An economic evaluation of single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured ectopic pregnancy

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Single-dose systemic methotrexate (50 mg/m2) was compared with laparoscopic surgery for the treatment of unruptured ectopic pregnancy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The parent study included women with an unruptured ectopic pregnancy, diagnosed by an algorithm using quantitative serum beta-human chorionic gonadotrophin (hCG) and transvaginal ultrasound, with or without a desire for future fertility. To be eligible for the trial, the women had to have a serum beta-hCG concentration of less than 5,000 IU/L and an adnexal mass of less than 3.5 cm, with no foetal heart activity and minimal haemoperitoneum. The exclusion criteria included unstable vital signs, generalised peritonism, a falling serum beta-hCG, and diagnostic uncertainty requiring laparoscopy. Other exclusion criteria were an ultrasonically diagnosed interstitial, cervical, ovarian or heterotopic pregnancy, and contraindications to methotrexate or to laparoscopy. Further details were provided elsewhere (Sowter et al., see Other Publications of Related Interest).

Setting
The setting was secondary care (Department of Obstetrics and Gynaecology in three hospitals in Auckland, New Zealand). The economic study was conducted in New Zealand.

Dates to which data relate
The effectiveness evidence and resource use were both obtained from the parent trial published in 2001. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
Many of the following clinical details were extracted from the reference paper (Sowter et al., see Other Publications of Related Interest).

Sample size calculations were reported in the parent study. These showed that 49 women would be needed in each arm to detect a 20% difference in success with a 80% power. Thirty-six per cent of the 218 women seen at the three hospitals were eligible, and 78% of them (62 women) were recruited and randomised (28% from the total population). Twenty-eight patients were randomised to laparoscopy and 34 to methotrexate. Extensive details of the included and ineligible patients, and the reasons for their exclusion, were provided in the reference paper. Recruitment was stopped due to a lower than expected rate and uncertainty about future funding. The sample appears to have been adequate for the study question.

**Study design**

This was an open, pragmatic, multi-centre, randomised controlled trial. Specific data described in the parent study included the method of randomisation, the duration of follow-up and the loss to follow-up. The randomisation was procedure was unblocked and was generated by a computer programme, with allocation details contained in sequentially numbered opaque envelopes. The duration of follow-up was 28 days and there was no loss to follow-up.

**Analysis of effectiveness**

The analysis of the clinical trial was conducted on an intention to treat basis. The primary outcome, on which the sample size was based, was the success rate related to trophoblast persistence. The groups were comparable at baseline.

**Effectiveness results**

Some of the following details were extracted from Sowter et al. (see Other Publications of Related Interest).

All 28 women randomised to laparoscopy received that treatment. Of these, 26 (93%) required no further treatment, while 2 were treated with methotrexate for persistent trophoblast (one of them required a second laparoscopy).

From the 34 women randomised to methotrexate, 22 (65%) were successfully treated with a single dose, 9 (26%) failed to show an adequate fall in beta-hCG concentration and received a second dose, and 3 (9%) required laparoscopy the first week. From the 9 women who received a second dose, 5 needed no further treatment, 2 were operated on, and 2 had a third or four dose of methotrexate.

Women treated in the methotrexate group had better physical findings on the SF-36 survey, but there were no differences in the psychological outcomes. The methotrexate group had greater and more prolonged vaginal bleeding.

**Clinical conclusions**

A single dose of systemic methotrexate is less effective than laparoscopic salpingotomy. It is well tolerated, but should only be offered as an alternative to surgery in women with mild symptoms and low beta-hCG concentrations. In the authors' setting, methotrexate could be offered to no more than a quarter of women with tubal pregnancies.

**Measure of benefits used in the economic analysis**

This economic evaluation focused on a cost comparison (see Effectiveness Results).

**Direct costs**

The cost categories included the following:

investigative costs (all investigation during diagnostic work-up and treatment, excluding protocol-driven laboratories, based on laboratory and ultrasound costs charged to other hospital departments);

drug costs (based on negotiated purchase price by Auckland Healthcare, plus dispensing and other pharmacy costs)
included in the overhead costs; the hourly cost of time in the gynaecology unit (based on departmental accounts); operative and anaesthesia costs (fixed costs per case such as the capital costs of laparoscopy, instruments and consumables, and variable costs per case such as theatre overheads, other anaesthesia costs and staff costs, dependent on the duration of the procedure); the inpatient hotel costs related to number of hours spent at the gynaecology ward (including nursing, medical, support staff costs, consumables and corporate overheads); and follow-up costs based on the number of follow-up visits (in turn, based on the hourly overheads and medical staff costs in the gynaecology unit).

One series of unit costs was applied to value actual resource use for all women (the National Women’s Hospital set was used as the authors judged it more accurate and reliable). The consumables were valued at market prices including general tax (12.5%). An annual discount rate of 6% and a useful life of 5 years were used to calculate the fixed equipment costs. The unit costs and the resources were presented separately. The price year was 1998.

**Statistical analysis of costs**
The costs were treated stochastically.

**Indirect Costs**
A modified human capital-cost approach was used. Information on the trial participants and the partner’s employment, distance from the hospital, and informal carers, was obtained. Using this information, the indirect costs were based on the reduction in paid production due to each woman’s treatment, the reduction in unpaid production due to each woman’s treatment, and additional indirect costs. The reduction in paid production related to lost income arising from the absence of women, partners and other carers from work. It was valued at the same rate as the mean daily income. The reduction in unpaid production related to the time women were unable to perform normal domestic activities. It was valued at the same rate as the mean daily income for women and, to avoid double counting, it included only women without paid employment. The additional indirect costs covered transport and other medical and non-medical expenses.

