Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia


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
The study examined the use of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of menorrhagia. The LNG-IUS is an intrauterine system that releases 20 microg levonorgestrel every 24 hours over 5 years.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised menstruating women aged between 35 and 49 years, who had completed their desired family size and were complaining of menorrhagia.

Setting
The setting was a hospital. The economic study was carried out in Finland.

Dates to which data relate
The effectiveness and resource use data were gathered from October 1994 to October 2002. The price year was 1996.

Source of effectiveness data
The effectiveness evidence was 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 included in the effectiveness study.

Study sample
Power calculations were carried out in the planning phase of the study. These suggested that a sample of 115 patients in each group would have been appropriate to detect statistically significant differences in the primary outcome measures, with 80% power at a significance level of 5%. Of the 598 women initially referred to the study hospitals by general practitioners or gynaecologists, 362 were excluded because they were either not eligible (n=184) or they refused to participate (n=178). Therefore, a sample of 236 women was randomised. There were 119 women in the LNG-IUS group and 117 women in the hysterectomy group. The mean age of the whole sample was 43 (+/- 3.4) years (age range: 25 - 49), parity was 2.1 (+/- 1.1) and the body mass index was 25.8 (+/- 4.8).
Study design
This was a prospective, randomised clinical trial that was carried out at five university hospitals in Finland. Randomisation was carried out separately for each centre on random clusters, using numbered, opaque and sealed envelopes. The length of follow-up was 5 years. The follow-up visits took place 6 and 12 months after treatment, and 5 years after enrolment. Women who underwent hysterectomy were visited 4 weeks after the intervention. Overall, 5 women in the LNG-IUS group and 7 women in the hysterectomy group were lost to follow-up. The approaches used to deal with missing data for each questionnaire used were extensively described.

Analysis of effectiveness
The analysis of effectiveness appears to have been based on treatment completers only. However, almost the full sample of women initially included in the study was considered in the final analysis (n=232 or 99%). The primary health outcomes were:

- LNG-IUS and hysterectomy outcomes;
- QoL, measured using the 5D-EuroQol (EQ-5D) and the Rand-36 scale;
- general health, measured by a visual analogue scale;
- anxiety;
- depression; and
- sexuality-related aspects.

Laboratory tests, such as the measurement of menstrual blood loss (MBL) and blood haemoglobin concentration, were also evaluated. The baseline comparability of the study groups was not discussed.

Effectiveness results
In the LNG-IUS group, at the end of follow-up, 57 (48%) women (of whom 8 had a replacement LNG-IUS) had the LNG-IUS in situ and 10 (8%) were without LNG-IUS (of whom 1 had had thermoablation). Of the 57 women with the LNG-IUS in situ, 43 (75%) reported amenorrhoea or oligomenorrhoea, 11 (19%) reported irregular bleeding, and 3 (6%) reported scanty regular bleeding.

Hysterectomy was performed in 50 women (42%). Fifteen (30%) of these 50 women developed complications.

Among the 60 women who did not continue treatment with the LNG-IUS, the reason for removing the LNG-IUS was intermenstrual bleeding in 42 women (70%), heavy bleeding in 19 (32%), and hormonal symptoms in 18 (30%). Some women had more than one complaint.

In the hysterectomy group, 109 of the 117 women underwent hysterectomy, including 2 who had the surgery 12 months after randomisation.

Three bladder perforations and one bowel perforation were included in the intraoperative complications.

Postoperative complications occurred in 33 (30%) women.

Overall satisfaction was high with both treatments. The proportion of women who were satisfied or very satisfied was 94% in the LNG-IUS group and 93% in the hysterectomy group.

EQ-5D scores improved in both groups compared with baseline values (LNG-IUS group, p=0.002; hysterectomy group, p=0.001), with no substantial difference between the groups. In both groups, QoL measured by the RAND-36 questionnaire improved significantly in all dimensions except physical functioning.
General health status, as measured by a visual analogue scale, was significantly improved in the hysterectomy group, (p=0.04), but not in the LNG-IUS group, (p=0.08). However, no substantial difference between the groups was found.

The anxiety and depression scores also improved significantly, with no substantial difference between the groups. Sexual function scores showed no substantial within- or between- group changes, except that participant satisfaction with the partner declined in the LNG-IUS group, (p=0.006).

MBL was measured in 227 women at baseline. Objective menorrhagia (i.e. MBL =/> 80 mL) was present in 132 (58%) women. At 5 years, only 4 of 57 women with LNG-IUS in situ who had bleeding (out of 11 having irregular bleeding and 3 having regular scanty bleeding) contributed samples for MBL.

Blood haemoglobin and serum ferritin concentrations were comparable between the groups.

Clinical conclusions
The effectiveness analysis showed that similar outcomes were observed between the groups. Thus, the two interventions were considered equivalent.

Measure of benefits used in the economic analysis
The clinical outcomes and QoL scores were equivalent between the groups, thus no summary benefit measure was used in the economic evaluation. In effect, a cost-minimisation analysis was carried out.

