Ectopic pregnancy: an update

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Purpose of review

This review discusses recent publications that investigate the epidemiology, diagnosis and treatment of ectopic pregnancy.

Recent findings

Transvaginal ultrasound is being used with increasing confidence for the diagnosis of ectopic pregnancy, and methotrexate now has an established role in the treatment of ectopic pregnancy. No serum markers have been found that can reliably differentiate intrauterine from extrauterine pregnancy. As more experience has been gained with medical therapy, it is apparent that it is possible to identify a subgroup of women in whom it is unlikely to succeed. The use of adjunctive therapy such as mifepristone does not appear to increase the effectiveness of methotrexate. Screening for ectopic pregnancy in at risk women has been suggested, but it may be of only limited value. In the surgical management of ectopic pregnancy the effect on fertility of salpingotomy and salpingectomy remains uncertain, although recent cohort studies suggest that salpingotomy may be associated with a better subsequent intrauterine pregnancy rate than salpingectomy. A number of case reports of pregnancies at unusual sites continue to be published, but in the last 2 years there has been a dramatic increase in the number of caesarean scar pregnancies reported.

Summary

Medical therapy now has an established role in the treatment of ectopic pregnancy, but it is clear that careful patient selection is essential. In the surgical management of ectopic pregnancy the effects of salpingotomy and salpingectomy on subsequent fertility are uncertain and need further investigation.

Keywords

ectopic pregnancy, diagnosis, surgery, methotrexate

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Abbreviation

hCG human chorionic gonadotropin

1040-872X

Introduction

Ectopic pregnancy remains an important cause of morbidity in early pregnancy. There is evidence that its incidence in some countries is falling. Ultrasound has proven to be very reliable for its diagnosis but the addition of serum markers other than hCG has yet to prove helpful. For women treated surgically no clear evidence is yet available to determine if salpingotomy is preferred to salpingectomy. For medically treated patients a number of studies have attempted to reduce the failure rate of methotrexate by either using adjunctive therapy or determining which subgroup of women are most likely to be treated successfully. This review discusses recent publications that investigate the epidemiology, the diagnosis and both the medical and surgical management of ectopic pregnancy.

Epidemiology

There were 13 maternal deaths between 1997 and 1999 resulting from ectopic pregnancy in the UK and, despite falling mortality rates, ectopic pregnancy still accounts for 80% of first trimester maternal deaths [1]. Nearly 32 000 ectopic pregnancies are diagnosed in the UK annually [1]. The incidence in the UK appears to have changed little in the last decade, with 9.6 per 1000 pregnancies in 1991–93 and 11.1 per 1000 pregnancies in 1997–99 (1). In other countries, however, the incidence of ectopic pregnancy appears to be decreasing. Between 1990 and 2001, Norway reported a fall in incidence from 17.2 to 9.5 per 10 000 women years and a fall in the ratio of ectopic pregnancies to live births from 26.4 to 14.9 per 1000 [2]. In the USA, estimated yearly numbers of ectopic pregnancies have fallen from 58 178 in 1992 to 35 382 in 1999 [3]. It has been suggested that falling rates of pelvic inflammatory disease may be responsible for these changes in Norway [2]. In the USA, the increasing use of outpatient therapy for ectopic pregnancy has been shown to make incidence data increasingly unreliable [3] and this apparent fall in incidence may be an overestimate.

Diagnosis of ectopic pregnancy

Transvaginal ultrasound has largely replaced laparoscopy in the diagnosis of ectopic pregnancy, but the search for serum markers that reliably distinguish intrauterine from extrauterine pregnancy continues. The potential benefits and problems associated with using transvaginal ultrasound for screening for ectopic pregnancy in at risk women have also been recently investigated.

Assessment

In one recent UK series [4] of 4255 consecutive women presenting to an early pregnancy clinic, 86 of the 96 ectopic pregnancies treated surgically were visualized prior to laparoscopy and transvaginal ultrasound had a sensitivity of 89.9% and a specificity of 99.8%. Positive and negative predictive values of 92.5% and 99.8% were obtained. Similar findings from other centres suggest that transvaginal ultrasound can very reliably predict the presence of ectopic pregnancy and the role of laparoscopy as a diagnostic tool is limited to a small number of women with symptoms and normal ultrasonography [5,6].

Three-dimensional transvaginal ultrasonography

With such high levels of diagnostic accuracy being achieved with two-dimensional transvaginal ultrasonography, three-dimensional ultrasound seems unlikely to ever play a major role in the management of suspected ectopic pregnancy. One possible role is in the determination of the exact location of unusually sited ectopic pregnancies. This is highlighted by a recent case report of three-dimensional transvaginal ultrasonography being used to confirm a diagnosis of interstitial pregnancy [7], when the location of the ectopic pregnancy relative to the uterine cavity was unclear.

