Clinical Outcomes and Costs With the Levonorgestrel-Releasing Intrauterine System or Hysterectomy for Treatment of Menorrhagia

Randomized Trial 5-Year Follow-up

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Context Because menorrhagia is often a reason for seeking medical attention, it is important to consider outcomes and costs associated with alternative treatment modalities. Both the levonorgestrel-releasing intrauterine system (LNG-IUS) and hysterectomy have proven effective for treatment of menorrhagia but there are no long-term comparative studies measuring cost and quality of life.

Objective To compare outcomes, quality-of-life issues, and costs of the LNG-IUS vs hysterectomy in the treatment of menorrhagia.

Design, Setting, and Participants Randomized controlled trial conducted between October 1, 1994, and October 6, 2002, and enrolling 236 women (mean [SD] age, 43 [3.4] years) referred to 5 university hospitals in Finland for complaints of menorrhagia.

Interventions Participants were randomly assigned to treatment with the LNG-IUS (n=119) or hysterectomy (n=117) and were monitored for 5 years.

Main Outcome Measures Health-related quality of life (HRQL) as measured by the 5-Dimensional EuroQol and the RAND 36-Item Short-Form Health Survey, other measures of psychosocial well-being (anxiety, depression, and sexual function), and costs.

Results After 5 years of follow-up, 232 women (99%) were analyzed for the primary outcomes. The 2 groups did not differ substantially in terms of HRQL or psychosocial well-being. Although 50 (42%) of the women assigned to the LNG-IUS group eventually underwent hysterectomy, the discounted direct and indirect costs in the LNG-IUS group ($2817 [95% confidence interval, $2222-$3530] per participant) remained substantially lower than in the hysterectomy group ($4660 [95% confidence interval, $4014-$5180]). Satisfaction with treatment was similar in both groups.

Conclusions By providing improvement in HRQL at relatively low cost, the LNG-IUS may offer a wider availability of choices for the patient and may decrease costs due to interventions involving surgery.

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MENORRHAGIA IS AN IMPORTANT cause of ill health in women worldwide. About one third of women report heavy menstrual bleeding at some time in their lives.[1] Menorrhagia is the presenting symptom among the majority of women who undergo hysterectomy,[2,3] and recent data suggest that menorrhagia is an increasingly common health problem.[4]

The levonorgestrel-releasing intrauterine system (LNG-IUS) (Schering Co, Turku, Finland) has been advocated for the treatment of menorrhagia as an alternative to surgery.[5] The LNG-IUS is an intrauterine system that releases 20 µg of levonorgestrel every 24 hours over 5 years. The LNG-IUS was developed during the 1980s and licensed first for contraception in Finland in 1990. The estimated number of current LNG-IUS users worldwide is

See also pp 1447 and 1503.

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more than 4 million, in approximately 100 countries. In many countries the LNG-IUS is licensed both for contraception and treatment of menorrhagia. In the United States, the system is so far approved for contraception only (Tarja J. Butzow, MD, PhD, Schering Co, Finland, written communication, December 17, 2003).

Studies of hysterectomy, endometrial ablation, and the LNG-IUS have raised important questions about health outcomes and the allocation of resources for treatment of menorrhagia. Hysterectomy is effective but can be associated with complications and costs. Endometrial ablation may be an alternative to hysterectomy for the short term, but its benefit lessens over time.[6] The LNG-IUS is an effective and reversible treatment modality for menorrhagia. The LNG-IUS reduces menstrual blood loss (MBL) more than tranexamic acid,[7] nonsteroidal antiinflammatory drugs,[8] danazol,[8] oral progestogens,[8] combined oral contraceptives,[8] or long-term norethisterone.[9] No difference in patient satisfaction or health-related quality of life (HRQL) has been found between the LNG-IUS and endometrial destruction, and both are effective in reducing MBL.[10,11] The LNG-IUS also reduced the preference for hysterectomy.[5] We have shown that the LNG-IUS is more cost-effective than hysterectomy after 1 year of follow-up.[12] Whether there is a longer-term advantage is unknown.

We conducted a randomized trial of the LNG-IUS and hysterectomy for the treatment of menorrhagia and report herein the clinical findings, quality-of-life outcomes, and costs after 5 years of follow-up.

