Treatment of tubal pregnancy in the Netherlands: an economic comparison of systemic methotrexate administration and laparoscopic salpingostomy


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
Systemic methotrexate administration for the treatment of patients with tubal pregnancy. Treatment was started immediately after laparoscopy and completed on an outpatient basis. One full therapeutic course consisted of four doses of methotrexate given intramuscularly (1.0 mg/kg, on days 0, 2, 4, and 6), and four doses of folinic acid administered orally (0.1 mg/kg, days 1, 3, 5, and 7), followed by 7 days without medication. During the methotrexate course patients were instructed not to use alcohol or aspirin, to refrain from sexual intercourse, to avoid exposure to sunlight, to drink at least 1.5L of fluid daily, and to use 0.9% saline mouthwashes or, in the case of stomatitis, chlorhexidine 0.12% mouthwashes.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of haemodynamically stable patients with laparoscopically confirmed unruptured tubal pregnancy and no signs of active bleeding. The diagnosis of ectopic pregnancy resulted from a non-invasive diagnostic strategy combining transvaginal ultrasonography and human chorionic gonadotropin (hCG) concentration measurements in patients with a clinically suspected ectopic pregnancy. Patients with self-limiting forms of ectopic pregnancy were excluded from therapeutic intervention and their cases were managed expectantly. Exclusion criteria were unstable vital signs; foetal cardiac activity; ultrasonographically detected interstitial, cervical, ovarian, or heterotopic pregnancy; contraindications to systemic methotrexate administration (leucopenia, thrombocytopenia, elevated liver enzyme activities, and elevated serum creatinine concentration); and contraindications to laparoscopic surgery (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome).

Setting
The study setting was a hospital. The economic analysis was carried out in the Netherlands.

Dates to which data relate
Effectiveness and resource use data corresponded to the period between January 1994 and September 1996. The price year appears to have been 1996.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.
Link between effectiveness and cost data
Costing was performed prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size (based on a previous study, the authors expected an 80% tubal patency rate after laparoscopic salpingostomy; a sample size of 100 patients would allow the study to detect a difference in total patency rate, in favour of systemic methotrexate, of 18%, with a two-sided chi-square test at \( p = 0.05 \), and with a power of 80%). Among the 100 patients included in the trial 51 women with a mean (SD) age of 31.3 (5.9) years were randomly allocated to receive systemic methotrexate and 49, with a mean (SD) age of 31.8 (4.4) years, were randomly allocated to undergo laparoscopic salpingostomy. Of 267 patients with the diagnosis of ectopic pregnancy in the two main study centres, 104 (39%) were primarily excluded for not meeting the inclusion criteria, and 43 (16%) refused to give informed consent. Thus 120 patients were eligible for random assignment. At the other 4 academic hospitals 20 patients could be randomly assigned. At laparoscopy 40 of 140 patients were excluded for the following reasons: 13 had tubal rupture, 5 had active intra-abdominal bleeding, 4 had no tubal pregnancy, 14 had no ectopic pregnancy, and in 4 cases laparoscopic salpingostomy was not possible.

Study design
The study was a multicentre, randomised, controlled trial carried out in 6 Dutch centres. The duration of the follow-up was until the decline of the hCG concentration below the detection threshold, or until resolution of the ectopic mass was completed by transvaginal ultrasonography. The study appears to have had no loss to follow-up. Randomisation was carried out by means of a computer program with block randomisation, and with stratification for pre-existing tubal pathology and initial serum hCG concentration. To prevent selection bias, a surgeon, unaware of the randomisation outcome, assessed the secondary exclusion criteria. All patients in both treatment groups were discharged the next day if possible. One week after random assignment transvaginal ultrasonography was performed by an observer not blinded to treatment allocation. In the systemic methotrexate group ultrasonography was repeated with a 2-week interval until complete resolution of the ectopic mass had occurred. Furthermore, ultrasonography was performed whenever complications were expected.