Serum markers

The value of a number of potential biochemical markers for ectopic pregnancy continues to be explored. After disappointing results with creatinine kinase [8] and fetal fibronectin [9], substances including glycodelin [10], smooth muscle heavy-chain myosin [11], leukaemia inhibitory factor [12], tumour necrosis factor [13] and IL-8 [13] have recently been evaluated. None have proved sufficiently sensitive or specific in the diagnosis of ectopic pregnancy. Markers have generally been early pregnancy proteins, or markers of inflammation or muscle damage, and so are unlikely to be able to differentiate reliably between intrauterine and extrauterine pregnancy. The ideal marker would be specific for tubal damage or only be present following endometrial implantation. Smooth muscle heavy-chain myosin [11] and leukaemia inhibitory factor [12], which respectively might be specific for tubal damage or endometrial implantation, do not appear to be sufficiently discriminatory.

Progesterone

A number of studies have assessed the role of progesterone in the noninvasive diagnosis of ectopic pregnancy or have incorporated it into a diagnostic algorithm [14,15]. However, it is primarily an indication of pregnancy viability rather than location. A value of 25 ng/ml (80 nmol/l) or more is associated with a normal intrauterine pregnancy in 98% of cases, while a value of less than 5 ng/ml (16 nmol/l) identifies a nonviable pregnancy, regardless of location [16]. Most women with an ectopic pregnancy will have a progesterone level between these concentrations at presentation, limiting the clinical usefulness of progesterone measurement in the diagnosis of ectopic pregnancy [17]. The most likely future role of progesterone measurement is in helping to direct treatment towards expectant, medical or surgical management [18].

Screening for ectopic pregnancy

The likelihood that with early detection of ectopic pregnancy more conservative treatment will be successful has led some authors to investigate the effectiveness of ectopic pregnancy screening programmes. In a decision-analysis study of women with at least one risk factor for ectopic pregnancy, Mol *et al.* [19] concluded that the cost-effectiveness of any screening programme is strongly dependent on the prevalence of ectopic pregnancy in the population screened. At a prevalence of 6%, a programme using transvaginal scanning and serum human chorionic gonadotropin (hCG) measurement would reduce the number of women with a ruptured ectopic pregnancy from 2.1 to 0.61 per 100 woman screened. At this prevalence, screening would cost approximately €933 per prevented tubal rupture, with 0.64 false positives (negative laparoscopies) per prevented tubal rupture. At a prevalence of 10% or more, screening becomes less expensive than watchful waiting because of the increased need for operative laparoscopy rather than medical management. In low-risk populations (an ectopic pregnancy rate of 1%) a potential increase in the rate of tubal rupture following screening exists because of the false-negative rate associated with screening. In a high-risk group, the benefit attributable to screening may be reduced by noncompliance with screening or women presenting with symptoms prior to screening.

Surgical therapy

A large proportion of women with an ectopic pregnancy will require surgical treatment. While a laparoscopic approach will be preferred for most of these women, the choice of salpingectomy or salpingotomy is controversial.

Salpingectomy or salpingotomy

There are no randomized controlled trials that specifically compare laparoscopic (or open) salpingectomy and salpingotomy. Systematic reviews published on this subject include data from observational studies, often a mixture of both cohort studies and case series, as well as a mixture of open and laparoscopic comparisons. These reviews suggest that there is no increase in the likelihood of subsequent intrauterine pregnancy after salpingotomy compared with salpingectomy. These data, however, must be interpreted with caution as the