METHODS

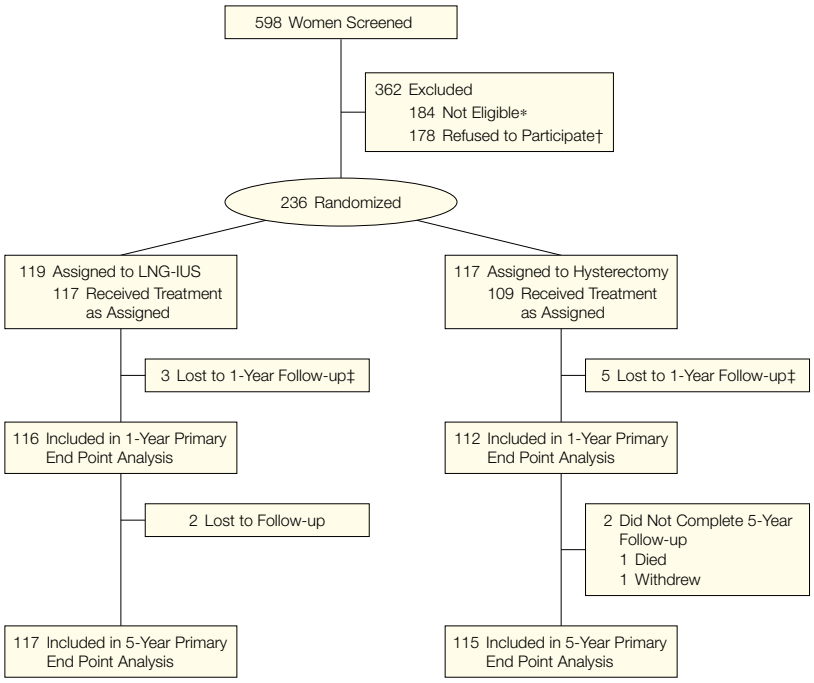
Full details of the original trial have been reported elsewhere.[12] Briefly, each woman who participated had been referred by a general practitioner or gynecologist for complaints of menorrhagia to 1 of the 5 university hospitals in Finland between October 1, 1994, and September 10, 1997. Overall, 236 women aged 35 to 49 years who were menstruating, had completed their desired family size, and were eligible for both treatments were randomized to receive the LNG-IUS (n=119) or hysterectomy (n=117) (FIGURE). The randomization was performed separately for each center on randomly varying clusters using numbered, opaque, and sealed envelopes. The follow-up visits took place 6 months and 12 months after the treatment, and again 5 years after the randomization. For women having hysterectomy, there was a planned visit 4 weeks after hysterectomy. Questionnaires were completed by participants and study gynecologists at baseline before randomization and at each follow-up visit. Participants completed a questionnaire at home containing HRQL instruments and questions on health care use, sick leave days, and travel costs separately for menorrhagia and other conditions. Gynecologists completed a form that included questions on participant menstrual problems, LNG-IUS–associated bleeding and reasons for discontinuing its use, operation details, and complications, as well as clinical status.

The ethics committees of all the university hospitals and STAKES (National Research and Development Center for Welfare and Health) approved the study. All participants provided written informed consent.

Health-Related Quality of Life

The 5-Dimensional EuroQol (EQ-5D)[13,14] was chosen as the primary measure of effectiveness because it provides a single numeric score for HRQL, is universally used, and has undergone validation in the Finnish general population.[15] The EQ-5D consists of five 3-level subscales that indi-

Figure. Study Flow



Trial profile representing 1-year follow-up has been previously published.[12] *Not eligible because of submucosal fibroids (n=84), lack of indication for hysterectomy (n=25), urinary and bowel symptoms or pain due to large fibroids (n=20), endometrial polyps (n=14), previous treatment failure with the levonorgestrel-releasing intrauterine system (LNG-IUS) (n=10), menopausal (n=7), metrorrhagia as a main complaint (n=7), ovarian tumors or cysts with diameter >5 cm (n=4), cervical pathology (n=3), history of malignancies (n=3), severe acne (n=3), severe depression (n=3), or uterine malformation (n=1). †Refusal to participate because of preference for hysterectomy (n=71), preference for medical treatment (n=37), refusal of any treatment (n=28), still planning pregnancy (n=11), preference for endometrial ablation (n=3), and other reasons (n=28). ‡Invited for 5-year follow-up.

