Ectopic pregnancy

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Ectopic pregnancy is an important cause of morbidity and mortality worldwide. Use of transvaginal ultrasonography and quantitative measurement of the β subunit of human chorionic gonadotropin (β-hCG) has led to a reduction in the need for diagnostic laparoscopy. Furthermore, with earlier diagnosis, medical therapy with methotrexate can be offered and surgery avoided in some women, though the best regimen remains unclear. In the surgical management of ectopic pregnancy, the benefits of salpingectomy over salpingostomy are uncertain. Although there have been advances in the management of ectopic pregnancy there are still questions to be answered.

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Ectopic pregnancy is an important cause of maternal morbidity and occasionally mortality. 1·3–2% of all reported pregnancies are extrauterine (figure 1).[1–4] Quantitative measurements of the β subunit of human chorionic gonadotropin (β-hCG) and transvaginal ultrasonography have improved the accuracy of diagnosis and allow earlier detection of ectopic pregnancies than was previously possible. Deaths associated with ectopic pregnancy have declined, though more than three-quarters of deaths in the first trimester and 9–13% of all pregnancy-related deaths are associated with pregnancies outside of the womb.[5,6] Mortality fell from 35·5 to 3·8 deaths per 10 000 women between 1970 and 1989 in the USA,[6] and from 16 to three deaths per 10 000 pregnancies between 1973 and 1993 in the UK.[5] In the developing world, however, mortality remains high—100–300 deaths per 10 000 in Cameroon.[7] The costs of treating ectopic pregnancy are considerable, with direct costs estimated at US$1 billion in the USA alone.[8] There are also intangible costs, such as ongoing infertility, to consider.[9]

Epidemiology

Are the rates of ectopic pregnancy rising or falling? The answer to this question is not straightforward, for two reasons. First, the rate of ectopic pregnancy is usually expressed as the number of cases per reported pregnancy, which might or might not include data for those that are terminated and that end in early miscarriage as well as for those that result in livebirths. Second, women with ectopic pregnancies are increasingly managed as outpatients and are not, therefore, necessarily included in hospital statistics. With such inconsistent data, an accurate estimate of the true incidence of ectopic pregnancy cannot be calculated.[10]

The annual incidence of ectopic pregnancy in the USA in 1948 was reported as 0·4% of pregnancies, but is now nearly 2%.[1,2] Over the past three decades, in many countries, the rate of ectopic pregnancy has followed a trend of initially doubling or more and then either slowing or declining.[5,11–15] For example, in Norway, Sweden, and the UK the rates either doubled or more between the 1970s and the 1990s, but are now declining.[5,11,12,15] The rise and fall in ectopic pregnancy rates could be explained in part by the increasing rates of chlamydia infection followed by the effect of prevention and the change in use of intrauterine devices.[1–3,12,14]

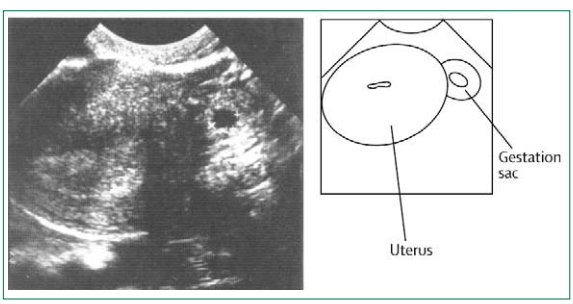

Figure 1: **Transvaginal ultrasound view of ectopic pregnancy at 6 weeks' gestation**

Risk factors

An understanding of the risk factors for ectopic pregnancy leads to swift diagnosis and helps to avoid surgery. Two main factors should be considered: the probability of conception and, after conception, the probability of implantation of the fertilised ovum outside of the uterus. As such, studies in this area should compare risk factors in women with an ectopic pregnancy with both pregnant and non-pregnant controls. Most risk factors—eg, tubal damage from either infection or disease—affect both the probability of conception and the probability of extrauterine implantation. Studies that compare with pregnant controls, therefore, can only report risk for those currently pregnant, whereas studies with non-pregnant controls take into account both probabilities.[16]

