Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial


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 interventional health technology was levonorgestrel-releasing intrauterine system (IUS) in the treatment of menorrhagia. The levonorgestrel-releasing IUS releases 20 micro g levonorgestrel from a polydimethylsiloxane reservoir over 24 hours for at least 5 years. The device was inserted during the randomisation visit.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study included women referred by general practitioners or gynaecologists to hospitals because of menorrhagia. The predefined exclusion criteria were: submucous fibroids, endometrial polyps, ovarian tumours or cysts (diameter greater than 5 cm), cervical disease, urinary and bowel symptoms or pain due to large fibroids, lack of indication for hysterectomy, history of cancer, menopause, severe depression, metrorrhagia as a main complaint, previous treatment failure with levonorgestrel-releasing IUS, severe acne, and uterine malformation. Eligible women were 35-49 years old, were menstruating, had completed their family, and were eligible for hysterectomy.

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

Dates to which data relate
Effectiveness and resource use data were collected between November 1994 and November 1997. The price year was 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 conducted retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size (the authors calculated a target of 115 patients in each treatment group; on the basis of an EQ-5D score SD of 19% (derived from a Finnish 34-49 year-old female population).
and alpha= 0.05, the study had 80% power to detect a 7.5% difference between the groups. The study sample consisted of a total of 236 patients (out of 598 women referred with menorrhagia) who were eligible and who agreed to take part. They were randomly assigned to treatment with the levonorgestrel-releasing IUS (n=119) with a mean (SD) age of 43.1 (3.5) years, or hysterectomy (n=117) with a mean (SD) age of 43.0 (3.2) years. Of the 362 women who were not randomised, 178 were not willing to participate in the study.

**Study design**

The study was a randomised, controlled trial carried out in five centres. The duration of the follow-up was 12 months after treatment. The number of patients who were lost to follow-up was 3 patients in the IUS group and 5 in the hysterectomy group. Randomisation was carried out separately for each centre in varying clusters, by use of numbered, opaque, sealed envelopes. Physicians and other study personnel involved in the randomisation or treatment did not participate in planning or execution of concealment. Women who had no indication of predefined exclusion criteria when referred were assessed by medical history, physical examination, cervical smear, transvaginal ultrasonography, and endometrial biopsy. When clinically indicated, hysteroscopy was also performed. At follow-up visits 6 months and 12 months after treatment, the woman and gynaecologist each completed a questionnaire.

**Analysis of effectiveness**

The principle used in the analysis of effectiveness was intention to treat. The primary health outcome measure was quality of life as measured by the EuroQol (EQ-5D) at 12 months. The other outcomes reported were health-related quality of life as measured by the RAND-36 questionnaire, general health state measured by visual analogue scale, anxiety measured by the validated Finish version of Spielberger and colleagues' 20-item state anxiety scale, depression as measured with the 13-item version of Beck's depression inventory, sexually-related factors as assessed by the McCoy sex scale, and complications. Menstrual blood loss was measured before randomisation and after 12 months by the alkaline haematin method. The comparability of the randomised study groups in terms of the baseline characteristics was not explicitly confirmed. It was reported that the 362 women ineligible or unwilling to take part did not differ from the study sample in terms of age, employment status, or occupation.

**Effectiveness results**

The effectiveness results were as follows:

12 months after treatment, the health related quality of life measured with the EQ-5D had improved significantly in both groups from baseline (change 0.10 (95% CI: 0.06 - 0.14) in both groups), (p=0.0001), but there was no difference between the groups. With the RAND-36 questionnaire, health-related quality of life also improved in all dimensions (p<0.001) in both groups. At 12 months, the only significant difference between the groups was in pain score (p=0.01) in favour of hysterectomy.

The general health state measured by visual analogue scale was significantly better (p<0.0001) after 12 months in both groups, again with no difference between the groups.

The anxiety (p=0.0007 IUS, p=0.0008 hysterectomy) and depression scores (p=0.0004 IUS, p=0.0002 hysterectomy) improved significantly, but there was no difference between the groups.

Sexual functioning scores showed deterioration in satisfaction with the partner in the levonorgestrel-releasing IUS group, (p=0.005) and decreasing sexual problems in the hysterectomy Group, (p=0.04) without difference between the groups.

At 12-month follow-up the IUS was in situ in 81(68%) women (a replacement IUS in five).

A total of 24 (20%) had undergone hysterectomy; 3 patients developed postoperative haematoma with pelvic infection, 2 wound infection, 1 postoperative fever, and 1 urinary retention.

In the hysterectomy group, postoperative complications included wound infection (12), wound rupture (2), infected pelvic haematoma (6), postoperative fever (2), peritonitis (1), ileus (2), urinary retention (4), severe abdominal pain (3),...
vesicovaginal fistula (1), and postoperative bleeding (2).

There were significant increases in both the IUS and hysterectomy groups in blood haemoglobin concentration (from 127 g/L (SD, 13) to 135 g/L (9) as opposed to from 125 g/L (12) to 132 g/L (13)) and serum ferritin concentration (from 18 IU/L (20) to 26 IU/L (28) compared with from 15 IU/L (17) to 25 IU/L (16).

