboestrol	5.6
Use of IUD	4.2–45.0
Documented tubal pathology	3.8–21.0
Moderate risk	
Infertility	2.5–21.0
Previous genital infections	2.5–3.7
Multiple sexual partners	2.1
Slight risk	
Previous pelvic/abdominal surgery	0.9–3.8
Cigarette smoking	2.3–2.5
Vaginal douching	1.1–3.1
Early age at first intercourse (<18 years)	1.6

*Single values=common odds ratio from homogeneous studies; point estimates=range of values from heterogeneous studies.

Although a proportion of women with ectopic pregnancy have no identifiable causal factors, the risk is increased by several factors: previous ectopic pregnancy, tubal damage from infection or surgery, a history of infertility, treatment for in vitro fertilisation, increased age and smoking[7]. A history of pelvic inflammatory disease has in some studies been found to be particularly important[35,36] and has been implicated in the increased incidence of ectopic pregnancy[36]. After acute salpingitis, the risk of an ectopic pregnancy is increased sevenfold[36]. This is particularly true of *Chlamydia trachomatis,* the main cause of pelvic inflammatory disease in the United Kingdom[37]. Comprehensive programmes to prevent chlamydia not only decrease the incidence of *Chl. trachomatis* infections but also the rate of ectopic pregnancies[38,39].

Previous female sterilization[40] and current use of an intrauterine contraceptive device[41] are only risk factors when patients with ectopic pregnancy are compared with pregnant controls and not with non-pregnant women. This is because overall the risk of pregnancy in these situations is low, but if pregnancy does occur an ectopic pregnancy is more likely. The risk of ectopic pregnancy after sterilisation is only 7.3 per 1000 within 10 years[40].

The incidence of ectopic pregnancy after assisted reproductive techniques is 4%, which is 2-3 times greater than the background incidence. The main risk factor in this group is tubal infertility. The incidence of heterotopic pregnancy (an ectopic pregnancy together with an intrauterine pregnancy) is also increased after assisted reproductive techniques[7].

However, it is important to keep in mind that many patients have no documented risk factors and no physical indications of ectopic pregnancy[3].

Symptoms, signs and presentation

The classic clinical triad seen in ectopic pregnancy is pain, abnormal vaginal bleeding, and a palpable adnexal mass. However, this is seen in only 45% of patients with ectopic pregnancy[2]. Abdominal pain with amenorrhoea is the most common presenting complaint in ectopic pregnancy[62,63]. Ectopic pregnancies usually present after seven (SD two) weeks of amenorrhoea[7]. Pain radiating to the shoulder, syncope, and shock occur in up to 20% of patients; abdominal tenderness in more than 75%; cervical motion tenderness up to 67%; and a palpable adnexal mass in about 50%[62-64].

Vaginal bleeding is the most common cause of presentation to the emergency department in the first trimester. Approximately half of patients with first trimester vaginal bleeding will lose the pregnancy. Clinical assessment is difficult, and sonography is necessary to determine if a normal fetus is present and alive and to exclude other causes of bleeding (eg. Ectopic or molar pregnancy). The main differential considerations of first trimester bleeding are spontaneous abortion, ectopic pregnancy or gestational trophoblastic disease. Approximately half of patients who present with vaginal bleeding have a spontaneous abortion. However, the most common cause of bleeding is spotting caused by implantation of the conceptus into the endometrium. A complete assessment of the first trimester pregnancy requires correlation of serum β-hCG levels with the appearance of the gestational sac using sonography[2].

The abdominal pain is usually lateral. However, history and physical examination alone do not reliably diagnose or exclude ectopic pregnancy, as up to 9% of women report no pain and 36% lack adnexal tenderness. The presence of known risk factors can increase suspicion, but any sexually active woman presenting with abdominal pain and vaginal

bleeding after an interval of amenorrhoea has an ectopic pregnancy until proved otherwise. Women who present in a collapsed state usually have had prodromal symptoms that have been overlooked. Tubal rupture is rarely sudden since it is due to invasion by the trophoblast. Therefore, if there is any suspicion, hospital referral for investigation is mandatory[7]. The diagnosis can be difficult unless the condition is suspected and can be confused with miscarriage, an ovarian accident, or pelvic inflammatory disease[7].

