Symposium: Tubal disease and fertility outcome

Controversies in the management of ectopic pregnancy

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Abstract

Ectopic pregnancy is a common clinical problem, but there appears to be much controversy surrounding the surgical management of its occurrence. This paper reviews the available evidence on the management of ectopic pregnancy. The discussion focuses initially around the choice of medical versus surgical treatment. Next, the question is addressed that if surgical management is deemed necessary, whether the approach should be laparoscopic or via open laparotomy. Lastly, if surgery is undertaken, should salpingectomy or salpingotomy be performed? Laparoscopy will remain the main method of treatment for women with ectopic pregnancy, as it provides obvious advantages over open surgery. On balance, salpingotomy should be the surgical treatment of choice for the majority of women with ectopic pregnancy, as it results in a higher subsequent pregnancy rate, although there is a slightly higher recurrent ectopic pregnancy rate and persistent trophoblastic disease rate when compared with women treated with salpingectomy. There is also a place for medical treatment of women with low concentrations of human chorionic gonadotrophin. A variable dosing methotrexate regimen is more effective compared with single dose regimen, and the fixed multiple regimen is associated with a high rate of side effects.

Keywords: ectopic pregnancy, methotrexate treatment, salpingectomy, salpingotomy

Introduction

Ectopic pregnancy occurs in approximately 1 in 150 pregnancies; for such a common anomaly, there seems to be a great deal of controversy, extending from the aetiology of the disease to its clinical management. It is still relatively unclear why the fertilized embryo stops and develops in the Fallopian tube instead of the uterine cavity. There is also much disagreement regarding the best surgical management of this occurrence.

With the advent of transvaginal ultrasound scanning, serum beta-human chorionic gonadotrophin (βHCG) measurements and improved clinical algorithms, clinicians are getting better at the early diagnosis of the condition. With the advent of minimal access surgery, laparoscopic management of ectopic pregnancy appears to be favoured by many patients and surgeons. There has also been increasing use of medical management compared with surgery.

Conservative management of ectopic pregnancy includes expectant management and medical management. As a general principle, conservative management should be considered as a first-line treatment, provided that the overall clinical picture suggests that it is safe to do so. There have been several excellent reviews on the expectant and medical management of ectopic pregnancy (Hajenius et al., 2007), and there seems to be a well-accepted consensus on these aspects of management. In contrast, there are still a number of controversies regarding the surgical management of ectopic pregnancy.

This paper reviews the available evidence on the management of ectopic pregnancy. The discussion focuses initially around the choice of medical versus surgical treatment. Next, the question is addressed that if surgical management is deemed
necessary, whether the approach should be laparoscopic or via open/laparotomy. Lastly, if surgery is undertaken, should salpingectomy or salpingotomy be performed?

Medical versus surgical treatment

Should medical or surgical treatment be the primary treatment of choice? There are many advantages for medical treatment compared with surgery. It is relatively non-invasive, possibly cheaper and relatively ‘skill free’ to administer. Currently, the most commonly used form of medical treatment is methotrexate, a chemotherapeutic drug given at a dose of 1 mg/kg or based on surface area calculation of 50 mg/m². Methotrexate may be given in a single or multiple doses. There are currently no randomized controlled trials on medical treatment versus salpingectomy. For the purpose of this review, only the use of the two main forms of methotrexate systemic treatment (single or multiple doses) versus salpingotomy will be discussed.