included studies are subject to a wide range of biases relating to patient selection, surgical procedures used, length of follow-up and the proportion of patients lost to follow-up [20–26]. There are four recent cohort studies that specifically compare laparoscopic tube-sparing and radical treatments of ectopic pregnancy [27–29,30•]. Silva *et al.* [27] examined reproductive outcomes prospectively in 143 women undergoing laparoscopic salpingectomy or laparoscopic salpingotomy. The intrauterine pregnancy rates were similar when comparing the two groups (intrauterine pregnancy 60% after salpingotomy versus 54% after salpingectomy; relative risk 1.11, 95% CI 0.74–1.68). In a study of 155 women, Job-Spira *et al.* [28] reported subsequent intrauterine pregnancy rates with salpingotomy that were comparable to those following salpingectomy (hazard ratio 1.22, 95% CI 0.68–2.20). The cumulative pregnancy rates at 1 year were 72.4% after salpingotomy and 56.3% after salpingectomy. In a study by Mol *et al.* [23] of a cohort of 135 women, the fecundity rate ratio when comparing laparoscopic salpingotomy with salpingectomy during the 18-month follow-up period was 1.4 (95% CI 0.68–2.7) for women with a healthy contra-lateral tube and 3.1 (95% CI 0.76–12) for women with contra-lateral tubal disease. The 3-year cumulative pregnancy rate was 62% after salpingotomy and 38% after salpingectomy. In a recent study by Bangsgaard *et al.* [30•] reviewing a cohort of 276 women undergoing salpingotomy or salpingectomy, the subsequent cumulative pregnancy rate at 7 years was 89% following salpingotomy and 66% following salpingectomy (log rank $P<0.05$). The hazard ratio for intrauterine pregnancy following salpingectomy was 0.63 (95% CI 0.42–0.94) when compared with salpingotomy.

In summary, only one of these studies shows a significant difference in fertility after salpingotomy compared with salpingectomy, suggesting that there may be a higher subsequent intrauterine pregnancy rate associated with salpingotomy [30•]. Data from future randomized controlled trials examining this question are urgently needed.

Medical therapy

Medical therapy has an established place in the treatment of ectopic pregnancy, and in selected patients it appears to be as effective as surgery. It is clear, however, that many women with an ectopic pregnancy are not suitable for medical therapy and recent studies have investigated possible ways of improving the efficacy of medical therapy and better predicting in whom medical treatment will be successful.

Comparing medical and surgical therapy

As well as numerous case series reporting on methotrexate therapy, two recent randomized trials have compared methotrexate therapy in its most widely used form with laparoscopic surgery [31,32]. Comparing systemic methotrexate (at a dose of 1 mg/kg) with conservative laparoscopic surgery, Saraj *et al.* [32] found a 78% success rate (30 of 38 women) for one dose of methotrexate compared with 92% (34 of 37 women) for laparoscopic surgery (difference not significant). In the methotrexate group 16% (six women) required additional methotrexate and 5% (two women) required surgery during follow-up. Eight percent (three women) of the laparoscopic surgery group had persistent trophoblast. In a second randomized trial comparing methotrexate (50 mg/m^2) with conservative laparoscopic surgery, Sowter *et al.* [31] reported success rates of 65% (22 of 34 women) for a single dose of methotrexate and 93.0% (26 of 28 women) for laparoscopic surgery (95% CI of difference in success rate 10–47%; $P<0.05$). Nine women (26%) in the methotrexate group required more than one dose of methotrexate and five women (15%) underwent laparoscopy during follow-up. Two women in the laparoscopy group had persistent trophoblast. An economic evaluation conducted alongside the trial showed medical treatment associated with reduced direct and indirect costs [33], although at hCG levels above 1500 IU/l these benefits were lost due to the need for prolonged follow-up and surgical intervention.

Improving the efficacy of medical therapy

In early reports of medical therapy, systemic methotrexate was used in a multiple dose regime of 1 mg/kg of methotrexate intramuscularly alternating daily with 0.1 mg/kg of leucovorin for up to four doses of each drug [34,35]. Treatment side effects and the observation that some women only require one dose of methotrexate have led to the use of a single dose of methotrexate therapy (at a dose of 50 mg/m^2) with further doses being given 1 week later if hCG levels had failed to fall by at least 15% between day 4 and day 7 after treatment. The efficacy of single and multiple-dose regimens have recently been compared in a metaanalysis of all available studies [36]. This metaanalysis of 26 studies included 267 women receiving a multiple-dose treatment and 1067 treated with single-dose therapy. The success rates (defined as not requiring surgery) were 88.1% (940 of 1067) for single-dose therapy and 92.7% (241 of 260) for multiple-dose therapy, but the chances of failure were greater with single-dose therapy (odds ratio 1.71; 95% CI 1.04–2.82). Importantly, this difference was much more marked when results were adjusted for serum hCG values and the presence of fetal cardiac activity (odds ratio 4.74; 95% CI 1.77–12.62). Side effects were lower with single-dose therapy (odds ratio 0.44; 95% CI 0.31–0.63). Amongst women who were due to receive a single dose, 13.6% required two or more doses. These results suggest that it may be time to re-evaluate the role of multiple-dose therapy in selected women.