DIAGNOSIS

Early diagnosis is important to prevent potentially life-threatening complications. It can be made before the 7th week of pregnancy (ie, about 4-5 weeks after conception). Serial measurements of serum human chorionic gonadotrophin (β-hCG), pelvic ultrasonography, measurements of serum progesterone, and uterine curettage have been combined into various diagnostic algorithms[65-67]. Some investigators, who find progesterone measurements redundant and prefer to avoid uterine curettage, have developed algorithms based on only transvaginal ultrasonography and serial β-hCG measurements. These diagnostic algorithms have made confirmatory visualisation by laparoscopy unnecessary[66,67]. Exceptionally, with the possibility of heterotopic pregnancy, particularly after in-vitro fertilisation, laparoscopic visualisation and treatment may be warranted[10].

Historical perspective

The first step forward in the diagnostic management of ectopic pregnancy was the introduction of laparoscopy in the late 1960s. This procedure solved the dilemma of prolonged clinical observation and the risk of performing an unnecessary laparotomy in suspected cases. Laparoscopy remained the only reliable method for diagnosing and excluding ectopic pregnancy until well into the 1980s. Around this time, several non-invasive diagnostic tools were developed. More sensitive and specific pregnancy tests became available, which reduced the need to rule out ectopic pregnancy in women with a negative result on a pregnancy test[6]. In addition, rapid methods for measuring serum concentrations of human chorionic gonadotrophin (β-hCG) were introduced. On the basis of these developments, Kadar et al were the first to recognise the importance of combining ultrasound with serum human chorionic gonadotrophin measurements. They introduced the discriminatory serum human chorionic gonadotrophin zone in 1980. According to this

concept, a diagnosis of ectopic pregnancy is most likely whenever intrauterine pregnancy is not detected by ultrasound at serum β-hCG concentrations above the threshold of 6500IU/l[6].

Unfortunately, the clinical usefulness of this combination was hampered by many patients with ectopic pregnancies having β-hCG well below 6500 IU/l. However, the introduction of transvaginal sonography changed this. Its superior resolution allowed much smaller intrauterine and ectopic pregnancies to be detected immediately. This brought the optimal serum β-hCG cut-off value down to between 1000 and 2000 IU/l for those patients with inconclusive sonographic findings[6].

Modern diagnostics

Ectopic pregnancy as a potentially life-threatening gynecologic emergency that requires urgent intervention. In all sexually active women of reproductive age who present with lower abdominal pain, with or without vaginal bleeding, an ectopic pregnancy must be excluded[1].

Ectopic pregnancy is usually diagnosed in the first trimester of pregnancy. The most common gestational age at diagnosis is 6 to 10 weeks. Documentation of risk factors (Table 1) is an essential part of history-taking, and asymptomatic clinic patients with risk factors may benefit from routine early imaging. However, more than half of identified ectopic pregnancies are in women without known risk factors. The physical findings depend on whether tubal rupture has occurred. Women with intraperitoneal hemorrhage present with significant abdominal pain and tenderness, along with various degrees of hemodynamic instability. However, women without rupture may also present with pelvic pain or vaginal bleeding, or both[3].

Referral should preferably be to a unit dedicated to managing problems early in pregnancy as this allows ease of investigations and continuity of outpatient care. The initial investigations are a sensitive pregnancy test and ultrasonography. The presence of an intrauterine pregnancy generally excludes ectopic pregnancy, although other ultrasound findings have to be considered, especially if symptoms are atypical, severe, or persistent. The use of quantitative measurement of serum concentrations of β-human chorionic gonadotrophin together with transvaginal ultrasonography has improved the diagnosis.

There is, however, controversy about the concentration of serum human chorionic gonadotrophin that is diagnostic. In the presence of an ectopic mass or fluid in the pouch of Douglas, a cut off point for a serum concentration of human chorionic gonadotrophin of 1500 IU/l is recommended, but in the absence of any ultrasound signs the higher concentration of 2000 IU/l should be the cut off point before an ectopic pregnancy is diagnosed[42]. Ectopic pregnancies produce lower concentrations of β-hCG than normal pregnancies, but the change in concentrations provides more information[43]. In a normal pregnancy, serum concentrations of β-hCG double every 2-3.5 days in the fourth to eighth week of gestation reaching a peak around the eighth to 12th week, as calculated from the last menstrual period (Figure 2)[44]. A failure of this increase is suggestive of an ectopic pregnancy although it is also associated with early pregnancy failure. A two day sampling interval has been recommended if paired serum samples are being tested[43]. The accurate diagnosis of ectopic pregnancy can be life saving, reduce invasive investigations, and allow conservative treatment[7].