Many studies[16–21] have identified the risk factors for ectopic pregnancy (table 1). A third of cases are associated with tubal damage caused by infection or surgery, and another third with smoking.[16] No known cause can be established for the remaining third. Tubal infection contributes less to ectopic pregnancy risk than smoking, though the risk of ectopic pregnancy increases with the number of pelvic infections.[22] Techniques of

Search strategy and selection criteria

I searched the Cochrane Library (Issue 3, 2004), MEDLINE (1990–2004), and EMBASE (1990–2004) with the search term: "ectopic pregnancy" alone and in combination with "epidemiology", "diagnosis", "treatment", "methotrexate", "laparoscopic surgery", "salpingostomy", and "salpingectomy". I searched the reference lists of articles identified by this search for further studies. Only articles published in English were searched.

	Adjusted OR (95% CI) [17,18]*	OR (95% CI) [16,19]
Previous tubal surgery	4·0 (2·6–6·1)	4·7–21·0
Infertility (risk increases with length of infertility)	2·1–2·7	2·5–21·0
Previous genital infection confirmed	3·4 (2·4–5·0)	2·5–3·7
Previous miscarriage	3·0 (>2)	-
Previous induced abortion	2·8 (1·1–7·2)	-
Past or ever smoker	1·5 (1·1–2·2)	2·5 (1·8–3·4)
Current smoker (risk increases with amount smoked per day)	1·7–3·9	2·3–2·5
Age 40 years and older	2·9 (1·4–6·1)	-
Intrauterine device use (>2 years)	2·9 (1·4–6·3)	4·2–45·0
Previous intrauterine device	2·4 (1·2–4·9)	-
Sterilisation†	-	9·3 (4·9–18·0)
Previous ectopic pregnancy	-	8·3 (6·0–11·5)
Documented tubal pathology	3·7 (1·2–4·8)	2·5–3·5
More than one sexual partner	-	2·1–2·5
Diethylstilboestrol exposure	-	5·6 (2·4–13·0)

OR single values=common ORs from homogeneous studies; point estimates=range of values from heterogeneous studies. No CIs given if range of OR provided. *Adjusted for previous pelvic infection, smoking, recruitment area, level of education, and age. †Compared with pregnant controls only.

Table 1: **Risk factors for ectopic pregnancy**

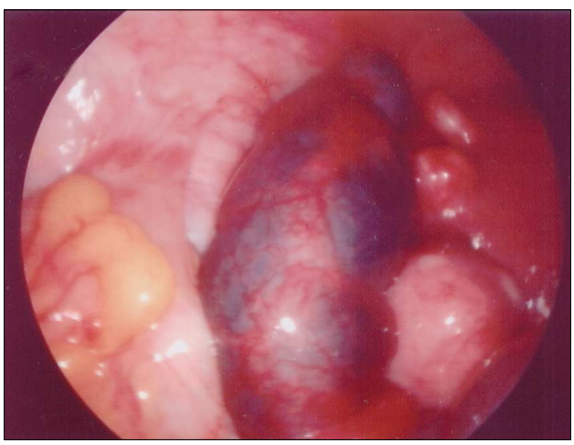

Figure 2: **Laparoscopic view of ectopic pregnancy**

assisted reproduction increase the risk of ectopic pregnancy two-fold to 4%.[21,23] The raised likelihood of tubal disease and need for surgery in this population are obvious confounders. Indeed, results of stepwise logistic regression analysis[23] show that tubal-factor infertility and previous myomectomy account for 85% of ectopic pregnancies in women who receive fertility treatment.

