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Methotrexate in tubal pregnancy (reply)

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SIR—Essentially, Petra Hajenius and colleagues¹ report that systemic methotrexate and laparoscopy were equally successful in managing haemodynamically stable patients with unruptured tubal pregnancy. This is an important finding because it shows that laparoscopy remains the optimum treatment for such cases, and medical management seems to have little to commend it. Both methods involve a diagnostic laparoscopy to confirm the diagnosis and assess the state of the pelvis and tubal pregnancy to exclude those cases in whom medical therapy is likely to be unsuccessful.

Women managed laparoscopically are treated at the time of diagnosis, whereas medical treatment involves giving otherwise healthy young women a systemic cytotoxic drug and folic acid over 7 days, with the added inconvenience of having to avoid sunlight (and alcohol) during this time and to have several mouthwashes each day. There is no benefit in terms of inpatient hospital stay because patients undergoing laparoscopic salpingostomy can easily be treated as day cases.² There is no benefit in terms of follow-up because patients having methotrexate have to be monitored for an indeterminate time until resolution of the ectopic mass is confirmed on ultrasound. Nor is there benefit in reduced complications—indeed the converse is true in this study (61% *vs* 22% in the salpingostomy group, with 4% of patients having major complications of Stevens-Johnson syndrome and colitis after methotrexate).

Although treatment costs were not compared in this study, we suspect there are no financial benefits to medical treatment either, and certainly laparoscopic management is less disruptive to the patient.

Laparoscopic surgery is becoming the standard of care in many hospitals, especially for the management of ectopic pregnancy. The benefits of laparoscopic management over laparotomy are well proven.^{3,4} The situation seems to be the same with respect to medical treatment. Not only does laparoscopic salpingostomy seem to be the optimum management for the unruptured tubal pregnancy, but laparoscopic surgery is also the more versatile treatment option as it can be

used to manage cases with tubal rupture by laparoscopic salpingectomy.⁵ The skills are therefore well worth acquiring.

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- 1 Hajenius PJ, Engelsbe S, Mol BWJ, et al. Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. *Lancet* 1997; **350**: 774–79.
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SIR—I have several comments about Petra Hajenius and colleagues' report.¹ First, laparoscopic salpingostomy is the treatment of choice in patients with tubal pregnancy. The reported failure rate, or rate of persistent ectopic pregnancy, ranges from 3% to 29%.² Treatment of persistent ectopics with a single dose of methotrexate has been successful in 62 of 64 reported cases.³ In France, in a regional database of all ectopic pregnancies, the failure rate after conservative laparoscopic treatment was only 3.5% in 1996. It is therefore surprising that this randomised trial recorded 28% with persistent trophoblast and a need for rescue salpingectomy in 8%. This is the first reported series in which the total failure rate was so high. The main difficulty in this trial is the quality of the control group, and I believe that we need further experience in laparoscopy treatment before doing a randomised trial.

Second, methotrexate can be given systemically (intramuscularly) or by local injection under ultrasound or laparoscopic guidance. Studies that used single-dose methotrexate (1 mg/kg body weight or 50 mg/m²) have shown the same success rate. Why did Hajenius and colleagues use four doses given intramuscularly with 61% having side-effects? Moreover, folic acid was given but pharmacokinetic analysis has shown that the use of citrovorum rescue was unnecessary.⁴ With only one dose the incidence of side-effects ranged from none to 34% in patients treated systemically and always less than 5% in those treated locally.

So, the protocol for methotrexate is not, in my opinion, appropriate according to published data. Additionally, one of the main advantages of medical treatment is its non-invasiveness and there is little value of laparoscopy before medical treatment since the risk of general anaesthesia and trocar insertion are still present. Furthermore, we reported a randomised trial comparing laparoscopic salpingostomy and ultrasound-guided injection of methotrexate, with 19 of 20 patients treated successfully in each group.⁵ We undertook a randomised trial comparing intramuscular administration and local injection of methotrexate (unpublished data), and the success rate was 77% and 92%, respectively (χ^2 , $p < 0.05$). So, local injection (under guidance or laparoscopy) seems more efficient.

However, I believe that the initial project proposed by Hajenius et al remains the only satisfactory protocol to define the appropriate place for medical versus surgical treatment, but randomised trials must be sustained by a clinical background and a knowledge of the recent data that are often gained after pilot studies are done.