Use of β̃-human chorionic gonadotropin measurement

It is important to confirm pregnancy. In the emergency department, pregnancy is diagnosed by determining the urine or serum concentration of human chorionic gonadotrophin (β-hCG). This hormone is detectable in urine and blood as early as 1 week before an expected menstrual period. Serum testing detects levels as low as 5 IU/L, whereas urine testing detects levels as low as 20–50 IU/L. In most cases, screening is done with a urine test, since obtaining the results of a serum test is time-consuming and is not always possible in the evening and at night. However, if pregnancy is strongly suspected, even when the urine test has a negative result, serum testing will be definitive[3].

ELISA routinely detects serum β-HCG concentrations as low as 1.0 IU/L. In normal pregnancy, β-HCG concentrations double roughly every 2 days[68]. Abnormal pregnancies, intrauterine or ectopic, have impaired β-HCG production with longer doubling times; thus, serial measurements aid assessment of pregnancy viability. Serial measurements can also signal the optimum time for diagnostic transvaginal ultrasonography; intrauterine gestations can be imaged reliably when concentrations are above 1500 IU/L[69]. Absence of an intrauterine gestation with β-hCG concentrations above this cut-off is diagnostic of an ectopic pregnancy[67]. Serial measurements can also be used to document effectiveness of

diagnostic curettage; a failure to decline by 15% is diagnostic of an ectopic pregnancy[68].

A qualitative urine dipstick test for β-hCG (urinary pregnancy test) must be carried out. This is a quick, easy, and sensitive test. It has a sensitivity of 99% at a urine β-hCG level greater than 25 IU/L. If a woman has a negative urinary pregnancy test, this almost invariably means that she does not have an ectopic pregnancy. However, if it is positive, the woman should have an USS[1].

A single serum measurement of the β-hCG concentration, however, cannot identify the location of the gestational sac[3]. Serial β-hCG measurement is often used for women with first-trimester bleeding or pain, or both, but, as with a single measurement, serial measurement cannot confirm the location of the gestational sac. In a normal pregnancy, the first-trimester β-hCG concentration rapidly increases, doubling about every 2 days (Figure 2). An increase over 48 hours of at least 66% has been used as a cutoff point for viability. Ectopic pregnancy may present with rising, falling or plateau β-hCG levels; thus, serial measurement is most useful to confirm fetal viability rather than to identify ectopic pregnancy. In a patient with a subnormal increase in β-hCG concentration, nonviability is assumed, and more invasive investigations can be used to clarify the nature of the abnormality (i.e., miscarriage vs. ectopic pregnancy)[3].

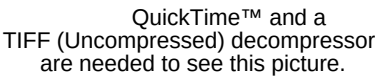

Figure 2

Mean (SE) serum concentrations of human chorionic gonadotrophin (β-hCG) in normal pregnancy (adapted from Braunstein et al 1996[44])[7].

A recent study identified patients with only a 53% increase in serum β-hCG levels over 2 days who had a viable intrauterine pregnancy[76]. Thus, demonstration of normal doubling of serum levels over 48 hours supports a diagnosis of fetal viability but does not rule out ectopic pregnancy, and a rising β-hCG concentration that fails to reach 50% suggests a failing or ectopic pregnancy, as does a plateau. Falling levels confirm nonviability but do not rule out ectopic pregnancy[3].

Use of serum progesterone measurement

Measurement of the serum concentration of progesterone has been investigated as a potentially useful adjunct to serum β-hCG measurement, since progesterone levels are stable and independent of gestational age in the first trimester[3]. A meta-analysis, published in 1998, of studies assessing a single progesterone level demonstrated good capacity of low levels (<5 ng/mL) to correctly diagnose pregnancy failure, but this cutoff was unable to discriminate between ectopic pregnancy and intrauterine pregnancy[14]. Both high (>22 ng/mL) and low (<5 ng/mL) cutoff points have since been studied for their ability to correctly identify nonviable pregnancy and ectopic pregnancy[11,15]. Rapid progesterone analysis can identify 2 important sub-groups of patients in the emergency department with symptomatic first-trimester bleeding or pain, or both: stable patients with progesterone levels above 22 ng/mL, who have a high (but not certain) likelihood of viable intrauterine pregnancy; and patients with levels of 5 ng/mL or less, who almost certainly have a nonviable pregnancy. Invasive diagnostic testing (e.g., D&C) could be postponed in the former patients but offered to the latter, as could treatment with methotrexate, without fear of interrupting a potentially viable intrauterine pregnancy[3].

Progesterone measurements are useful as a single-time screening device. Measurement of serum progesterone is not useful in patients already identified as being at high risk of ectopic pregnancy. The assay takes only 2–3 hours, so it quickly identifies patients in need of comprehensive investigation. A single measurement can exclude ectopic pregnancy with 97.5% sensitivity for concentrations of 79.5 nmol/L (25 ng/mL) or higher[10].