Risk factors for ectopic pregnancy in women who conceive after contraceptive failure are different to those for women trying to conceive.[17] All contraceptives—hormonal and mechanical—protect against ectopic pregnancy.[19] Results of a review[24] of published and unpublished data of pregnancies after contraceptive failure showed, however, that ectopic pregnancy was more likely in women who had taken progestin-only oral contraceptives, had progestin-only implants or an IUD, or had been sterilised than in pregnant women in the general population. Overall, the likelihood of an ectopic pregnancy in women who have an IUD in place at time of conception varies from one in two in women with a levonorgestrel-based device to one in 16 in women with a copper device.[24] The risk of ectopic pregnancy after sterilisation is increased nine-fold, and is especially high for those sterilised by electrocautery and in women younger than age 30 years.[25] A third of pregnancies that arise after sterilisation are ectopic.[24]

Diagnosis

Increasingly, ectopic pregnancies are diagnosed before the onset of symptoms, allowing early, conservative treatment. The typical triad of symptoms includes bleeding and abdominal pain after a period of amenorrhoea.[26] The clinical presentation can, therefore, be confusing, since symptoms overlap with miscarriage. A third of women have no clinical signs and 9% no symptoms of ectopic pregnancy.[27,28] As a result, almost half of cases are not diagnosed at the first surgery visit after conception.[28,29] Ectopic pregnancy should be considered in all women who present with a history of fainting and vaginal bleeding. The introduction of quantitative β-hCG and transvaginal ultrasound as diagnostic techniques has greatly reduced the need for laparoscopy, which is used now only to confirm diagnosis in women who have symptoms but whose ultrasound scans are inconclusive.[30–32]

Transvaginal ultrasonography

The presence of an intrauterine pregnancy on transvaginal ultrasonography excludes ectopic pregnancy unless a heterotopic pregnancy is suspected in women, for example, undergoing fertility treatment (figure 2).[21] Findings of a systematic review[33] of ten studies indicate that transvaginal ultrasound can identify any non-cystic adnexal mass with a sensitivity of 84·4% and a specificity of 98·9%, and has positive and negative predictive values of 96·3% and 94·8%, respectively. Endometrial thickness at the time of a transvaginal ultrasound has no effect on result.[34] Three-dimensional ultrasound has little to offer in the management of suspected ectopic pregnancy other than, perhaps, to identify the location of unusually sited ectopic pregnancies—eg, in a caesarean section scar.[35]

Serum β-hCG measurements

Ultrasound is inconclusive in up to 18% of women, in whom measurement of serial β-hCG concentrations is necessary to guide management.[36] A doubling of β-hCG concentrations over 48 h is often used to predict viability,[37–40] though the results of a large study published in 2004[41] suggest that the slowest increase associated with viability is 53% after 2 days. Ideally, β-hCG concentrations should be plotted on a graph of the normal values for pregnancy and used in conjunction with ultrasound findings.[38] A decline or a slowing of rising concentrations of β-hCG cannot discriminate between a miscarriage and an ectopic pregnancy. The combined approach of measurement of

β-hCG and transvaginal ultrasound detects ectopic pregnancy with 97% sensitivity and 95% specificity, avoiding the need for further invasive tests, such as a dilatation and curettage.[42] There is some debate about the lowest concentration of β-hCG at which a viable pregnancy should be visible on an ultrasound scan (the discriminatory zone).[43,44] An intrauterine gestation is usually visible on a transvaginal scan at a β-hCG concentration of 1500 IU/L or more, but in the absence of obvious signs, such as a mass or fluid in the pouch of Douglas, a higher cut-off point of 2000 IU/L should be used. If only transabdominal ultrasound is available then the discriminatory zone is 6500 IU/L. In the case of multiple pregnancies, β-hCG concentrations will be greater than 2000 IU/L before the intrauterine gestation sacs are visible on ultrasound.[45]