The data were obtained from Auckland labour market statistics and the New Zealand Automobile Association. The unit costs and the resources were presented separately. The price year was 1998.

**Currency**
New Zealand dollars (NZ$). The exchange rate was NZ$1 = 0.31 UK pounds sterling (€).

**Sensitivity analysis**
To evaluate uncertainty in the unit direct costs, a one-way sensitivity analysis was undertaken. Values of 50, 150 and 200% of the base-case unit costs were used. A sensitivity analysis was also undertaken, using pretreatment beta-HCG levels. A scenario analysis was conducted to estimate what the overall potential reduction in treatment costs per ectopic pregnancy would be if all eligible women in the total trial population were treated with methotrexate. The likely effects on the treatment costs of using upper limits for pretreatment beta-HCG concentration of 1,500 and 1,000 IU/L for medical therapy were also determined. The authors also collected resource use data on women who were not eligible to participate or who declined to take part in the trial, some of who were treated with additional therapies not compared in the trial.

**Estimated benefits used in the economic analysis**
The authors did not derive a summary measure of benefits since the evaluation focused on measuring cost-differences.
Cost results
The mean total direct costs per woman were significantly lower in the methotrexate group (NZ$1,470) than in the laparoscopic group (NZ$3,083). The mean difference was NZ$1,613 (95% confidence interval, CI: 1,166 - 2,061).

The mean indirect costs were also significantly lower in the methotrexate group (NZ$1,141) than in the laparoscopic group (NZ$1,899). The mean difference was NZ$758 (95% CI: 277 - 1,240). Most of this difference was due to a lower number of working days being lost in the methotrexate group.

Although the difference in mean total direct costs was sensitive to the theatre and hotel costs, in all cases the differences in total costs remained higher in the laparoscopy group. The total direct cost-difference was greatest at the lower initial beta-hCG concentration, owing to reduced theatre and hotel time in women treated with methotrexate.

The total indirect cost-difference behaved in the same way. If all 79 eligible women were treated with methotrexate, a potential reduction of NZ$580 per woman for each of the 218 total population could be achieved. The overall reduction in indirect costs would have been NZ$273.

Upper limits for pretreatment beta-HCG concentration of 1,500 and 1,000 IU/L would have reduced the eligible population. The reduction in direct costs would subsequently have decreased to NZ$422 (1,500 IU/L limit) and NZ$386 (1,000 IU/L limit) per ectopic pregnancy, respectively.

The costs of treating 149 of the trial women were also presented in the paper.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Treating suitable patients with ectopic pregnancy with systemic methotrexate results in a significant reduction in the direct costs. The indirect costs borne by the women and their carers are only likely to be reduced in women with pretreatment beta-human chorionic gonadotrophin (hCG) concentrations below 1,500 IU/L.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for their selection of the comparators. Laparoscopic surgery results have proven to be similar to standard surgery, and recent non-controlled evidence has suggested methotrexate as a possible alternative.

Validity of estimate of measure of effectiveness
The authors chose an optimal design to compare the alternatives (a randomised controlled study), but they had to abandon recruitment before reaching the desired sample size due to the smaller number of patients meeting the inclusion criteria. The authors described the study population in full. Those women eligible constituted about one third of the population, demonstrating the potential use of methotrexate to a sub-group of patients with ectopic pregnancy. The patient groups were shown to be comparable at baseline. The analysis was adequately performed on an intention to treat basis.

Validity of estimate of measure of benefit
The economic evaluation focused on cost comparisons, including indirect and direct costs. As such, no summary measure of benefit was used in the economic analysis.

Validity of estimate of costs
The economic perspective was not explicitly stated, but the authors performed and reported two independent analyses.
One analysis was of the direct costs, which appears to have been carried out from a hospital perspective. The other analysis, of the indirect costs, used the human capital approach. The authors used a rigorous costing methodology that included all relevant cost categories. The costs and the quantities were reported separately. The resource use quantities were taken from a single study and a statistical analysis of the costs was performed. The authors used one series of unit costs and, having acknowledged that variations may exist, explored them in a sensitivity analysis. Discounting was adequately used in order to calculate the fixed equipment costs. The price year was reported.

Other issues
The authors compared their results with other economic evaluations. They also addressed the generalisability of their findings through a sensitivity analysis of the different categories of unit costs, and by evaluating the potential impact of treating all eligible women with methotrexate. Resource use for women not entering the trial was also evaluated.

Implications of the study
This study showed that 20 to 25% of women with ectopic pregnancies could be reliably treated with methotrexate, with a considerable reduction in both the direct and indirect costs. It was the first study to be based on a randomised controlled trial and, in common with earlier studies, focused on the short-term outcomes. Although direct cost-savings would still be made, the increase in indirect costs suggested that methotrexate is only likely to be preferable if the serum beta-hCG concentration is below 1500 IU/L. As the authors stated, longer term economic evaluations, which include other outcomes such as the need for assisted contraception, are required.

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Other publications of related interest

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