Ultrasound imaging

A woman with a positive β-hCG test should have a sonographic scan. In addition to having a transabdominal ultrasound scan, a symptomatic woman with a positive urinary pregnancy test should also have a transvaginal ultrasound scan performed[1]. Transvaginal ultrasonography has transformed the assessment of women with problematic early pregnancy, allowing earlier, clearer visualization of both normally developing embryos and abnormalities[3].

The spectrum of sonographic findings in ectopic pregnancy is broad. Identification of an extrauterine gestational sac containing a yolk sac (with or without an embryo) confirms the diagnosis. A normal gestational sac, an ovoid collection of fluid adjacent to the endometrial stripe, can be visualized by means of the transvaginal probe at a gestational age of about 5 weeks. It can often be seen when 2 or 3 mm in diameter and should be consistently seen at 5 mm. Suggestive findings include an empty uterus, cystic or solid adnexal or tubal masses (including the tubal-ring sign, representing a tubal gestational sac), hematosalpinx and echogenic or sonolucent cul-de-sac fluid[3]. The detection of any non-cystic extraovarian adnexal mass, living ectopic pregnancy, tubal rings, or complex cystic or solid masses is highly specific for ectopic pregnancy (98.9%), with a high positive predictive value (96.3%), sensitivity of 84.4%, and negative predictive value of 94.8% [3].

Since the hormonal environment in ectopic pregnancy can produce an intrauterine fluid collection that mimics a gestational sac, a sac alone cannot confirm intrauterine pregnancy[16]. As the embryo matures, more sonographic signs become visible. Once the sac is implanted within the endometrium, its position relative to the endometrial wall changes, producing the intradecidual-sac sign and then the double decidual-sac sign[3].

The most definitive sonographic finding is the visualization of an extrauterine gestational sac with a yolk sac or an embryo. Nonvisualization of an intrauterine or extrauterine gestational sac in a patient with a positive pregnancy test may be due to an early intrauterine gestation or an early ectopic gestation. Correlation with serum quantitative β-hCG is important[2]. The presence of an extra ovarian adnexal mass is the most common sonographic finding in ectopic pregnancy, because the fallopian tube us the most common location for an

ectopic pregnancy. This adnexal mass may represent a dilated fallopian tube with a gestational sac and may or may not be associated with a hematosalpinx[2].

A β-hCG level that has risen above the discriminatory threshold in the absence of sonographic signs of early pregnancy is considered presumptive evidence of an ectopic pregnancy. With the evolution in ultrasound technology, the discriminatory threshold has dropped from 6500IU/L with a transabdominal approach to between 1000 and 2000IU/L with transvaginal imaging[17].

Ultrasonographic identification of an intrauterine pregnancy (gestational sac plus yolk sac or other embryonic sign) rules out ectopic pregnancy in most patients[16]. The exception is in patients with ovulation induction and assisted conception, who are at risk of heterotopic pregnancy (dizygotic twins, 1 intrauterine and 1 extrauterine). Although this phenomenon is exceedingly rare in the general population (estimated frequency 1 per 3889 to 30000 pregnancies)[19], in the setting of assisted reproduction it may occur in 1 in 100 pregnancies[20].

Many prospective studies have shown that "formal" transvaginal ultrasound imaging (i.e., that performed by ultrasound technicians and interpreted by radiologists) in the emergency department has high accuracy in confirming intrauterine and ectopic pregnancy. Most protocols can establish a diagnosis with the initial scan in more than 75% of emergency department patients. A diagnosis can often be established even in the subgroup of patients with β-hCG levels below the discriminatory threshold. In some studies, transvaginal scanning has identified up to one-third of the patients with below-threshold β-hCG levels who had ectopic pregnancy[18,77]. Given the likelihood of a definitive diagnosis, even with below-threshold β-hCG levels, ultrasonography is the best initial investigation in problematic early pregnancy[3].

The addition of ED-based ultrasonography to structured protocols for assessing symptomatic patients in the 1st trimester of pregnancy has led to a dramatically decreased stay in the emergency department[21] as well as a decrease in the incidence of complications associated with missed ectopic pregnancy and tubal rupture[13].

Transvaginal ultrasonography should therefore be the initial investigation for pregnant patients presenting to the emergency department with first-trimester bleeding or pain. Not only is it highly accurate in identifying ectopic pregnancy, but also it offers patients what they are most expecting from their visit: information about the health and viability of their pregnancy. No combination of history-taking, physical examination and laboratory tests can make the same claim. The use of ED-based ultrasonography offers rapid bedside detection of a viable intrauterine pregnancy or a high risk of ectopic pregnancy. Emergency physicians without access to bedside ED-based ultrasonography should arrange formal ultrasonography for all patients with early-pregnancy complaints[3].