Direct costs
The analysis of the costs took a societal perspective. The direct medical costs included were hospital services (operations, inpatient days, procedures and outpatient visits), travel and medications. The unit costs were presented separately from the quantities of resources used for most items. Resource consumption was mainly estimated using data obtained from medical records and self-reported data. The quantities of resources used referred to the sample of patients included in the clinical trial. The time horizon of the analysis was 5 years and, in general, data from medical records and questionnaires were available for the first and the last year of the study. To calculate costs for years 2 to 4, cost data were taken from questionnaires for the last year and these data were used to calculate an average cost. The average cost was then multiplied by 4 and added to the cost for the first year. The hospital costs were derived from a system of pricing based on diagnosis-related groups at Helsinki University Hospital. The primary care costs were calculated from the unit costs of these services in the Helsinki Occupational Health Care Centers. The costs were gathered in 1996 and 2001. The costs assessed in 2001 were discounted at an annual rate of 3%. The price year was 1996.

Statistical analysis of costs
No statistical analyses of the costs were performed. The costs were presented as average values with 95% confidence intervals (CIs).

Indirect Costs
The indirect costs (i.e. sick leave days as productivity losses) were included in the analysis because a societal perspective was adopted. The unit costs were presented separately from the quantities of resources used. Days of sick leave came for the sample of patients enrolled in the clinical trial. The costs were estimated using the average daily gross wage for women in Finland, which included social security contributions. The price year was 1996. An annual discount rate of 3% was applied.

Currency
Finnish markkaa (FIM). FIM were converted to US dollars ($) using purchasing power parities in 1996 at the following rate: $1 = FIM 5.89.
Sensitivity analysis
Several univariate sensitivity analyses were carried out due to the uncertainty in the estimation of some economic data. For example, a 5% discount rate was applied as an alternative value to the 3% conventional rate. Daily gross wages were reduced to one third. Costs for years 2 to 4 (including visits to private physicians, Papanicoulaou tests and medications) were also varied. Two different hysterectomy prices were considered.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The discounted total direct costs per patient were $1,892 (95% CI: 1,352 - 2,189) in the LNG-IUS group and $2,787 (95% CI: 2,312 - 3,133) in the hysterectomy group.

The discounted indirect costs per patient were $925 (95% CI: 725 - 1,232) in the LNG-IUS group and $1,873 (95% CI: 1,650 - 2,096) in the hysterectomy group.

The discounted total costs per patient were $2,817 (95% CI: 2,222 - 3,530) in the LNG-IUS group and $4,660 (95% CI: 4,014 - 5,180) in the hysterectomy group.

All these differences were statistically significant. The sensitivity analysis confirmed the results of the base-case results.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as a cost-minimisation analysis was performed.

Authors' conclusions
The levonorgestrel-releasing intrauterine system (LNG-IUS) was as effective as conventional hysterectomy for the treatment of menorrhagia, but the 5-year costs were substantially lower among LNG-IUS women. Satisfaction in both groups of women was very high.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (i.e. hysterectomy) was appropriate as it reflected the standard surgical approach for the treatment of menorrhagia. The authors stated that endometrial ablation may be an alternative to hysterectomy for the short term, but its benefits are reduced over time. Thus, endometrial ablation was not considered as a possible alternative. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a well-conducted clinical trial, which was appropriate for the study question. Thus, the potential impact of selection bias and confounding factors should be ruled out. The method of sample selection and details of the follow-up were clearly described. Further, the authors reported how missing data were handled. The very low dropout rate represents a further strength of the analysis. The size of the sample was justified on the basis of statistical calculations. The baseline comparability of the study groups was not clear. Moreover, since the trial was open-label, assessment bias might have affected the results of the study. The evidence came from several centres, which enhances the representativeness of the patient sample. The authors noted that different hysterectomy approaches were used to reflect actual treatment patterns.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-minimisation analysis was conducted. Please refer
to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The adoption of a societal perspective was appropriate since both the direct and indirect costs were considered. Details of the cost calculation were reported and the unit costs were provided separately from the quantities of resources used. These factors enhance the possibility of replicating the analysis in other settings. The sensitivity analysis addressed the issue of uncertainty surrounding some cost estimates, which enhances the transferability of the cost analysis. Statistical analyses were not carried out to assess the significance of cost-differences, but the use of CIs increases the validity of the cost estimates. The price year was given, which aids reflation exercises in other time periods.

**Other issues**
The authors reported some results from other studies, but made no clear comparisons with the results of the current analysis. The issue of the generalisability of study results to other countries was explicitly addressed; the authors stated that the extensive use of sensitivity analyses makes the current findings transferable to other settings. The generalisability of the study results was further enhanced by the fact that details of the unit costs and resource consumption were given. The study referred to women seeking medical attention for menorrhagia and this was reflected in the authors' conclusions.

**Implications of the study**
The study results suggested that LNG-IUS might be a cost-effective treatment for menorrhagia.

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