Systemic single/variable dose of methotrexate versus laparoscopic salpingotomy

The Cochrane review combined four randomized controlled trials involving 265 women with a small unruptured tubal ectopic pregnancy (Fernandez et al., 1998; Saraj et al., 1998; Sowter et al., 2001; El-Sherbiny et al., 2003). The combined results showed that one single dose of systemic methotrexate intramuscularly was significantly less successful than laparoscopic salpingotomy in the elimination of tubal ectopic pregnancy (OR 0.38, 95% CI 0.20–0.71). This was mainly due to the inadequate fall in serum HCG concentrations, for which an additional injection was required. However, if there was a flexible protocol and a ‘variable dose’ regimen was followed, then treatment success rose, and the combined results showed no evidence of a difference with laparoscopic salpingotomy (OR 1.1, 95% CI 0.52–2.3). However, this will mean that some women will require a second dose of methotrexate. Three studies examined tubal patency in a total of 115 women and found no significant differences between single/variable dose methotrexate treatment versus laparoscopic salpingotomy (Saraj et al., 1998; Sowter et al., 2001; El-Sherbiny et al., 2003). There was also no significant difference in the subsequent intrauterine pregnancy rate. There were no adverse effects in the laparoscopy group although in the methotrexate group there were two cases of minor mouth ulcerations, two cases of dry eyes and a further case of vaginal dryness.

Fixed multiple-dose intramuscular injection versus laparoscopic salpingotomy

Hajenius et al. (1997) described a multicentre trial involving 100 haemodynamically stable women with a laparoscopically confirmed ectopic pregnancy (Hajenius et al., 1997). These women were randomized into either having systemic methotrexate (days 1, 3, 5, 7) or laparoscopic salpingotomy. The Cochrane authors reported a ‘non-significant tendency to a higher treatment success with systemic methotrexate treatment (OR 1.8, 95% CI 0.73, 4.6)’ (Hajenius et al., 2007). There was no significant difference in tubal patency, intrauterine pregnancy or repeat pregnancy rate. However, a significant proportion of women in the methotrexate group reported complications or side effects (61%) compared with 12% in the salpingotomy group.

Is it worth the trade-off?

From the above discussion, one can conclude that the flexible/variable dosing regime and fixed multiple dosing regimen are just as effective as laparoscopic salpingotomy, whilst the single dose regimen is less effective. However, multiple doses of methotrexate are associated with a higher rate of side effects. Methotrexate is a folic antagonist, and can be associated with serious side effects such as myelosuppression, hepatitis, gastrointestinal mucositis, pleuritis, alopecia, dermatitis, renal and possible teratogenic effects. Hence, it is vital that both gynaecologists and patients understand these side effects.

Selection criteria

Studies have used various criteria as guidance as to the suitability of patients to undertake medical management. These include: serum HCG not more than 500 IU/l (Sowter et al., 2001) or 10,000 IU (El-Sherbiny et al., 2003); no fetal heart seen on ultrasound scan (Saraj et al., 1998; Sowter et al., 2001; El-Sherbiny et al., 2003); ectopic pregnancy of relatively small size no more than 3.5 cm (Saraj et al., 1998; Sowter et al., 2001) or 4 cm (El-Sherbiny et al., 2003); and no signs of active bleeding.

In the authors’ unit, the protocol is a flexible/variable regime. A single dose methotrexate regime is used if the serum HCG is low (3000 IU/l), the patient is haemodynamically stable with minimal symptoms, and has no contraindications for the use of methotrexate. However, there is a strict follow-up protocol, and patients who have a suboptimal fall of HCG (<15%) between days 4 and 7 may require a second dose of methotrexate. No doubt, different gynaecological units will have different protocols that are suited to the local facilities and needs. Regular audits, training and education of healthcare professionals would help to ensure that the protocol continues to be effective.

When is surgery necessary?

Surgery may offer many significant advantages in the management of ectopic pregnancies compared with medical treatment. Firstly, in the vast majority of cases, a firm diagnosis of the presence or absence of an ectopic pregnancy can be made. Secondly, follow-up arrangements are generally less prolonged and less demanding. Thirdly, after surgery patients can attempt to conceive as soon as they recover from the operation whereas if a chemotherapeutic agent such as methotrexate is used, patients will have to wait at least 3 months because of the potential teratogenic effects of methotrexate.

Laparotomy or laparoscopy?