Uterine curettage

This procedure, carried out in the office rather than the operating theatre, is useful when the β-hCG concentration is below the cut-off for ultrasonographic diagnosis. It expedites diagnosis without need for delays while awaiting further β-hCG measurements. Curettage should be done only after a non-viable pregnancy has been documented either by a serum progesterone concentration of 15.9 nmol/L (5 ng/mL) or lower or by the absence of a rise in β-hCG after 2 days[65]. A decrease in the β-CG concentration of 15% or more 8–12 h after curettage is diagnostic of complete abortion. If β-hCG concentration does not fall, ectopic pregnancy is diagnosed[65].

THERAPEUTIC APPROACH

Treatment options for tubal ectopic pregnancy are; (1) surgery, e.g. salpingectomy or salpingo(s)tomy, either performed laparoscopically or by open surgery; (2) medical treatment, with a variety of drugs, that can be administered systemically and/or locally by various routes and (3) expectant management.

Expectant and medical management are possible, and should be considered in selected cases, but they are not widely practised in the United Kingdom. Surgery remains the mainstay of treatment, possibly overtreating a number of cases[7].

Expectant management

Some ectopic pregnancies resolve spontaneously through regression or tubal abortion, and expectant management is possible in selected cases. This is not related to the size of the ectopic pregnancy on an ultrasonogram[45,46] but the initial serum titre of human chorionic gonadotrophin, and the trend in titres are independent predictors of success[47]. It is important, therefore, 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[45,47]. Overall, if the initial serum concentration of β-hCG is less than 1000 IU/L, expectant management is successful in up to 88% of patients[47].

However, about 90% of women with ectopic pregnancy and serum β-hCG levels greater than 2000 IU/L require operative intervention owing to increasing symptoms or tubal rupture[11,12]. Tubal rupture can also occur when serum β-hCG levels are low or declining, or both[22]. Expectant management should be offered only when transvaginal ultrasonography fails to show the location of the gestational sac and the serum levels of β-hCG and progesterone are low and declining. Because of the possibility of tubal rupture, these patients must be carefully monitored until the serum β-hCG concentration falls below 15 IU/L; at this point almost all ectopic pregnancies resolve spontaneously, without rupture[3].

Medical treatment

Methotrexate (MTX), a folic acid antagonist, inhibits DNA synthesis in actively dividing cells, including trophoblasts[3]. It is used for medical management in patients before rupture who are haemodynamically stable[7]. Administered to properly selected patients, it has a success rate of up to 94%[26].

The criteria for MTX treatment of ectopic pregnancy are as follows[3]:

- Hemodynamic stability
- Ability and willingness of the patient to comply with post-treatment monitoring
- Pretreatment serum β-hCG concentration less than 5000IU/L
- Absence of ultrasound evidence of fetal cardiac activity

Specific protocols for methotrexate treatment have been established, Box 1. MTX can be given intramuscularly or injected into the ectopic pregnancy, a route that delivers high concentrations locally with smaller systemic distribution. However, rates of successful treatment are lower than with systemic methotrexate, and it requires a laparoscopic or ultrasound guided needle procedure[7].

Box 1: Protocol for methotrexate treatment of ectopic pregnancy[3].

Pretreatment investigations
•Complete blood count
•Blood group typing and antibody testing
•Liver and renal function tests
•Measurement of serum level of β human chorionic gonadotropin (β-hCG)
•Transvaginal ultrasonography

Treatment day 0
•Inject methotrexate (50 mg/m 2) intramuscularly
•Inject RhoGAM (300 μg) intramuscularly if needed
•Discontinue folinic acid supplements
•Advise patient to refrain from strenuous exercise and sexual intercourse

Day 7
•Measure serum β-hCG concentration
•Perform transvaginal ultrasonography
•Inject second dose of methotrexate if decline in β-hCG level is < 25%

Weekly
•Measure serum β-hCG concentration until level is < 15 IU/L
•Perform transvaginal ultrasonography

Any time
•Perform laparoscopy if patient has severe abdominal pain or acute abdomen or if ultrasonography reveals more than 100 mL of blood in the abdomen