Serum progesterone concentrations

By contrast with β-hCG concentrations, progesterone concentrations change little in the first 8–10 weeks of gestation. Furthermore, serum progesterone concentrations are higher in women with viable intrauterine pregnancies than in those with ectopic or miscarrying pregnancies. As such, this hormone could be used to help diagnose ectopic pregnancy.[42,46,47] A value of more than 80 nmol/L is associated with a healthy intrauterine pregnancy in 98% of women, whereas a concentration of less than 16 nmol/L is indicative of a non-viable pregnancy, irrespective of location.[48] It is noteworthy that for 2% of women a progesterone concentration of 80 nmol/L or more will not rule out an ectopic pregnancy. Women at high risk of extrauterine pregnancy should, therefore, be monitored carefully, irrespective of their progesterone readings.[47] Furthermore, most women with an ectopic pregnancy will have a progesterone concentration between 16 nmol/L and 80 nmol/L at presentation, limiting the clinical usefulness of progesterone measurement in the diagnosis of ectopic pregnancy.[49] A progesterone concentration of less than 15 nmol/L is associated with miscarriage in 85%, ectopic pregnancy in 14%, and a viable pregnancy in 0·2% of women.[47] Unfortunately, women undergoing assisted reproduction have very high progesterone concentrations (secondary to the multiple induced ovulations) even in the presence of an ectopic pregnancy.[50] A systematic review[46] of the accuracy of a single progesterone measurement concluded that although the progesterone concentration could identify women at risk for ectopic pregnancy, its discriminative capacity is insufficient to diagnose ectopic pregnancy with certainty.

A decision analysis,[51] comparing screening by progesterone measurement alone with screening by transvaginal ultrasound and β-hCG measurement concluded that the former offered no advantage. This finding might reflect the fact that the two tests (β-hCG and progesterone) are closely related. Some investigators[47,48] are enthusiastic about the use of progesterone concentrations in combination with dilatation and curettage, recommending dilatation and curettage if the progesterone concentration is less than 2 nmol/L. Since expectant management is a successful strategy for many women with early miscarriage, however, such a policy seems unnecessary.[52]

Dilatation and curettage

Dilatation and curettage is recommended as a diagnostic method for use in conjunction with low progesterone or β-hCG concentrations and in women in whom transvaginal ultrasound suggests a non-viable intrauterine pregnancy.[47,48] The absence of chorionic villi is associated with an ectopic pregnancy in 40% of women with an empty uterus on ultrasound.[53] An ectopic pregnancy is suggested in women whose β-hCG concentrations do not fall by at least 15% in the 12 h after dilatation and curettage, or in whom the histological findings do not include chorionic villi.[48] However, use of dilatation and curettage in the diagnostic workup of suspected ectopic pregnancy has not been widely adopted, in part because the technique is generally considered invasive with a risk of adverse events, and in part because many women who miscarry can be managed without the need for curettage.[51,52,54]

Biochemical markers

The ideal marker for ectopic pregnancy would be specific for tubal damage or present only after endometrial implantation. Various markers have been assessed, including creatinine kinase[55] and fetal fibronectin,[56] but none is sufficiently sensitive or specific for the diagnosis of ectopic pregnancy.

Screening for ectopic pregnancy

Early diagnosis is the key to non-surgical management of women with ectopic pregnancies. Should women who are at increased risk, therefore, be routinely screened for ectopic pregnancy? Results of a decision analysis[51] of women with at least one risk factor for ectopic pregnancy concluded that screening reduced the number of women with tubal rupture, but with a false positive rate of 0·64 per prevented tubal rupture. The findings also showed that the cost-effectiveness of a screening programme would depend on the prevalence of ectopic pregnancy in the population screened. If the prevalence of ectopic pregnancy was 6% then the number of women with ruptured ectopic pregnancies fell from 2·1% to 0·6%. There may be some justification for screening: women who have had previous ectopic pregnancies, since the prevalence of a repeat ectopic pregnancy is more than 10%;[57] women with a history of pelvic inflammatory disease (prevalence of 9%);[58] and women with subfertility and known tubal disease (prevalence of 16%).[59] However,

the implications and costs of false-positive results should be considered.

Treatment

Although surgery is the mainstay of management for ectopic pregnancy, options of medical or expectant management are available for a proportion of women (table 2).[60,61]

Surgical therapy

The decision to manage an ectopic pregnancy surgically will depend on the likelihood of success of non-surgical treatment. Since medical therapy is less likely to succeed, surgery is the preferred approach for ectopic pregnancy when there are signs of cardiac activity and β-hCG concentrations are greater than 5000 IU/L.[62,63] Other indications for surgery include an adnexal mass greater than 4 cm in diameter and free fluid in the pelvis on transvaginal ultrasound, although results of recent studies[64] suggest these factors are not always predictors of failure with medical management. As few as 38% of women are successfully treated with methotrexate when their β-hCG concentrations are higher than 5000 IU/L. If the criteria of a β-hCG concentration of less than 5000 IU/L, presence of an adnexal mass less than 4 cm in diameter, and absence of cardiac activity are adopted as an indication for medical therapy, then more than three-quarters of women who present with ectopic pregnancy will need to be managed surgically.[65]

Open or laparoscopic surgery?