Clinical conclusions
Hysterectomy was successful in the treatment of menorrhagia in this study, but it was associated with several complications. The levonorgestrel-releasing IUS was also successful in decreasing menstrual blood loss in most women. However, about a third of devices were removed, and 20% of the women underwent hysterectomy during the first year of follow-up. Health-related quality of life and other measures of psychosocial well-being improved in both groups. At 12 months, there were no significant differences in outcome measures between the treatment groups, except for pain.

Measure of benefits used in the economic analysis
The only benefit measure considered in the economic study was improvement in the RAND-36 pain score from the baseline since the study groups were equivalent in terms of other health outcome measures.

Direct costs
Costs were not discounted due to the short time frame (one-year) of the cost analysis. Some quantities were reported separately from the costs. Cost items were reported separately. The cost analysis covered the costs of health care, medications, and travelling. The perspective adopted in the cost analysis appears to have been that of society. Data on the use of hospital services were derived from the medical records and from the questionnaires. Information on other visits to doctors for menorrhagia was obtained from the questionnaires. The costs of health care and medications during the waiting time for hysterectomy were based on a separate questionnaire. Pricing of hospital procedures was based on a pricing system (using diagnostic related groups) employed in the study hospital. The price year was 1996.

Statistical analysis of costs
It appears that Student’s t test was used to test differences between the groups in terms of costs.

Indirect Costs
Indirect costs were not discounted due to the short time frame of the cost analysis. The indirect cost analysis covered the costs of productivity losses (absence from work) during the follow-up. The productivity loss per sick-leave day was defined as the average daily gross wage of women in Finland (1996), including social security contributions. The perspective adopted in the cost analysis appears to have been that of society. The price year was 1996.

Currency
Finnish marks (FIM). The currency conversion was based on the rate of purchasing power parities in 1996 (US$1 was equal to FIM 5.89).

Sensitivity analysis
The authors performed a sensitivity analysis to test the results based on a lower estimate of productivity loss (a third of the average wage rate).

Estimated benefits used in the economic analysis
The incremental improvement in pain score from the baseline was 11.8 (95% CI: 6.9 -16.8) for the IUS group and 21.1 (95% CI: 16.0 - 26.3) for the hysterectomy group, (p=0.01).
Cost results
The total estimated cost per woman was $1,530, (95% CI: 1,203 - 1,853) in the IUS group and $4,222, (95% CI: 3,808 - 4,636) in the hysterectomy group. Both direct cost per woman and productivity losses (absence from work) per woman were significantly lower in the IUS than in the hysterectomy group. In the sensitivity analysis (with a lower estimate of productivity loss), the total mean cost per woman was again lower in the IUS group than in the hysterectomy group.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was conducted for pain, which was the only measure showing better outcomes in the hysterectomy group. It was found that a 1% improvement in the RAND-36 pain score cost about $270 in the hysterectomy group. The use of levonorgestrel-releasing IUS was the weakly dominant strategy (with equal efficacy and much lower costs) in terms of the primary health outcome and other outcome measures except for pain.

Authors’ conclusions
The significant improvement in health-related quality of life highlights the importance of treating menorrhagia. During the first year the levonorgestrel-releasing IUS was a cost-effective alternative to hysterectomy in treatment of this disorder.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator, which was deemed to be the more effective treatment strategy (by definition) although its associated morbidity and complications cannot be ignored. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high owing to the randomised nature of the study design, the power analysis performed, and the fact that the effectiveness analysis was based on intention to treat. In response to a critique, the authors further reported that a sensitivity analysis showed that the waiting time for hysterectomy had no association with the treatment outcomes. They further mentioned that subgroup analysis would be reported elsewhere. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The benefit measure was directly derived from the effectiveness analysis. The choice of the benefit measure appears to be justified.

Validity of estimate of costs
The validity of the cost analysis was enhanced by the following features: adequate details of the methods of cost estimation were given; the price year, conversion rate, and perspective adopted in the cost analysis were specified; statistical analyses were performed on cost data; the effects of alternative treatment strategies on indirect costs were addressed, and a sensitivity analysis was performed to address uncertainties involved with estimation of the costs associated with productivity loss. Furthermore it was reported that cumulative costs in the hysterectomy group were calculated from treatment, not from randomisation; and health-care costs and productivity losses from the waiting time were reported separately. However, the following features may have had adverse effects on the cost analysis: a resource use profile was not fully reported separately from the costs; the costing appears to have been performed retrospectively, which renders it prone to a number of biases; it is not entirely clear whether the cost data were based on true costs or on charges; the issue of the generalisability of the cost results to other settings or countries was not investigated through an extensive sensitivity analysis.

Other issues
The authors' conclusions appear to be justified given the uncertainties in the data. The issue of generalisability to other countries was not addressed although some comparisons were made with other studies. The degree to which the study sample was representative of the study population was addressed in the authors' comments; it was deemed that the study sample was representative of women who are candidates for both treatment modalities and that the results can be generalised to this population.

**Implications of the study**
It was suggested that long-term evaluation of these study groups is needed. Further need for hysterectomies, continuing requirement for cervical smears, risk of uterine cancers, and uncertainty about future vaginal bleeding during use of the levonorgestrel-releasing IUS will be more thoroughly assessed after 5 years of follow-up.

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