Opinion

Ectopic pregnancy: changing trends in management

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Synopsis

There is a chance that in the near future women could prefer expectant management rather than pharmacological management for stable cases of the same threshold of serum b-hCG level of 5000iu/l. It would appear there is no significant difference in the criteria for medical management of ectopic pregnancy when compared with the criteria for expectant management.

It is also possible in the future, that unless there is haemodynamic compromise in a patient or that the patient had other co-existing conditions like pelvic or abdominal masses, surgical option may become increasingly unacceptable. At that stage medical management, perhaps with an oral or systemic cytotoxic medication of superior efficacy compared to methotrexate, could take the centre stage in the management of a stable unruptured ectopic pregnancy. Thus, in those circumstances in the future, laparotomy (reserved for complicated and complex cases) rather than laparoscopy; medical and expectant management, could become the main acceptable options. This is because, as identified in the body of this paper, studies have shown that in selected cases of tubal pregnancy, systemic methotrexate has similar efficacy to laparoscopy. Why then subject a patient to laparoscopy when intramuscular methotrexate can treat her with about the same efficacy, saving costs with less morbidity and mortality? Complicated and complex cases are identified in this paper as cases of ruptured ectopic pregnancy or tubal abortion with haemodynamic compromise and cases where co-existing lesions like pelvic or abdominal masses, respectively. It can be difficult to achieve successful pneumoperitoneum during laparoscopy in complicated and complex cases. It is also possible that as science advances, medical option could become less important than expectant management with the latter increasingly taking the upper hand for reasons stated in the body of this article.

Surgical options

It is established that the majority of tubal ectopic pregnancies are managed surgically. Laparoscopy is preferable to laparotomy due to its many advantages, such as; shorter operation time, less intraoperative blood loss, shorter hospital stay, lower costs, lower analgesic requirements and less adhesion formation.[1]

Evidence strongly suggests that there is no difference in terms of health benefits between laparoscopy and laparotomy, including the key outcome of subsequent successful pregnancy.[1] Thus, over the years, the trend has increasingly changed and currently laparotomy for ectopic pregnancy is reserved for complicated cases where the patient is unstable haemodynamically and in complex cases where there are co-existing pelvic and abdominal masses, in which the practitioner felt that achieving pneumoperitoneum would likely be unsuccessful and a waste of time. Thus, if you are a senior specialist trainee, currently you will have to justify to your consultant why the patient had laparotomy instead of laparoscopy.

On laparoscopic management, it has been concluded that for women with a tubal ectopic pregnancyand about to have surgery, salpingotomy does not significantly improve fertility prospects compared with salpingectomy when the contralateral tube is healthy with no fertility reducing factors present.[1] Fertility reducing factors are identified in this paper as the following; previous ectopic pregnancy, previous abdominal or pelvic surgery, previous pelvic inflammatory disease and damage to the contralateral tube. However, the situation is different when there is existing fertility reducing factors and a compromised contralateral tube. In such a situation, the stated cumulative pregnancy rate of 60.75% for salpingotomy is superior to 56.2% that for salpingectomy,[1] thus making salpingotomy preferable in such clinical situation. Another study,[2] found cumulative pregnancy rate of 75% for salpingotomy and 40% for salpingectomy in the same clinical situation.

Medical and expectant management

There is a minority of cases currently managed expectantly and medically (pharmacologically) and this is very important as due consideration can prevent unnecessary morbidity and exposure to cytotoxic/antineoplastic methotrexate and its side effects and consequences. It is worth noting from the outset that this medical management is slightly different from the medical management of persistent trophoblastic activity using methotrexate following salpingotomy in women with fertility reducing factors and a compromised contralateral tube. In the latter scenario, according to a study, there is a case for medical intervention because persistent trophoblast occurred more frequently in the salpingotomy group, 7% versus <1%; relative risk [RR] 15.0, 95% CI 2.0-113.4).[3] This supports medical intervention in these situations. However, it is also sensible to take on board the fact that repeat ectopic pregnancy occurred in 8% of women who had salpingotomy compared to 5% of those who had salpingectomy (RR 1.6, 95% CI 0.8-3.3).[3]

Persistent trophoblast is said to exist when there is failure of serum b-hCG levels to fall as expected after initial surgical treatment. This is mainly a problem occurring after salpingotomy rather than following salpingectomy. If trophoblastic tissues persist, serum b-hCG levels

can return uneventfully to normal without medical intervention.[4] and this provides a sensible rationale to follow-up these women with serial b-hCG measurements after salpingotomy, and then administering methotrexate if levels plateau or start to rise. For cases where b-hCG is falling, this fall provides reassurance to the patient and her practitioner that the condition is resolving.