The choice of open or laparoscopic surgery will depend on whether the patient is haemodynamically stable. In women with no signs of shock, laparoscopic surgery is generally favoured over laparotomy. However, with the exception of shorter hospital stay and convalescence, there is little evidence of an increased benefit of laparoscopic surgery over laparotomy. A systematic review[66] of three randomised controlled trials[67–69] showed that open salpingostomy when compared with laparoscopic salpingostomy increased rates of elimination of the tubal pregnancy (2·4% *vs* 12·5%), mainly because of the higher persistent trophoblast rate with laparoscopic surgery. There was no difference in the subsequent tubal patency or in subsequent rate of intrauterine pregnancy or repeat ectopic pregnancy, but perioperative blood loss was higher with open surgery. Laparoscopic surgery was much cheaper than open surgery mainly because of the shorter hospital stay.[70] Further studies are needed to establish whether the persistent trophoblast rate is as high as in the original studies. However, I agree with others[71] that, in the absence of strong evidence of harm, a laparoscopic approach should be favoured.

Salpingectomy or salpingostomy?

There has been considerable debate about whether salpingectomy or salpingostomy should be done at the time of surgery for an ectopic pregnancy. The possible advantages of removing the tube completely include almost entirely eliminating the risk of persistent trophoblast and that of a subsequent ectopic pregnancy, whereas the possible advantage of conserving the fallopian tube is that future fertility is preserved. There are no randomised controlled trials published that specifically compare laparoscopic or open salpingectomy and salpingostomy. Several reviewers[72–77] suggest that subsequent intrauterine pregnancy rates are similar after both approaches. Four non-

Surgery	Methotrexate*	Expectant management
Indication		
Signs of rupture	No evidence of rupture	No evidence of rupture
β-hCG >5000 IU/L	β-hCG ≤5000 IU/L	β-hCG <1500 IU/L
Laparoscopy needed for diagnosis	β-hCG rising at 48 h	Declining β-hCG within 48 h
Suspected heterotopic pregnancy	Normal blood count, platelets, and liver enzymes	Patient understands need for ongoing surveillance
	Patient understands need for longterm surveillance	
Procedure		
Salpingostomy—If contralateral tube damaged or missing	Multiple dose—methotrexate 1 mg per kg intramuscularly, alternate days (days 1, 3, 5, 7) + leucovorin 0·1 mg per kg intramuscularly, alternate days (days 2, 4, 6, 8). Continue until β-hCG falls ≥15% in 48 h or four doses methotrexate given. A repeat course can be given if β-hCG concentration not <40% of initial value on day 14.	Confirm patient is in close proximity to medical services throughout follow-up
Salpingectomy—If there is uncontrolled bleeding or extensive tubal damage on side of ectopic pregnancy, in instances of recurrent pregnancy in same tube or sterilisation failure		Repeat β-hCG measurement and transvaginal ultrasound scan within first 48 h
Laparotomy—If haemodynamically unstable or laparoscopy considered too difficult	Single dose methotrexate 50 mg per m^2 intramuscularly. Repeat dose if β-hCG is not, <15% between days 4 and 7. Up to four doses can be given if β-hCG does not decline by 15% every week.[61,65]	
Follow up		
Weekly β-hCG measurement until not detected	Weekly β-hCG measurement until not detected	Weekly β-hCG measurement until not detected
No sexual intercourse or pelvic examination until resolved	No sexual intercourse or pelvic examination until resolved	No sexual intercourse or pelvic examination until resolved
Methotrexate 50 mg per m^2 for persistent ectopic pregnancy	Any pregnancy should be delayed for 3 months because of the teratogenecity of methotrexate	Methotrexate or surgery for persistent ectopic pregnancy

*Dose calculated by body surface area with nomogram.