The laparoscopic approach offers significant advantages when compared with laparotomy, as it results in less blood loss, a shorter hospital stay, shorter operating time, less analgesia, and a shorter convalescence than laparotomy. One might expect that in this
day and age there remains very little role for laparotomy in the management of ectopic pregnancies. However, it should be emphasized that many around the world would still justifiably be performing laparotomy on patients with ectopic pregnancies, due to the lack of endoscopic facilities. There have been three randomized controlled trials published in the early 1990s examining the effectiveness of laparotomy versus laparoscopy in the treatment of ectopic pregnancy. Combining the results of these three studies, the Cochrane review (Hajenius et al., 2007) reported that laparoscopic salpingotony is less successful than laparotomy salpingolomy in the elimination of tubal pregnancy (RR 0.90, 95% CI 0.83–0.97). This resulted mainly from the higher persistent trophoblastic rate in the laparoscopic surgery group (RR 3.6, 95% CI 0.63–21). There was, however, no difference in the future number of intrauterine pregnancies (IUP) (RR 1.2, 95% CI 0.88–1.5) or the repeat ectopic pregnancy rate (RR 0.43, 95% CI 0.15–1.2) between the laparoscopic group compared with the laparotomy group.

The higher persistent trophoblastic rate in the laparoscopic salpingolomy group suggests that there is a trade-off for the various advantages of laparoscopic conservative surgery (salpingolomy) in the management of ectopic pregnancy. The likely explanation is that surgeons were better able to completely remove the ectopic tissue from the tube during laparotomy than at laparoscopy. This is not at all surprising, given that all the randomized controlled trials were conducted in the 1990s, when laparoscopic skills were not as well established and instruments were not as refined. Many surgeons were in the 'learning phase' of laparoscopic surgery. The results could have been quite different if the randomized controlled trials were conducted today. Nevertheless, it does highlight the need to pay meticulous care to the complete removal of the ectopic tissue during laparoscopic salpingolomy, and to ensure that trainees acquire the proper skills in this respect. Furthermore, it is important to highlight that there were no randomized controlled trials comparing laparoscopic salpingolomy with laparotomy salpingolomy. On balance, there is little place for open surgery in the routine management of women with ectopic pregnancy, except for the rare incidences of a severely compromised patient, and this view is reciprocated by many other gynaecologists (Orazi and Cosson, 2003; Garry, 2006; Takaes and Chakhtoura, 2006). Most gynaecologists will resort to a route that will stop the bleeding quickly when patients are in hypovolaemic shock with a large amount of haemoperitoneum, and in most centres this will be via laparotomy.

Salpingectomy or salpingolomy?

Once surgical treatment is decided, the next question is whether one should remove the Fallopian tube or not. In terms of the reproductive outcome, some reviewers have suggested that salpingectomy offers very little advantage to salpingolomy, whilst others seem to claim that the pregnancy rate for salpingolomy is higher than salpingectomy. A critical appraisal of the literature has been performed, with respect to whether salpingolomy or salpingolomy was a more effective method of treatment. The first and foremost concern for many gynaecologists would be the issues surrounding future fertility post-salpingolomy or salpingolomy.