NICE,[5] recommended that women undergoing salpingotomy have a serum b-hCG level taken 7 days after surgery and then weekly until a negative result is obtained. Studies had reported persistent trophoblast rates of 3.9-11.0% after salpingotomy.[1] It had also recommended that those having medical intervention meet the following criteria;

1. No significant pain
2. An unruptured ectopic pregnancy, with a mass smaller than 35 mm with no visible heartbeat.
3. A serum b-hCG between 1500 and 5000iu/l.
4. No intrauterine pregnancy (as confirmed on ultrasound scan).

These imply that the patient is stable. The patient must know the need for follow-up and accept it. On the other hand, the RCOG Green-top Guideline[1] states that; a good candidate for methotrexate has the following characteristics:

A. Haemodynamic stability
B. Low serum b-hCG, ideally less than 1500 iu/l but can be up to 5000 iu/l
C. No fetal cardiac activity seen on ultrasound scan
D. Certainty that there is no intrauterine pregnancy
E. Willingness to attend for follow-up
F. No known sensitivity to methotrexate

These again imply that the patient is stable haemodynamically.

However, though these recommendations[1,5] constitute a careful balance to make sure patients' safety is most assured, the opinion of the author is that these criteria can also fit in for patients undergoing expectant management, making medical management less relevant. It may also make women who had been informed of the side effects of methotrexate to prefer expectant management. Most common side effects are excessive flatulence and bloating due to intestinal gas formation; a transient mild elevation in liver enzymes and stomatitis.[6] Other side effects are; marrow suppression, pulmonary fibrosis, nonspecific pneumonitis, liver cirrhosis, renal failure and gastric ulceration.

Also, taking into account that patients about to receive methotrexate are usually advised the following;

A. Avoid unprotected vagina intercourse till bhcg becomes undetectable
B. Avoid pregnancy for three months due to theoretical risk of teratogenicity with methotrexate
C. Avoid alcohol
D. Avoid pelvic examinations as this can increase risk of rupture of ectopic pregnancy
E. Avoid food and vitamins containing folic acid as methotrexate is antifolate
F. Avoid exposure to sun light to reduce risk of methotrexate dermatitis
G. Avoid nonsteroidal anti-inflammatory drugs as these interact with methotrexate to cause or exacerbate bone marrow suppression, aplastic anaemia or gastrointestinal toxicity. Paracetamol alone or with codeine as in cocodamol or codydramol is thus recommended for pain relief. This advice is very unnecessary and a burden if the ectopic pregnancy can be safely managed expectantly currently or in the future. It can also make patients prefer expectant management to cytotoxic methotrexate.

Currently, it has been reported that the use of prophylactic methotrexate at the time of laparoscopic salpingotomy has, according to a study, reduced the rate of persistent trophoblast compared with simple salpingotomy alone (1.9% versus 14.5%; RR 0.13, 95% CI 0.02-0.97).[7] In the author's opinion, this could be more convenient and reduce the duration of serial b-hCG measurements following salpingotomy.

The criteria for expectant management is namely; patients must be willing and able to attend for follow-up, have minimal pain, and have low or declining serum b-hCG levels. In one study,[8] the selection criteria for expectant management was stated as follows; clinical stability with no abdominal pain; no evidence of significant haemoperitoneum on ultrasound scan; an ectopic pregnancy measuring less than 30 mm in mean diameter with no evidence of embryonic cardiac activity; a serum b-hCG level of less than 1500iu/l and the woman's consent. All women were followed up until the serum b-hCG level was less than 20iu/l. This again essentially fits in for medical management. Both management options also have success rates dependent on careful patient selection. The reported success rate ranges from 57-100% for expectant management,[9] while that for medical management in the largest single study to date of its kind is 90.7%.[10] However, in another study,[11] the success rate was 65-95%. This study, however, had included cases with already decreasing serum b-hCG levels that would have certainly resolved without any medical intervention.

One then wonders whether there is any clinically significant benefit of giving a single systemic dose of methotrexate rather than expectant management. In the author's experience and in a study,[12] there are cases that would have resolved on their own accord without any medical intervention. This Multicentre Randomised Control Trial, found no difference in primary treatment success rate of single systemic dose of methotrexate compared with expectant management, reporting the rate to be 76% and 59% respectively. However, in this study, only 21% of the study cases were those of visualised ectopic pregnancy while the majority were pregnancies of unknown location.

The predictors of success for medical and expectant management are essentially the same, in the opinion of the author. Thus, there is likely to be a future inclination to expected management compared to medical management.

Methotrexate is most commonly used as a single dose of 50mg/m3 in these cases instead of a repeat surgery though no formal comparative studies have been performed to assess which one is best; that is repeat surgery for persistent trophoblastic disease after salpingotomy or methotrexate.

Intramuscular methotrexate is the most commonly used drug for the pharmacological treatment of tubal ectopic pregnancy. However, oral methotrexate can be used successfully but a study[13] found out that oral use had few advantages to be recommended for clinical use over the systemic approach. Two Randomised Controlled Trials,[14,15]

compared methotrexate treatment with laparoscopic surgery and concluded both have same efficacy in certain cases of tubal ectopic pregnancy.