Analysis of effectiveness
The principle used in the analysis of effectiveness was reported to have been intention to treat. The clinical outcomes were treatment success, tubal preservation, and homolateral tubal patency. Treatment success was defined as complete elimination of the tubal pregnancy (serum hCG \(<2 \text{ IU/L}\) and preservation of the tube. Homolateral tubal patency was assessed by hysterosalpingography 3 months after completion of treatment. The side effects of systemic methotrexate therapy and complications were recorded for both treatment groups. Logistic regression analysis was used to compare the overall tubal patency with adjustment for pre-existing tubal pathology and initial serum hCG concentration. The baseline characteristics of the 2 groups appeared to be equally distributed.

Effectiveness results
The effectiveness results were as follows:

Of 51 patients in the methotrexate group, 42 (82%) were successfully treated with one course; 2 patients (4%) needed a second course for persistent trophoblast. Surgical intervention was needed in 7 patients (14%); salpingectomy was necessary in 5 of these patients for tubal rupture.

Of the 49 patients allocated to the salpingostomy group, 35 (72%) were successfully treated by laparoscopic salpingostomy alone; salpingostomy was needed in 4 patients (8%), and 10 (20%) needed methotrexate for persistent trophoblast.

The primary treatment success rate was 82% in the methotrexate group versus 72% in the salpingostomy group (rate ratio 1.2; 95% CI: 0.93 - 1.4).
The tube was preserved in 46 (90%) patients in the methotrexate group versus 45 (92%) in the salpingostomy group (rate ratio 0.98; 95% CI: 0.87 - 1.1).

Homolateral tubal patency could be assessed in 81 patients: the tube was patent in 23 (55%) of 42 patients in the methotrexate group and in 23 (59%) of 39 patients in the salpingostomy group (rate ratio 0.93; 95% CI: 0.64 - 1.4).

Only 20 (39%) patients underwent systemic methotrexate therapy without any side effects or complications, compared with 38 (78%) patients in the salpingostomy group.

Clinical conclusions
Both treatments appeared to be equally effective in eliminating tubal pregnancy and in preserving tubal patency.

Measure of benefits used in the economic analysis
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported. Given the equal efficacy of the two alternative procedures, the economic study was, therefore, reduced to a cost-minimisation analysis.

Direct costs
Costs were not discounted due to the short time frame of the cost analysis. The resource use profile was reported separately from the costs. Unit cost items were reported separately. Cost analysis covered the costs of resources used during confirmatory laparoscopy, laparoscopic salpingostomy, conversions to salpingostomy, conversions to open surgery, initial injections with methotrexate, hospital stay in days from the moment of random assignment, additional surgical and medical treatments, blood transfusions, consultations by other subspecialities, transvaginal sonogram, serum hCG concentration measurements, and visits to the outpatient clinic. The perspective adopted in the cost analysis was that of society. Data on resources used for treatment were prospectively collected in the case record forms and costs of both treatments were calculated by multiplying actual expenses for resource units at a single centre and resource unit use measured in all centres. Each patient was sent a questionnaire concerning professional domiciliary care and transportation costs. Resource unit prices reflected unit costs for staff, materials, equipment, housing, depreciation, and overhead. It was deemed that, since the Dutch healthcare system is managed on a non-profit basis, the calculated costs were an appropriate measure of the social cost of direct medical care. The price year appears to have been 1996. Trial-specific resource use was excluded from the analysis.

Statistical analysis of costs
Confidence intervals around the mean costs of each treatment and around the differences in costs were obtained by means of a bootstrap sampling procedure. For this purpose 2,000 random samples with replacement were drawn from the distribution of total costs in the 2 treatment groups. Subgroup analysis based on the presence of abdominal pain and the initial serum hCG concentration was performed to evaluate whether the costs of both treatments depended on patient characteristics.

Indirect Costs
Indirect costs were not discounted due to the short time frame of the cost analysis (a period of 10 weeks). Indirect cost analysis covered the costs of non-professional domiciliary care and labour loss. Quantities were reported separately as were unit costs. The perspective adopted in the cost analysis was that of society. Each patient was sent a questionnaire concerning non-professional domiciliary care and productivity loss. The value of productivity loss was calculated with the friction method from age- and sex-stratified data for the Dutch population. The price year appears to have been 1996.