cate dimensions of mobility, self-care, usual activities, pain, and mood. The EQ-5D score index, which ranges from 0 to 1, was calculated by using relative weights for subscales obtained from a Finnish population survey.[15] Better HRQL is indicated by higher scores. A validated Finnish version of the RAND 36-Item Short-Form Health Survey (RAND-36)[16,17] was also used for measurement of HRQL. The RAND-36 survey is composed of 8 multi-item dimensions: general health, physical functioning, mental health, social functioning, energy, pain, and physical and emotional role functioning. There is a range from 0 to 100 in each subscale, with higher scores indicating better HRQL. General health was assessed using a visual analog scale (scale range, 0-100).

Other Psychological Measures

Measurement of anxiety was accomplished using the validated Finnish version of the Spielberger 20-Item State-Trait Anxiety Inventory, with a range of 20 to 80.[18] Measurement of depression was accomplished using the 13-item version of the Beck Depression Inventory, with a scale of 0 to 39.[19] For both scales, higher scores are indicative of more symptoms. Sexuality-related elements were evaluated using the McCoy Sex Scale as modified by Wiklund.[20,21] This scale contains 3 subscales: sexual satisfaction (5 items; subscale range, 5-35), sexual problems (2 items; subscale range, 2-14), and participant satisfaction with the partner (3 items; subscale range, 3-21).

Satisfaction

Overall satisfaction with the treatment was assessed by a 5-level question (from very unsatisfied to very satisfied). This assessment approach has been used previously.[10,22]

Cost Analysis

Data on direct costs including use of hospital services (operations, inpatient days, procedures, and outpatient visits) and medication, and on indirect costs including sick leave days as productivity losses, were obtained from medical records and the questionnaires. Information was obtained from the questionnaires for Papanicolaou tests, physician appointments out of hospital related to menorrhagia, and out-of-pocket costs due to menorrhagia (all direct costs) during the first and the last study years.

A system of pricing based on diagnosis related groups in use at Helsinki University Hospital was used to determine prices of hospital procedures. The first-year costs were based on 1996 price levels, and the annual costs thereafter on 2001 price levels. Hysterectomy unit cost comprised 1 preoperative visit, the operation itself, and 1 to 5 inpatient days ($1864 in 1996 and $2055 in 2001). If a longer hospital stay was required, the additional days were priced according to the average bed day price ($247 and $297, respectively) for the university hospital. Primary health care service costs were calculated from the unit costs of these services in the Helsinki Occupational Health Care Centers. The definition of the production loss cost per sick leave day was an average daily gross wage for women in Finland, which included social security contributions ($71 and $85). The costs were discounted by the commonly recommended rate of 3% per year[23] to 1996 (average year for treatment decisions). The currency conversion had its basis in purchasing power parities in 1996 (US $1 = FIM 5.89).[24]

The uncertainty relating to analytical methods was handled by performing sensitivity analyses. Discounting was also performed using another commonly used rate of 5%.[23] Because of difficulties in measuring costs of production loss properly, a sensitivity analysis using a lower estimate of production loss (one third of the average wage rate)[25] was also performed. Checking the questionnaires and subsequently the medical records to double-check information provided in the questionnaires produced comprehensive data on costs for the 5 study years. Only the costs of Papanicolaou tests, physician appointments out of hospital related to menorrhagia, and out-of-pocket costs due to menorrhagia during years 2 to 4 were uncertain and had to be specified. To address this uncertainty, the following sensitivity analysis was performed. To calculate costs for years 2 through 4, cost data were taken from questionnaires for the last year in both groups. The data were used to calculate an average cost, which was then multiplied by 4 and added to the cost for the first year. This summary figure was used as the estimated costs of Papanicolaou tests, physician appointments out of hospital related to menorrhagia, and out-of-pocket costs due to menorrhagia for all 5 years. This approach provides a good estimate of actual costs because the first-year cost is likely different from the others and costs for the subsequent 4 years are likely to be similar. These costs were marginal, only 1% to 4% of total costs. None of the 4 women lost to follow-up during this period underwent gynecological surgery, as ascertained by checking the Finnish Hospital Discharge Register for intercurrent surgeries. Because of different pricing systems applied in other countries, we also performed a sensitivity analysis with 2 different hysterectomy prices (80% of the base case and hysterectomy price in the United States in 1996[26]).