Reproductive outcomes

Subsequent intrauterine pregnancy rate

Studies examining the pregnancy rates of women after salpingectomy or salpingolomy were all retrospective and observational. There is, to date, no randomized controlled trial comparing the two surgical techniques. The systematic reviews of many studies suffer from the deficiency of performing comparisons on studies that are of various different characteristics; furthermore, many of these studies did not adjust for confounding factors such as age, social factors and tubal damage; and hence caution should be exercised in the interpretation of these results. For example, in the study by Bouyer et al. (2000), the mean age of the women in the salpingectomy group was significantly higher than the conservative group, and age is an important determinant of fertility. Furthermore, earlier meta-analysis combined studies that were significantly different in characteristics such as the inclusion of women who underwent both laparoscopic and open surgery (Clausen, 1996); and some studies included women who had partial as well as complete salpingolomy (Yao and Tulandi, 1997). For example, Yao and Tulandi (1997) identified nine comparative studies published from 1960 to 1993, and reported that among the 2635 total patients, 528 in the salpingolomy group and 1246 in the salpingeciomy group desired fertility. The rate of subsequent IUP was comparable in the two groups: 53% in the salpingolomy group and 49.3% in the salpingectomy group. In a review by Clausen et al. (1996), who reviewed 40 studies over 40 years, a 46% IUP rate for salpingolomy and 44% IUP rate for salpingolomy was reported. Thus, it would appear that if one analysed the results of earlier studies, the pregnancy rates were similar for salpingolomy versus salpingectomy. Both these meta-analyses have included studies that were performed during the 'prelaparoscopy' era and as well as 'early laparoscopic experience'. Laparoscopic surgery has only been developed in the early 1990s, and since then there has been significant advancement in techniques, technology and equipment. In order to minimize the discrepancy in results due to technological advances in laparoscopic equipment and skill between the 'pre- and post-1990s era', it has been decided to analyse the results of studies performed after the 1990s; there were four recent observational studies controlled for confounding factors such as age, presence of tubal pathology and social factors examining the reproductive outcome of salpingolomy versus salpingolomy (Table 1). Combining the results, the IUP rate of conservative surgery is 68%, compared with that of radical surgery (48%). Bouyer et al. (2000) (not included in the meta-analysis, as no raw data provided), in a population study of 835 ectopic pregnancies in France registered between 1992 and 1996, found that among 291 women attempting to become pregnant, the 18-month cumulative rates of spontaneous IUP were 57 (95% CI 44–70) for salpingolomy versus 73% (95% CI 65–80) with salpingolomy. Thus, overall, there appears to be a higher pregnancy rate for women with salpingolomy compared with salpingectomy.

Presence of contralateral damaged Fallopian tube

Several studies have examined the pregnancy rate in women with contralateral tubal disease and show a trend towards a higher rate of subsequent intrauterine pregnancy following
laparoscopic salpingotomy compared with salpingectomy. This led to the recommendation by the Royal College of Obstetricians and Gynaecologists that ‘salpingotomy should be considered as the primary treatment... in the presence of contralateral tubal disease...’ (Royal College of Obstetricians and Gynaecologists, 1999). However, it is well accepted that visual inspection of the external appearances of the Fallopian tube during laparoscopy may not necessarily be an accurate assessment of the presence or absence of tubal disease. It could therefore be argued that even in the presence of a normal tube, one should give the patient the benefit of the doubt and aim to perform a salpingotomy wherever possible, unless there is evidence of gross hydrosalpinx or severely damaged tube in the ipsilateral tube. In such cases, salpingotomy, i.e. leaving the diseased tube, may compromise the success of IVF (Ozmen et al., 2007).

Repeat ectopic pregnancy rate

One of the main arguments for performing a salpingectomy instead of salpingotomy is to eliminate the likelihood of a repeat ectopic pregnancy. However, Yao and Tulandi’s (1997) meta-analysis of nine studies reported that the recurrent ectopic pregnancy rate after salpingectomy was 9.9%, which was only slightly lower than 14.8% after salpingotomy. This was comparable with a study by Clausen et al. (1996) that reported a recurrent ectopic pregnancy rate of 15% after salpingotomy compared with 10% after salpingectomy. In addition, further recent larger cohort studies have shown that if confounding factors such as evidence of tubal damage, age and social factors were removed from the analysis, the rate of recurrent ectopic pregnancy from either salpingectomy or salpingotomy is more or less the same (Job-Spira et al., 1996; Mol et al., 1998; Bouyer et al., 2000; Bangsgaard et al., 2003). The rather high repeat ectopic pregnancy rate following salpingectomy almost certainly occurred as a consequence of repeat ectopic pregnancy recurring in the contralateral tube. Women should therefore be counselled appropriately, that laparoscopic salpingectomy for ectopic pregnancy only slightly but not substantially reduces the likelihood of a subsequent pregnancy being an ectopic. The literature gives little data on whether a recurrent ectopic pregnancy after salpingotomy is more likely to be ipsilateral or contralateral. Needless to say, meticulous surgical technique, accurate case selection and precise diagnosis can no doubt reduce the risk of recurrent ectopic pregnancy on the same side (Nardo, 2005). Furthermore, recent developments in robotic surgery may further contribute to the ‘fine-tuning’ of surgical techniques, leading to less inflammation at the surgical site and less adhesion formation (Bocca et al., 2007). Nevertheless, whether a patient had salpingectomy or salpingotomy, she should be counselled appropriately for the risk of recurrent ectopic pregnancy in future pregnancies.