The use of adjunctive therapy in the form of an antigestational agent – mifepristone – has recently been evaluated. Initial pilot studies appeared promising [37], but in a subsequent multicentre randomized trial [38••], mifepristone did not improve the efficacy of methotrexate therapy: 212 women were treated with either methotrexate and placebo or methotrexate and mifepristone (600 mg orally) and success rates of 79.6% (90/133) and 74.2% (72/97) were found in the two groups. However, in a sub-group of women with progesterone levels greater than 10 ng/ml, the mifepristone–methotrexate group had a success rate of 83.3% (15/18) versus 38.5% (5/13) in the methotrexate only group. The role of mifepristone in this group merits further study.

The route of methotrexate administration has also been recently revisited. Most recent case series have reported on intramuscular rather than local ultrasound-guided methotrexate administration and there is a wide variation in reported success rates [25,26]. No randomized trial comparing route of administration has been undertaken, but in a recent review [39] of 137 women treated by either intramuscular (50 mg/m^2) or local ultrasound-guided administration (1 mg/kg) the overall success rate was 67.1% and 92.5% in the two groups. Multivariate analysis confirmed a higher success rate with locally administered methotrexate (odds ratio 9.7; 95% CI 3.1–30).

Predicting methotrexate failure

It is becoming increasingly apparent that in clinically stable women the serum hCG level at presentation is the most important factor in the failure of medical treatment. In a recent prospective cohort study of 50 women with an ectopic pregnancy treated with single-dose methotrexate, a success rate of 97% was found at an hCG level below 2000 IU/l, falling to 74% at levels above 2000 IU/l. Ectopic pregnancy size was not associated with treatment failure [40]. Similar results have been reported in two recent retrospective studies. Tawfiq *et al.* [41] reported on 60 patients treated with a single-dose methotrexate regimen and found a 92.5% success rate in women with a serum hCG level below 4000 IU/l, falling to 35% at serum levels above 4000 IU/l (odds ratio 52; 95% CI 4.88–556). Potter *et al.* [42] reported on 81 women similarly treated and found success rates of 98% in women with hCG levels of less than 1000 IU/l, falling to 80% at levels between 1000 and 4999 IU/l and 38% at levels above 5000 IU/l.

Nontubal ectopic pregnancies

A steady number of case reports and small case series continue to be published describing ectopic pregnancies at unusual sites. Most case reports have described successful or unsuccessful treatment with systemic or local methotrexate or by operative laparoscopy. Such reports are useful in guiding clinicians managing these rare problems, but they should be used with caution as factors such as serum hCG level, ectopic size, or the presence of active bleeding might be relevant to treatment success and this may not be apparent in single case reports.

One type of nontubal pregnancy that has been recently described in much larger case series than previously is caesarean section scar pregnancy. No more than 18 cases had been described in the literature prior to 2002, but three case series have been published since then, including a total of 38 patients [43–45]. There is no obvious reason for this apparent increase, but it may be the result of greater awareness of this type of ectopic pregnancy and an increase in caesarean section rates worldwide. In one of these recent series the incidence of caesarean scar pregnancy was 0.13% (10/7980 pregnancies) for women with a previous section and this form of ectopic pregnancy represented 5% (10/198) of ectopic pregnancies in women with at least one previous caesarean section. Another series reported an incidence of one per 1800 women attending an early pregnancy clinic [45].

A common definition [46] has been adopted in these recent case series. Diagnostic criteria included (1) the trophoblast must be mainly located between the bladder and the anterior uterine wall; (2) no fetal parts must be visible within the uterine cavity; (3) on a sagittal view, a discontinuity in the anterior wall of the uterus should be identified. It has been suggested that caesarean scar pregnancies are of two types [46]. One is due to implantation of the gestation sac on the scar with progression either towards the cervico-isthmic space or towards the uterine cavity. Such a pregnancy may progress normally or be treated medically, but with an increased risk of haemorrhage from the implantation site. The other type is a deep implantation into a post-caesarean section scar defect with progression towards rupture and bleeding during the first trimester of pregnancy. In this type prompt surgical treatment may be preferred. More than 50% of the women in these recent series had two or more previous caesarean sections and this type of ectopic pregnancy may become more frequent as caesarean section rates remain high.

Conclusion

A combination of transvaginal ultrasound and serum hCG measurement can reliably diagnose ectopic pregnancy in most women, although in asymptomatic women screening is probably only effective in very high risk groups. Data from randomized trials are required to assess the role of salpingotomy and salpingectomy in surgically treated women. For medically treated women with high hCG or progesterone levels, further evaluation

of more frequent methotrexate administration and the use of adjunctive therapy such as mifepristone are needed, as it is increasingly clear that currently used single-dose regimes can only be confidently used in women presenting at low serum hCG levels.

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