Laboratory Investigation

Measurement of MBL occurred before randomization and after 12 months (reported previously[12]) and 5 years. Menstrual blood loss was measured using the alkaline hematin method[27] and was calculated as the average total for the duration of the participant's menstrual period. Blood hemoglobin concentrations were measured using a Coulter Counter T660 (Coulter Electronics Ltd, London, England). Serum ferritin was measured by a direct chemiluminescent immunoassay method (Chiron Diagnostics, Halsteed, England). The blood samples were drawn during period days 1 to 7.

Statistical Analysis

The target of 115 patients in each treatment group was based on power calculation. Based on an EQ-5D standard deviation (SD) of 19 percentage points (as per an analysis including a Finnish 34-

to 49-year-old female population[15]) and an α level of .05, the study had 80% power to detect a between-group difference of 7.5 percentage points. There was a mean of 5% missing data for HRQL measurement, which was treated in the analysis as follows. For the EQ-5D, if responses on fewer than 3 dimensions were missing, a mean value for the nonmissing responses was used; otherwise, the scale was coded as missing. For the RAND-36 scales having dimensions with 4 or more items, missing data were handled by computing an individual mean value of the nonmissing responses for those having responded to at least 50% of the scale items. Otherwise, the total scale was coded as missing. For the RAND-36 scales having dimensions with fewer than 4 items, no missing values were allowed (ie, the scale was coded as missing). For the general health assessment via visual analog scale, there was also a mean of 5% missing data, for which a mean value for the nonmissing responses was used. For the Spielberger, Beck, and McCoy questionnaires, there was a mean of 9% missing data and the individual mean was used if less than one third of the items were missing; otherwise, the scale was coded as missing. Using these adjustments, the means for the individual participants were used to handle the missing data except in 1%, for whom group means were used because of the extent of the missing data. If not indicated otherwise, all analyses were performed according to the intention-to-treat principle. Changes in outcome measures within the groups were tested by the paired-sample *t* test and differences in score changes between the groups were tested by the *t* test for independent samples. The Wilcoxon signed rank test was used for testing the baseline scores for the subgroup analyses. All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Probability values ≤.05 were considered statistically significant.

RESULTS

The study was conducted between October 1, 1994, and October 6, 2002. At baseline, the mean age of the 236 participants was 43 years (SD, 3.4), parity was 2.1 (SD, 1.1), and body mass index calculated as weight in kilograms divided by the square of height in meters was 25.8 (SD, 4.8) (some characteristics have been reported previously and some outcomes given herein include 1-year outcomes from that prior report[12]). Of 234 women reporting, 99 (with similar distribution between randomization groups) indicated having some medical treatment for menorrhagia in the prior 6 months and 135 reported having none. After 5 years of follow-up, 232 women (99%) of mean age 48 years (SD, 3.3) were analyzed for the main outcome measures. Overall satisfaction with the treatments was high; 94% of the women in the LNG-IUS group and 93% of the women in the hysterectomy group were satisfied or very satisfied.

LNG-IUS Outcomes

Of the 119 women randomized to treatment with the LNG-IUS, insertion of the intrauterine system could not be achieved in 2 women, 1 having cervical stricture and 1 having submucosal fibroid identified during the randomization visit. Of all women, 115 (97%) attended the 5-year follow-up, and 2 (2%) mailed the questionnaire without having a physical examination. Two (2%) women were lost to follow-up.

Five years after randomization, 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). Hysterectomy had been performed in 50 women (42%) (12 vaginally, 8 abdominally, and 30 laparoscopically, including bilateral oophorectomy in 6). Overall, 8 women underwent bilateral oophorectomy and 4 underwent unilateral oophorectomy. Fifteen (30%) of these 50 women developed complications, including postoperative pelvic infection (9), strong abdominal pains (3), wound infection (2), heavy perioperative bleeding (1), intestinal occlusion (1), postoperative bleeding (1), postoperative fever (1), and urinary retention (1).