Ovarian function

One possible complication of salpingectomy is the impairment of blood supply to the ovary and thus ovarian reserve. In attempting to minimize the complication of salpingectomy, i.e. compromise of ovarian blood supply, some surgeons advocate partial salpingectomy, i.e. only removing the distal part of the tube, and leaving the proximal stump. However, this is not advisable, for two reasons. Firstly, leaving the stump may increase the likelihood of ectopic pregnancy following IVF, and secondly, leaving a long stump behind may have a similar effect to that of a hydrosalpinx, adversely affecting pregnancy rate and increasing miscarriage rate following IVF. Considering the anatomical relationship between the ovary and the Fallopian tube (Figure 1), it becomes apparent that the infundibuloo–ovarian ligament is in close proximity to the suspensory ligament of the ovary; the latter carries the ovarian artery, which together with the collaterals from the uterine artery, forms the main blood supply to the ovaries. Hence, whilst performing a salpingectomy, one must keep close to the Fallopian tube and away from the suspensory ligament, otherwise there is a risk of compromising the blood supply to the ovary. The use ofatraumatic forceps to help elevate the Fallopian tube away from the suspensory ligament of the ovary will allow the surgeon to divide the infundibulo-ovarian ligament without significantly compromising the blood supply from the ovarian artery (Figure 2). Several studies have reported a decrease in ovarian function in women who had salpingectomy compared with those who had salpingotomy (Lass et al., 1998; Chan et al., 2003; Meng and

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Table 1. Reproductive outcome after conservative versus radical surgery for ectopic pregnancy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration of follow-up (years)</th>
<th>Total number of patients treated</th>
<th>Conservative surgery No. of patients attempting to conceive</th>
<th>Radical surgery No. of patients attempting to conceive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangsgaard et al., (2003)</td>
<td>1.5</td>
<td>276</td>
<td>208 (161 (77))</td>
<td>68 (39 (57))</td>
</tr>
<tr>
<td>Mol et al., (1998)</td>
<td>3</td>
<td>237</td>
<td>56 (30 (54))</td>
<td>79 (24 (30))</td>
</tr>
<tr>
<td>Ory et al., (1993)</td>
<td>3</td>
<td>188</td>
<td>38 (19 (50))</td>
<td>50 (29 (58))</td>
</tr>
<tr>
<td>Silva et al., (1993)</td>
<td>N/A</td>
<td>143</td>
<td>60 (36 (60))</td>
<td>26 (14 (54))</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>844</td>
<td>362 (246 (68))</td>
<td>223 (106 (48))</td>
</tr>
</tbody>
</table>

IUP = intrauterine pregnancies; N/A = not available.
Figure 1. Anatomical relationship of the ovary and Fallopian tube: (A) suspensory ligament of ovary; (B) infundibulo-ovarian ligament; 1: medial tubal artery; 2: lateral tubal artery; 3: uterine artery; 4: ovarian artery; 5: anastomosis of medial and lateral tubal arteries.

Figure 2. Fallopian tube with ectopic pregnancy. A complete salpingectomy is outlined by the grey dotted line. A partial salpingectomy is performed if the tube is transected at the position outlined by the white dotted line.

Zhu, 2006). Most of these studies performed ovarian function assessment by measuring antral follicular count, ovarian volume and ovarian stromal flow by power Doppler ultrasonography (2D or 3D). Although Meng and Zhu (2006) and Lass et al. (1998) found no difference in pregnancy rates between women who had previous salpingectomy and the control group, they showed that the salpingectomy group had significantly fewer follicles and number of oocytes retrieved. The findings of these studies imply that surgery does impact on the functional physiology of the ovaries and hence in carrying out a salpingectomy, a complete salpingectomy, paying careful attention to ovarian blood supply, is more preferable to a partial salpingectomy.