Patients with an unruptured ectopic pregnancy measuring 4 cm or less on ultrasonography are eligible for this treatment but those with larger masses or evidence of rupture are ineligible. There are two commonly used methotrexate regimens, variable-dose methotrexate or single-dose methotrexate[10]. Methotrexate in a single dose is more convenient than the variable dose regimen but may carry a higher risk of persistent ectopic pregnancy[78]. Close follow up with serial measurements of serum concentrations of β-hCG is required. A second course of treatment may be necessary, and some patients may require surgical intervention. Methotrexate treatment may produce significant side effects, but side

effects of methotrexate therapy are usually mild and self-limiting, and include stomatitis, conjunctivitis, pleuritis, dermatitis, alopecia, gastritis, enteritis, elevated liver enzyme concentrations and bone marrow suppression[3]. About 30% of patients will have side effects with a single dose and 40% with multiple doses[3]. The side-effects are transient and resolve within 3–4 days after methotrexate therapy is discontinued. Impaired liver function is the most common side-effect. Stomatitis, gastritis and enteritis, and bone-marrow suppression are less common[10].

The overall success rate is greater with multiple-dose MTX therapy than with single-dose therapy (93% vs. 88%); however, single-dose therapy is less expensive, has a lower rate of side effects (29% vs. 48%), requires less intensive monitoring, does not require rescue with folinic acid and is effective for most women. The 2 regimens have not been directly compared in randomized trials[3].

Direct injection delivers very high concentrations of methotrexate to the site of implantation. The smaller systemic distribution of the drug decreases toxic effects. However, this approach has the substantial disadvantage that laparoscopic or ultrasonographic needle guidance is needed. Rates of successful treatment are lower than with systemic methotrexate. This approach thus offers no advantage over systemic methotrexate[7,10].

Persistent ectopic pregnancy occurs after variable-dose methotrexate therapy, but less commonly than after surgery. Persistence is defined as the need for a second course of therapy[10].

The success in ectopic pregnancy depends mainly on β-hCG concentration: a meta-analysis of data for 1327 women with ectopic pregnancy treated with MTX showed that resolution was inversely associated with β-hCG level, and that increasing levels were significantly correlated with treatment failure. Fetal cardiac activity was also associated with MTX treatment failure[3].

Patients in whom laparoscopy may be challenging (including those with many previous laparotomies and scarring) may have a better outcome with MTX treatment. In the presence

of relative contraindications, such as high serum β-hCG levels (5000 IU/L[11]) and the presence of fetal cardiac activity, multiple-dose treatment should be considered[3].

Patients treated with MTX should be followed closely. The serum β-hCG concentration should be measured weekly. An increased level is uncommon 3 to 4 days after MTX administration. Patients may experience abdominal pain from tubal abortion or tubal distention due to hematoma formation. Severe abdominal pain, however, can be a sign of actual or impending tubal rupture. If the serum β- hCG concentration has not declined by at least 25% 1week after MTX administration, a second dose should be given. In general, a second dose is needed in 15% to 20% of patients[27,74]. Only 1% of patients need more than 2 doses[27]. The time for the serum β-hCG concentration to decline to less than 15IU/L is 33.6 days on average but may be up to 109 days[74].

Surgical management

Surgical management of ectopic pregnancy should be reserved for patients who refuse or have contraindications to medical treatment, those in whom medical treatment has failed and those who are hemodynamically unstable[3].

Surgery is the preferred treatment for ectopic pregnancy when there is rupture, hypotension, anaemia, diameter of the gestational sac greater than 4 cm on ultrasonography, or pain persisting beyond 24 hours[68].

Surgical treatments may be radical (salpingectomy) or conservative (usually salpingostomy), and they may be performed by laparoscopy or laparotomy. 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[7].

Laparoscopic surgery is generally preferred over laparotomy[10]. Three randomized studies have demonstrated that, compared with laparotomy, laparoscopic treatment of ectopic pregnancy is associated with lower cost, shorter hospital stay, less operative time, less blood loss, less analgesic requirement and faster recovery. Patients randomly assigned to laparoscopy also had fewer adhesions than patients treated with laparotomy (19% vs. 64%)[3]. Laparotomy is preferred, however, when the patient is haemodynamically unstable, the

surgeon is not trained in operative laparoscopy, or when the laparoscopic approach is technically too difficult[68].

Tube-sparing salpingostomy (in which the gestational sac is removed, without the tube, through a 1-cm-long incision on the tubal wall) is preferred to salpingectomy (removal of the tube), as the former is less invasive but has comparable rates of subsequent fertility and ectopic pregnancy[23-25]. However, 8% of patients have persistent ectopic pregnancy after salpingostomy[23]. Follow-up determinations are required until β-hCG is undetectable. Regardless of the type of surgery, contralateral tubal abnormalities predispose the patient to recurrent ectopic pregnancy. In a retrospective study of 276 women with ectopic pregnancy, the cumulative rates of spontaneous intrauterine pregnancy over 7 year were 89% after conservative surgery and 66% after radical surgery. There was no significant difference in the risk of repeat ectopic pregnancy (17% after conservative surgery and 16% after radical surgery). In summary, salpingostomy is preferred, particularly for women who wish to have another pregnancy[3]. Salpingectomy may be necessary for women with uncontrolled bleeding, recurrent ectopic pregnancy in the same tube, a severely damaged tube or a tubal gestational sac greater than 5 cm in diameter[26].