Table 2: **Management of ectopic pregnancy.**[60,61,65]

randomised studies,[78–81] comparing laparoscopic salpingostomy and salpingectomy, have been done. The results of three indicate similar subsequent intrauterine pregnancy rates for both techniques, with findings of the other study[81] suggesting a higher rate with salpingostomy. In this last study, however, there was considerable variation between the two groups of women studied that could explain the differences in subsequent fertility, such as a higher rate of tubal rupture and laparotomy in the women undergoing salpingostomy. In the presence of a healthy contralateral tube, therefore, neither salpingostomy nor salpingectomy offers an advantage with respect to future fertility. However, salpingostomy should be considered as the primary treatment option for tubal pregnancy in the presence of disease in the contralateral tube and the desire for future fertility.

Persistent ectopic pregnancy after laparoscopic salpingostomy arises in 4–15% of women.[21,60,65,82,83] Therefore, β-hCG concentrations should be followed-up until they are undetectable. Risk factors for persistent ectopic pregnancy are small ectopic pregnancies (<2 cm), early surgical intervention (<42 days from last menstrual period), and β-hCG values of 3000 IU/L or more.[84] The rate of persistent ectopic pregnancy was reduced in one study[85] from 14% to 2% with the use of prophylactic methotrexate, which also reduced the period of postoperative monitoring. However, to avoid one additional case of persistent trophoblast after conservative surgery, eight women would need to be treated with methotrexate. Monitoring of the β-hCG concentrations would, therefore, seem to be a better option, provided that the woman is amenable to monitoring.

Medical treatment

Methotrexate

Treatment with methotrexate is an alternative to surgery in up to a quarter of women with unruptured ectopic pregnancy. Methotrexate is a folinic acid antagonist that blocks DNA, and to some extent RNA, synthesis and cell division. As a result, tissues with a rapid cellular turnover, such as trophoblasts, are most susceptible to its action. Two regimens are commonly used for the administration of methotrexate (table 2). The first involves administration of methotrexate and leucovorin on alternate days until β-hCG concentrations begin to drop. This regimen has a success rate (defined as avoidance of surgery) of 93%.[61,83,86] The second regimen involves administration of a single dose of methotrexate, followed by repeated doses a week apart if β-hCG concentrations do not fall by 15% between days 4 and 7. Single dose is a misnomer, however, since in many studies at least 13% of women need two doses and 1% need more than two doses.[86] Nevertheless, more than 90% of women treated with the second regimen avoid surgery.[63]

Serious adverse events—eg, severe neutropenia and alopecia—associated with short-term use of methotrexate are rare, but less serious side-effects—eg, nausea, vomiting, diarrhoea, gastritis, abnormal liver function tests, stomatitis, transient pneumonitis, and bone marrow suppression—are more common.[87] Severe neutropenia and alopecia are rare. In a review[61] of 26 studies of methotrexate, side-effects arose in 30% of women and 12% of those treated were admitted to hospital. There are two case reports of life-threatening neutropenia with fever after a single dose and three doses of intramuscular methotrexate.[88] Reversible alopecia is also reported.[89] Later sequelae of methotrexate treatment include a case of haematosalpinx and two pelvic haematocoeles after the normalisation of β-hCG concentrations.[90] An increase in abdominal pain is reported by up to two-thirds of women during the treatment, and in many women additional surveillance will be needed to detect tubal rupture.