Technical aspects

Many surgeons regard salpingectomy as an easier procedure to perform in comparison to salpingotomy. Laparoscopic salpingectomy can be performed by using pre-tied ligatures, coagulation of the mesosalpinx with monopolar or bipolar diathermy forceps and cutting with scissors or the use of laser or staplers. Bipolar diathermy and laparoscopic scissors is simple and safe, and with the appropriate training, the necessary surgical skill may be easily acquired.
On the other hand, salpingotomy is usually performed by making an incision at the anti-mesenteric border of the Fallopian tube. This can be achieved with diathermy scissors, monopolar needle diathermy or laser. None of these methods has been shown to be better or worse than the other. Fujishita et al. (2004) showed that the cumulative pregnancy rate, the adhesion formation/reformation rate and the tubal patency rate was similar whether the opening of the tube was sutured or not (Fujishita et al., 2004). Bleeding from the diathermy site can be a troublesome problem. If extensive diathermy was applied to these bleeding sites, the tubal mucosa could be damaged. It has been suggested that local injection of vasopressin during the operation into the ectopic pregnancy might decrease bleeding; however, this has only been supported by a very small trial (Ugur et al., 1996). Furthermore, vasopressin may rarely be associated with serious cardiovascular side effects.

The use of hydrosalpingography is a useful method for ‘teasing’ through the trophoblastic tissue without the need to use the grasping forceps. If the entire gestational sac was expelled in one, rather than being removed ‘piece-meal’, the risk of persistent bleeding from the trophoblastic bed is less likely. The use of micro-diathermy can reduce the amount of tubal damage caused by diathermy as bleeding sites can be diathermed with point accuracy. Gentle tissue handling is also vital in the prevention of future peritubal adhesions, and this can be achieved by usingatraumatic instruments (e.g. atraumatic forceps) and by gently handling the Fallopian tube. At the end of the operation, adequate use of suction and irrigation to remove all residual blood in the pelvis is important to reduce the chances of fibrin deposition and adhesion formation/reformation. Some surgeons advocate the use of an adhesion prevention solution such as 4% icodextrin (Adept; Baxter Healthcare Limited, USA) which utilizes the hydrodilatation theory to prevent adhesion formation/reformation.

Incomplete treatment

Persistent trophoblastic disease (PTD) is exceedingly rare in women who have salpingectomy. However, PTD can occur in up to 8% of women who underwent salpingotomy. Hence, it is essential that following salpingotomy, women should be offered follow-up with β-HCG measurement so that treatment can be instituted if the β-HCG concentrations have not fallen satisfactorily. Methotrexate treatment appears to be the most effective treatment in such a scenario, and most women will respond to a single dose of methotrexate treatment at 50 mg/m² or 1 mg/kg.

Salpingectomy or salpingotomy?

It would appear from this review of the current literature that salpingotomy compared with salpingectomy is associated with a higher future pregnancy rate, a slightly higher recurrent ectopic pregnancy rate and a higher persistent trophoblastic disease rate, but it is less likely to compromise ovarian blood supply and ovarian function. On balance, current evidence supports salpingotomy as the surgical treatment of choice unless there is uncontrollable bleeding or the tube is grossly diseased.

Conclusion

Laparoscopy will remain an important aspect of treatment for women with ectopic pregnancy, as it provides obvious advantages over open surgery. Salpingotomy should be the surgical treatment of choice for the majority of women with ectopic pregnancy, as it results in a higher subsequent pregnancy rate. There is also a slightly higher recurrent pregnancy rate and a slightly higher persistent trophoblastic disease rate when compared with women treated with salpingectomy. There is a place for medical treatment in women with low HCG concentrations. A variable dosing methotrexate regimen is more effective compared with the single dose regimen, but the fixed multiple regimen is associated with a high rate of side effects.

References


Chan CC, Ng EH, Li CF, Ho PC 2003 Impaired ovarian blood flow and reduced antral follicle count following laparoscopic salpingectomy for ectopic pregnancy. Human Reproduction 18, 2175–2180.


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