Salpingectomy is clearly preferable in cases of uncontrollable bleeding, extensive tubal damage,or recurrent ectopic pregnancy in the same tube, and when the woman requests sterilization[70].

Generally, hospital stay (1.3 days) and convalescence (2.4 weeks) are shorter after laparoscopy than with laparotomy (3.1 days and 4.6 weeks respectively)[49,50]. Both techniques produce similar rates of complications[50] and persistent trophoblast[51]. If there is a risk of persistent trophoblast, follow up with serial measurements of serum concentrations of β-hCG is necessary. Since no single postoperative concentration of human chorionic gonadotrophin is predictive, follow up until complete resolution is necessary[48]. The need for a second laparoscopy should be based on symptoms rather than changes in concentrations of β-hCG[49-51]. In a randomised controlled trial, methotrexate and laparoscopic salpingostomy were equally effective[52].

Persistent ectopic pregnancy, the most common complication of laparoscopic salpingostomy, occurs at a frequency of 5–20%[68,71]. It occurs as a result of incomplete removal of trophoblastic tissue. It is diagnosed during follow-up when β-hCG concentrations measured once a week plateau or rise[72]. Factors increasing risk are small ectopic pregnancies (< 2 cm diameter), early therapy (< 42 days from last menstrual period), high concentrations of β-hCG (>3000 IU/L) preoperatively, and implantation medial to the salpingostomy site[73]. In high-risk cases, a single dose of methotrexate (1 mg/kg) can be administered postoperatively for prophylaxis[71,73].

The cost of salpingostomy is slightly more than salpingectomy in the short term. Both treatments are equally effective initially, but additional treatment for persistent ectopic pregnancies is occasionally required after salpingostomy. Although it is comparatively simple to cost the acute episode, calculating the long term costs of subsequent infertility treatment and treatment for recurrent ectopic pregnancy is more difficult[7].

Surgical versus medical treatment

Medical treatment with methotrexate bypasses expenses and complications associated with surgery and anaesthesia. It has become the primary treatment in many centres. The outcome of medical therapy now closely matches that of laparoscopic salpingostomy[10].

Several randomized studies found that MTX treatment in selected patients with ectopic pregnancy was as effective as laparoscopic treatment[28-31]. The 2 treatments were also equally effective in tubal preservation; however, the β-hCG concentration declined more quickly after laparoscopic surgery[28]. After MTX treatment the health-related quality of life may diminish, possibly owing to both long-term persistence of the ectopic pregnancy and the long treatment course. There were more physical symptoms after 2 days and 2 weeks in those given MTX, although symptoms were increased in both treatment groups. However, because of the noninvasive nature of MTX treatment, most patients are willing to cope with this short-term burden[32]. MTX treatment is less expensive than laparoscopic surgery[31,32], although in one study this was true only if the initial serum β-hCG level was less than 1500IU/L[32].

A study found that an advantage of linear salpingostomy was the predictable and consistent decline of circulating β-hCG, and consequently a reduced need for a close follow-up. Local MTX injection was safe, economic, effective, and easy to perform, and in our experience the surgical time was statistically shorter than that for linear salpingostomy. Therefore, in selected patients, local injection of MTX could be the treatment of choice for unruptured ectopic pregnancy, avoiding a longer and potentially more dangerous procedure. Long-term outcomes do not seem to differ between the two types of treatment[5].

FERTILITY AFTER TREATMENT

Women who have one ectopic pregnancy are at increased risk for another such pregnancy and for future infertility[9]. Rates of intrauterine pregnancy after expectant management are comparable to those achieved after medical or surgical management, varying between 80% and 88%[53,54], and rates for recurrent ectopic pregnancy vary between 4.2% and 5%[7]. A population based cohort study reported a pregnancy rate of 66% regardless of whether treatment was surgical or medical[55]. Of those who conceived, 90% achieved an intrauterine pregnancy and 10% had recurrent ectopic pregnancy. The risk factors for recurrent ectopic pregnancy are previous spontaneous miscarriage, tubal damage, and age greater than 30years[48]. After methotrexate, between 62% and 70% of women had a subsequent intrauterine pregnancy and around 8% had recurrent ectopic pregnancy[46,48].