One randomised controlled trial has been done to compare single-dose and multiple-dose regimens of methotrexate.[91] 51 women with a presumed ectopic pregnancy were randomly assigned single-dose or multiple-dose methotrexate. The β-hCG concentration for inclusion was less than 10 000 IU/L. Single-dose methotrexate was successful in 90% and multiple-dose in 86% of women. There was no evidence of a difference in median time to resolution and no difference in adverse events between regimens. The efficacy of single-dose and multiple-dose regimens have, however, been summarised in a meta-analysis[61] of the methotrexate groups of three randomised controlled trials and 23 non-randomised studies. The success rates (defined as not needing surgery) were 88% for single-dose therapy and 93% for multiple-dose therapy. It is noteworthy that this difference between dose regimens was much more pronounced when results were adjusted for β-hCG concentrations and the presence of fetal cardiac activity. There were fewer side-effects in patients treated with single-dose therapy than in those who received multiple doses. Among women in whom single-dose treatment was planned, 14% needed two or more doses. Although the evidence favours multiple-dose regimens, single-dose regimens where additional doses are given in accord with the β-hCG concentrations have similar success rates with less side-effects.

In clinically stable women, the β-hCG concentration at presentation is the most important determinant of failure of medical treatment. Overall, methotrexate is nearly 90% successful, irrespective of regimen, but success rates are inversely proportional to β-hCG concentrations. In a study[63] of 350 consecutive women who received single-dose methotrexate, the success rate of treatment was 92% in those who presented with a β-hCG of less than 5000 IU/L and 98% in those with β-hCG values of less than 1000 IU/L at presentation. Size of adnexal mass did not affect outcome. Lipscomb and

colleagues[63] concluded that previously identified relative contraindications to medical treatment might be invalid. A smaller, but more recent, study[92] presents a success rate of only 74% with single-dose methotrexate at β-hCG concentrations of more than 2000 IU/L.

Use of mifepristone as an adjunctive treatment to methotrexate for ectopic pregnancy has been assessed in two randomised controlled trials. Although results of initial pilot studies[93] seemed promising, those of a subsequent multicentre randomised trial[94] noted no benefit of the combined regimen over methotrexate alone. In the second trial,[95] involving 50 women, both treatment approaches were successful, but only one of 25 women in the mefipristone and methotrexate group needed a second dose of methotrexate, whereas in the methotrexate only group four of 25 needed a second dose. The time to resolve the unruptured ectopic pregnancy was also significantly faster in the group who received combination mifepristone and methotrexate.[95] Further studies are needed to consider the role and the cost of mifepristone in combination with methotrexate.

Medical versus surgical therapy

Four randomised controlled trials[65,83,86,93] have compared treatment with methotrexate with laparoscopic surgery. Two of the trials[65,96] compared single-dose regimens with laparoscopic salpingostomy, and the need for surgery for persistent trophoblast varied from 4% to 15%. In the trial that compared multiple-dose regimens with laparoscopic surgery,[83] 14% of the women assigned methotrexate needed surgery because of tubal rupture. There was no benefit in the direct injection of methotrexate.[97] There was no difference between the surgical and medical treatment groups in rates of tubal patency or subsequent intrauterine pregnancy.[83] Health-related quality of life was more severely impaired after repeated doses of systemic methotrexate than after laparoscopic salpingostomy,[97] but women who received single-dose methotrexate had much better physical functioning than those who were operated on.[65]

The costs of medical versus surgical treatments have been assessed in randomised and non-randomised trials.[70,98–102] One trial[98] reported that medical treatment with methotrexate was safe and effective when compared with salpingostomy, but that cost did not differ between the two options. However, if the cost of the diagnostic laparoscopy was not included in the analysis, there were cost savings with methotrexate. The investigators conclude that methotrexate could reduce the cost of treatment in women with low concentrations of β-hCG, in whom a diagnostic laparoscopy does not need to be done. Findings of another randomised controlled trial[99] indicate that if women suitable for treatment with methotrexate are identified, then direct costs are reduced by half. Longterm outcomes, such as the need for assisted conception and avoidance of repeat ectopic pregnancies, are generally not considered in cost-effectiveness analyses.

Expectant management

Expectant management of ectopic pregnancy is an option for women with early, unruptured ectopic pregnancies, and is successful in 50–70% of women.[60,103,104] In one study,[104] in women with β-hCG concentrations of 175 IU/L or less, treatment was successful in 96% of cases, whereas in those with β-hCG concentration of 175–1500 IU/L, expectant management was only effective in 66%. During follow-up, repeat monitoring through measurement of β-hCG concentrations and by transvaginal ultrasound is recommended until the β-hCG value is undetectable. Women suitable for expectant management should have declining β-hCG concentrations, though the threshold for treatment remains unclear and is a decision to be taken after discussion between the patient and her doctor.