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Authors' reply

SIR—Watermeyer and Penketh raise the issue of whether the term salpingostomy should be used for the surgical approach in which the tubal incision is allowed to heal in secondary intention. The term, which probably is indeed inappropriate from a semantic viewpoint, is used by many experts and could be regarded as jargon.^{1–3} In our study, haemostasis after salpingostomy was achieved with the same technique described by

Watermeyer and Penketh, apart from the use of a vasoconstricting agent because oripressin (Por 8) is not registered in the Netherlands.

In our study, treatment success was defined as complete elimination of the tubal pregnancy (serum hCG concentration <2 IU/L). Earlier, we established postoperative serum hCG clearance curves for the diagnosis of persistent trophoblast.⁴ Any substantial deviation from the curve indicates the presence of retained trophoblastic tissue. Persistent trophoblast may manifest itself at different moments in the postoperative period: early or late. Therefore, a single cutoff point is insufficient to detect persistent trophoblast. We do agree with Watermeyer and Penketh that not all patients with persistent trophoblast need to be treated. Patients with slow but steadily declining serum hCG concentrations might be managed expectantly, but those with rising or plateauing concentrations pose a clinical problem, for which systemic methotrexate is an elegant and satisfactory option. Unfortunately, no studies are available comparing expectant management and systemic methotrexate in patients with persistent trophoblast.

The conclusion from our study by Hart and Magos that laparoscopic treatment remains the "optimum treatment" and "standard of care" in patients with ectopic pregnancy, is premature. Apart from medical outcome measures, patients' health-related quality of life, patient preferences, and costs should also be taken into account in making treatment decisions. We will report on these topics soon, extrapolating the results to those who do not have a preceding laparoscopy. According to our findings, there is a well-defined place for non-invasive management with systemic methotrexate in a selected group of patients. With the results of our study at hand, we agree with Watermeyer and Penketh that future trials should be undertaken without a confirmative laparoscopy.

Fernandez criticises the high rate of persistent trophoblast (20%, not 28%). In our trial, five University Hospitals and one teaching hospital participated and surgery was done or supervised by trained and experienced laparoscopic surgeons. Although much lower rates have been reported by world experts in laparoscopic surgery, we believe our results to be a better reflection of the situation in a training setting, which increases the generalisability of our findings. He also claims the success rate of single dose methotrexate to be similar to the multiple-dose regimen. However,

published work shows a primary treatment success of single-dose methotrexate of 75% and of the multiple dose regimen of 95%. As we stated, future studies should focus on varying methotrexate dose, and such studies are being done.

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SIR—Folic acid does not interfere with methotrexate^{1,2} as Petra Hajenius and colleagues³ suggest it does. Folinic acid, which is an analogue of the vitamin folic acid, can reverse the effects of methotrexate. To reverse the effects of methotrexate, folinic acid has to be given in high doses. Folinic acid cannot be obtained over the counter, it must be prescribed.

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Helicobacter pylori and NSAID-induced ulcers

SIR—Francis Chan and colleagues (Oct 4, p 975)¹ show that *Helicobacter pylori* eradication is essential to prevent peptic ulcers caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs), whose risk is reduced by almost four-fold after the disappearance of the germ. Accordingly, the investigators conclude

that *H pylori* infection should be sought for and eradicated before the start of NSAID therapy. However, the degree of protection guaranteed by eradication of *H pylori* is similar to that achieved with two well-known acid-suppressant agents, famotidine and omeprazole.^{2,3} More importantly, both antisecretory drugs are effective even in patients who continue to harbour *H pylori* in their stomachs. Thus the relevance of *H pylori* eradication as a prophylactic measure in patients at risk of developing NSAID-associated peptic ulcers is not certain.

On the other hand, H₂ blockers have no effect on *H pylori* and omeprazole alone is only able to determine a temporary suppression, but not a true eradication of *H pylori*.⁴ Moreover, the decrease in gastric acid secretion as result of *H pylori* eradication can be excluded because the acid output stimulated by pentagastrin, which is the only stimulus capable of exciting the total population of functional parietal cells, does not change even 1 year after *H pylori* eradication.⁵ We conclude that the control of gastric-acid secretion is able to prevent NSAID-related ulcers independently of *H pylori* eradication. If these two different pathogenic approaches are equally successful, the mechanism responsible for NSAID-ulcers is not unique and the emphasis placed by Chan and colleagues on the need to eradicate *H pylori* as the first step to prevent NSAID ulcers should be reduced.

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