When comparing conservative and radical surgery, the results are conflicting, with pregnancy rates varying from no significant difference to lower rates of both intrauterine pregnancy and recurrent ectopic pregnancy after salpingectomy[7].

Irrespective of type of tubal surgery, laparoscopic treatment resulted in a higher rate of intrauterine pregnancy (77% versus 66%)[75] and a lower rate of recurrent ectopic pregnancy (7% versus 17%)[50] compared with laparotomy. A history of infertility is, however, an important factor, with an overall conception rate of 77% for all methods of surgical treatment and a rate of recurrent ectopic pregnancy of around 10%. 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[52]. Treatment should therefore be directed at therapeutic need and the wishes of the patient.

PREVENTION

Ectopic pregnancy can be prevented by decreasing the incidence of risk factors contributing to the condition. Multiple sexual partners, early age at first sexual intercourse, cigarette smoking, and vaginal douching increase risk[10], and are factors that can be prevented by the individual if given early and adequate information by health workers.

A history of pelvic inflammatory disease has in some studies been found to be particularly important[36] and has been implicated in the increased incidence of ectopic pregnancy[36]. After acute salpingitis, the risk of an ectopic pregnancy is increased sevenfold[36]. This is particularly true of *Chlamydia trachomatis,* the main cause of pelvic inflammatory disease in the United Kingdom[37]. Comprehensive programmes to prevent chlamydia not only decrease the incidence of *Chl. trachomatis* infections but also the rate of ectopic pregnancies[38,39]. Practicing safe sex, lowers your risk of ectopic pregnancy, because safe sex helps protect from sexually transmitted diseases (STDs) that can lead to pelvic inflammatory disease (PID). PID is a common cause of scar tissue in the fallopian tubes, which can cause ectopic pregnancy. Thus, ectopic pregnancy can be prevented by decreasing the incidence of pelvic inflammatory disease and *Chl. trachomatis* infections and improving their treatment[7].

Technological advances now allow routine diagnosis of ectopic pregnancy before clinical symptoms arise[10]. Since ectopic pregnancy cannot be diagnosed in the community, all sexually active women with a history of lower abdominal pain and vaginal bleeding should be referred to hospital early for ultrasonography and, if necessary, measurement of serum concentrations of β-hCG[7].

In patients at high risk of ectopic pregnancy, diagnosis should be made before symptoms occur—ie, such women should be carefully screened as soon as they report suspected pregnancy[57,61]. Screening by measurement of β-hCG concentrations and transvaginal ultrasonography has a sensitivity of 84–88%[57,61] and specificity of 100%[57]. Women with a history 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.

Ectopic pregnancy cannot be prevented in its entirety, but you can prevent life-threatening complications with early diagnosis and treatment. If one or more risk factors for ectopic pregnancy are present, health professionals can closely monitor the first weeks of pregnancy.

Early screening of high-risk, symptom-free women can avert tubal rupture, haemorrhage, and the need for emergency care[10]. These benefits of aggressive diagnosis outweigh the disadvantages of a false-positive rate of 1.2%[61].

CONCLUSION

Ectopic pregnancy is a common and serious problem, with a significant morbidity rate and the potential for maternal death, which requires urgent intervention[3]. Its incidence is increasing worldwide[7], and it is still the most common cause of maternal deaths in the first trimester[1]. Many patients have no documented risk factors and no physical indications of ectopic pregnancy[3]. In all sexually active women of reproductive age who present with lower abdominal pain, with or without vaginal bleeding, an ectopic pregnancy must be excluded[1].

Since ectopic pregnancy cannot be diagnosed in the community, all sexually active women with a history of lower abdominal pain and vaginal bleeding should be referred to hospital early for ultrasonography and, if necessary, measurement of serum concentrations of human chorionic gonadotrophin. Women with a history 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[7].

Ectopic pregnancy can be prevented by decreasing the incidence of risk factors contributing to the condition, and by improving the treatment of pelvic inflammatory disease and *Chl. trachomatis* infections[7]. The potentially life-threatening complications of ectopic pregnancy are prevented by urgent diagnosis and treatment of the condition.

Expectant and medical management of ectopic pregnancy are effective options in selected cases as long as adequate facilities for monitoring are available. If surgery is necessary, the laparoscopic route results in shorter hospital stay, but there is no clear advantage of salpingostomy over salpingectomy. The decision should therefore be made on an individual basis. Methotrexate and laparoscopic salpingostomy appear in studies to be equally successful in treating ectopic pregnancy.

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