Non-tubal and heterotopic ectopic pregnancies

95% of ectopic pregnancies are tubal, 2% are either interstitial or corneal, 2% are ovarian,[32] and the remainder are cervical or abdominal. There are increasing numbers of pregnancies reported within the scar left by caesarean section. No more than 18 cases had been described before 2002, but three case series[105–108] have been published since then, including a total of 38 patients. More than half of the women in these series had had two or more previous caesarean sections, suggesting that this type of ectopic pregnancy will become more frequent now that caesarean section is a popular option.

Heterotopic pregnancy is rare in spontaneous pregnancy (one in 10 000–50 000), but relatively common (0·3–1%) in pregnancies that arise after assisted conception.[23,109–111] Difficulties with diagnosis of ectopic pregnancies in women expecting more than one baby are common, resulting in late detection. Management is always surgical. Most women who have fertility treatment and who conceive are reviewed in the early weeks of pregnancy, and the diagnosis of ectopic pregnancy and heterotopic pregnancy should be considered.

Fertility after an ectopic pregnancy

Fertility after an ectopic pregnancy depends on how that pregnancy was managed and on the presence or absence of known risk factors. In a mean follow-up period of 28 months, 10% of 328 women with a history of ectopic pregnancy recorded in a large regional register[112] had a repeat ectopic pregnancy and 53% had babies after a viable pregnancy (although a third of these pregnancies resulted from in-vitro fertilisation). However, among these women, of those who had an initial ectopic pregnancy with an IUD in situ there were no repeat

ectopic pregnancies and 87% conceived within 1 year. Women who had had an ectopic pregnancy without an IUD in situ had a much lower rate of conception (44%), and repeat ectopic pregnancy was more likely (28%).

With respect to fertility after treatment for ectopic pregnancy, non-randomised studies[60] of expectant management showed rates of subsequent intrauterine pregnancy of 80–88% and rates of recurrent ectopic pregnancy of 4·2–5%, which is double the risk in the general population.[60] In women treated with methotrexate, 58–61% have subsequent intrauterine pregnancies and 7–8% have repeat ectopic pregnancies. The rate of intrauterine pregnancies in those treated with salpingostomy varies from 62% (3 years' follow-up) to 89% (7 years' follow-up), with a repeat ectopic pregnancy rate of 18%.[78–81] In women who have undergone salpingectomy, the rate of subsequent intrauterine pregnancy varies from 38% (3 years' follow-up) to 66% (7 years' follow-up) and the repeat ectopic pregnancy rate varies from 6–28%.[77] There are various difficulties in the interpretation of these studies because of their observational nature, however, and no definite conclusions can be drawn with respect to best choice of treatment. These figures can be used, however, as a guide.

Where should future research be focused?

Few well designed studies have been done into ectopic pregnancy—its prevention, management, and treatment. Randomised controlled trials to assess the benefits and harms of the three different management strategies—expectant management, medical management, and surgery—are a priority. All such studies should include longterm outcomes of fertility and repeat ectopic pregnancy, as well as health-related quality of life, treatment preferences, and cost-effectiveness analyses. Furthermore, registers of ectopic pregnancy, such as that set up in Auvergne, France,[2] should be created to identify risk factors and prognosis for future pregnancies.

Conclusions

The investigation and management of ectopic pregnancy has changed considerably over the past 15 years; the advent of β-hCG measurements and improved transvaginal ultrasound techniques has made laparoscopic diagnosis of ectopic pregnancy almost redundant and allowed for both expectant and medical management options. Improvements in laparoscopic surgery have meant that few women undergo the inconvenience and discomfort associated with open surgery, and tubal conservation is possible for many. There remain, however, important questions to be answered.

Conflict of interest statement

I was an investigator on the trial reported in reference 65, which was funded by Auckland Healthcare (a non-commercial organisation).

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