Before administering intramuscular methotrexate to a patient, it is essential that the diagnosis of ectopic pregnancy is confirmed or accurate. As most cases of ectopic pregnancies are seen on scan as inhomogeneous masses, it is good practice to repeat serum b-hCG in such cases in 48 hours. If serum b-hCG is falling, then expectant management seemed a more sensible option. On the contrary, if the serum b-hCG is rising at a rate that may be consistent with a viable intrauterine pregnancy, that is, 66% or more of initial value, in 48hours, then a repeat scan to check that the diagnosis is accurate before administering methotrexate, is advisable.

Though it can be given in a multiple dose regimen, methotrexate is most frequently given as a single intramuscular dose of 50 mg/m3. Serum b-hCG levels are measured on days 4 and 7, following intramuscular methotrexate. If the b-hCG level falls by more than 15% between days 4 and 7, then serum b-hCG levels are measured weekly until less than 15iu/l. If the level does not decrease by 15%, then it is good practice to repeat transvaginal ultrasound to exclude ectopic fetal heart activity and significant haemoperitoneum. It is at this stage that a second dose of methotrexate would be considered.

There are a number of predictors of success:

a. Initial serum b-hCG level

Success rates are higher with lower serum b-hCG levels. Success rates of 81-98% have been reported if serum b-hCG levels are less than 1000iu/l, compared with only 38% if b-hCG levels are greater than 5000iu/l.[16-18]

b. Pretreatment changes in serum b-hCG levels

The smaller the increase in b-hCG level prior to administration of methotrexate, the higher the chance of a successful medical management. A serum b-hCG increase of up to 11-20% over 48 hours prior to the administration of methotrexate has been associated with higher rates of success.[18,19]

c. Decrease in b-hCG levels from day 1 to day 4 after methotrexate

Success rates of 88-100% have been reported if the serum b-hCG level decreases from day 1 to day 4 post administration of methotrexate, compared with only 42-62% if the serum b-hCG level increases.[20,21]

d. Ultrasound appearance of the ectopic pregnancy

The presence of a yolk sac, fetal pole and/or fetal cardiac activity are significant predictors of failure.[10,16,22-24] Success rates were higher when no gestational sac was seen on scan. Methotrexate must not be given at first hospital visit of the patients, unless the diagnosis of ectopic pregnancy is absolutely clear and a viable intrauterine pregnancy has been excluded.[25] This is because errors of medication had occurred in the past and there are many well-documented cases of women with intrauterine pregnancies treated for suspected ectopic pregnancy with methotrexate.[26]

Success rates are inversely proportional to serum b-hCG levels, with lower success rates associated with higher initial serum b-hCG levels.[1] There has been interest in the use of other medications like; hyperosmolar glucose (500 mg/ml), 15-methyl-prostaglandin-$F_{2\alpha}$ (15-m-$PGF_{2\alpha}$; 10−7 to 10^{-3}mol/l) and prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$; 10^{-5} to 5 X10^{-3}mol/l) for the medical treatment of ectopic pregnancy by local injection and at in vitro research settings. A study,[27] attempted to assess the ability of some drugs used for local injection therapy of ectopic pregnancy to suppress the activities of cultured human placental tissue. Hyperosmolar glucose was the most effective drug and caused a marked decrease of the protein content in the culture wells and a reduction of progesterone secretion.

Regarding the effects of the two prostaglandins, only 15-m-$PGF_{2\alpha}$ affected the viability of the cells and reduced the protein content of the wells. The clinical effectiveness of the two groups of drugs, that is the hyperosmolar glucose group and the prostaglandins group, seemed to be similar but certain *in vitro* effects are different. Thus *in vivo* they may act on different target tissues,[27] the study concluded. The authors speculated that the combination of hyperosmolar glucose and prostaglandins might be an interesting approach for local injection therapy for tubal pregnancy.

While success has been reported with hyperosmolar glucose and prostaglandins, methotrexate remains superior in clinical settings and appeared to be the most widely used and studied in relation to treatment of ectopic pregnancy, including studies comparing its use with laparoscopic treatment.[13,14]

Has there been any widely acceptable study to identify what percentage of patients that were managed surgically, medically and expectantly, and of what relevance would that be currently and in the future? Such percentages, the author argue could vary widely with respect to geography, clinical settings, training and selection criteria, among other factors. The fact that ectopic pregnancy can rupture at low levels of serum b-hCG, even at 100iu/l, in the author's experience, adds a puzzle to the changing trends.

Science is a dynamic discipline as we know, the trends will keep changing as new evidence emerge and therefore the approach to management of ectopic pregnancy would keep changing in line with the emergence of new evidence.

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Conflicts of interest

None.

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