Currency
Dutch guilders (Dfl). A conversion to US dollars ($) was carried out at a rate of Dfl 1.67 = $1.
Sensitivity analysis
A series of non-probabilistic one-way sensitivity analyses was performed to explore the effect of plausible changes in key variables. A scenario was considered in which the systemic methotrexate therapy was administered without a confirmatory laparoscopy. Furthermore, a single-shot scenario was considered in which methotrexate therapy was administered in a single-shot regimen. A number of assumptions were made by the authors to assess the effects of the above two scenarios.

Estimated benefits used in the economic analysis
Not applicable. The reader is referred to the effectiveness results reported above.

Cost results
The mean total cost per patient in the methotrexate group was $5,721 (95% CI: $5,019 - $6,313) versus $4,066 (95% CI: $3,782 - $4,353) in the salpingostomy group. The mean difference was $1,655 (95% CI: $906 - $2,414). Stratification for initial serum hCG concentration showed that both direct and total costs of systemic methotrexate therapy in a scenario without laparoscopy were lower than those of laparoscopic salpingostomy among patients in whom the initial serum hCG concentration was less than 1,500 IU/L.

Synthesis of costs and benefits
Costs and benefits were not combined since the economic analysis was conducted on a cost-minimisation basis.

Authors' conclusions
Although systemic methotrexate administration is safe and effective for the treatment of tubal pregnancy, it does not necessarily reduce costs. Systemic methotrexate therapy could reduce costs if administered to patients with low initial serum human chorionic gonadotropin concentrations without confirmatory laparoscopy.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator, it being deemed to be a well-established treatment in the context in question. You, as a database user, should consider whether this is the case in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high given the randomised nature of the study design, the power calculations performed to justify the sample size, the comparability of the study groups, and the intention to treat basis for the analysis. The study sample also appears to have been representative of the study population.

Validity of estimate of measure of benefit
The analysis of benefits was based upon therapeutic equivalence of treatment alternatives. The economic analysis therefore included only costs.

Validity of estimate of costs
Features of the cost analysis which are likely to have enhanced its validity, were as follows: quantities were reported separately from the costs and the cost breakdown was reported; the price year, conversion rate, and perspective adopted in the cost analysis were specified; the data for resource use were collected prospectively and valuation was based on (something close to) true costs; the statistical analysis was performed to calculate the confidence intervals for the total costs and cost difference; the effects of the alternative modalities on indirect costs (productivity loss) were addressed. These features, along with the sensitivity analyses performed tend to increase the generalisability of the cost results.
Other issues

The authors’ conclusion appears to be justified. The issue of generalisability to other settings or countries was not directly discussed and it is not entirely clear whether the ranges considered in the sensitivity analysis were meant to cover this issue (or simply address variability in the estimates). Appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was addressed in the comments made by the authors of the original study; it was reported that only a minority of patients presenting with ectopic pregnancy (32%) could be included in this trial because of the rigorous selection criteria that were used in the study protocol; these selection criteria were based on uncontrolled studies updated until 1992, the year in which the study protocol was written and approved by the ethics committee of the study institution. In view of the strong presence of side effects in the methotrexate therapy, a cost-utility approach may have been a more informative framework in which to compare the two alternatives, as noted implicitly by the authors.

Implications of the study

The authors raise a number of issues concerning the implications of their results, as follows:

Subsequent fertility outcome still has to be awaited to show which treatment yields better fertility prospects;

Meta-analysis, pooling this study results with those of future trials, may ultimately give more precise estimates of the various outcomes for use in counselling of patients and decision analysis.

Future studies should focus on varying methotrexate dose in view of potential toxic effects and potentially adverse long-term reproductive effects to improve compliance.

The cost reductions from methotrexate therapy that were suggested by previous studies could only be realised in this study among patients with an initial serum hCG concentration of less than 1,500 IU/L. It should be noted here that this cut-off value was not previously hypothesised and that this finding should be confirmed in future studies.

This study was limited to the costs of the initial treatment of tubal pregnancy. Future fertility prospects are an important additional issue in the economic evaluation of treatment of tubal pregnancy. Costs incurred in the initial treatment of tubal pregnancy should be weighed against costs of future infertility treatment.

Apart from fertility prospects, patient preferences for both treatments should be taken into account.

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