Of the 57 women with the LNG-IUS in situ, 43 (75%) reported amenorrhea or oligomenorrhea, 11 (19%) reported irregular bleeding, and 3 (6%) reported scanty regular bleeding. The mean MBL (measured for only 4 women) was 17 mL (SD, 11.3; range, 8-32 mL). The rest of the women with the LNG-IUS had amenorrhea or only minimal spotting. Among the 60 women who did not continue treatment with the LNG-IUS, 42 (70%) reported intermenstrual bleeding; 19 (32%), heavy bleeding; and 18 (30%), hormonal symptoms (some had more than 1 complaint) for the reason of the removal of the LNG-IUS. Six women developed lower abdominal pain, 2 of whom were eventually found to have diverticulosis. Two women had the LNG-IUS removed after developing depression, 1 because of recurrent thromboembolic disease, and 1 because of benign ovarian cyst. One woman wanted hysterectomy without any specific indication. No participant discontinued the intervention because of menopause.

Hysterectomy Outcomes

Of the 117 women randomized to the hysterectomy group, 114 completed the 5-year follow-up, and 1 mailed the questionnaire without having a physical examination. One woman died in 2000 in a car crash. Only 1 woman withdrew from the study. Of the 117 women, 109 underwent hysterectomy, including 2 who had the surgery 12 months after randomization. Two women had the LNG-IUS inserted after randomization. Five women had cancelled their operation following reduced MBL or because of a job or family situation.

The hysterectomy was performed vaginally in 30 (28%) women, abdominally in 22 (20%), and laparoscopically in 57 (52%). Bilateral oophorectomy was performed in 5 cases. Overall, 7 women underwent bilateral oophorectomy and 5 underwent unilateral oophorectomy. Three bladder perforations and 1 bowel perforation were included in intraoperative complications. Postoperative complications occurred in 33 (30%) women, including wound infection (12), infected pelvic hematoma (6), urinary retention (4),

severe abdominal pain (3), ileus (2), postoperative bleeding (2), postoperative fever (2), wound rupture (2), peritonitis (1), ureter lesion (1), and vesicovaginal fistula (1).

HRQL, Other Psychosocial Outcomes

Scores on the EQ-5D were improved in both groups compared with baseline values (LNG-IUS group, $P=.002$; hysterectomy group, $P=.001$), with no substantial difference between the groups (TABLE 1).

In both groups, HRQL measured by the RAND-36 questionnaire improved significantly in all dimensions ($P<.01$) except physical functioning (LNG-IUS group, $P=.40$; hysterectomy group, $P=.30$), with no substantial differences between the groups.

General health status, as measured by visual analog scale, was significantly improved ($P=.04$) in the hysterectomy group but not in the LNG-IUS group ($P=.08$), with no substantial difference between the groups. The anxiety ($P=.001$ in both groups) and depression scores (LNG-IUS group, $P=.006$; hysterectomy group, $P=.001$) 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 ($P=.006$).

In a subgroup analysis of the LNG-IUS, the baseline RAND-36 scores for those having hysterectomy by 5 years were lower in 6 of 8 dimensions compared with those having the LNG-IUS in situ (general health, $P=.02$; physical functioning, $P=.01$; social functioning, $P=.004$; energy, $P=.009$; pain, $P<.001$; and physical role functioning, $P=.006$). The depression score was higher ($P=.02$). The follow-up score changes did not differ substantially. Similarly, the baseline scores for those in the LNG-IUS group undergoing hysterectomy compared with those in the hysterectomy group were lower in 6 dimensions (general health, $P=.03$; mental health, $P=.05$; social functioning, $P=.003$; energy, $P=.02$; pain, $P=.02$; and physical role functioning, $P=.04$). The anxiety ($P=.03$) and depression scores ($P=.01$) were higher. The follow-up score changes did not differ substantially. Of note, these subanalyses are not based on intention-to-treat; thus, the evidence may be less robust than the other data.

Laboratory Tests

Menstrual blood loss was measured in 227 women at baseline; objective menorrhagia (ie, MBL ≥80 mL) was present in 132 (58%) women. The mean MBL was 130 mL (SD, 116) in the LNG-IUS group and 128 mL (SD, 116) in the hysterectomy group. At 5 years, only 4 of 57 women with LNG-IUS in situ

Table 1. Baseline Outcome Scores and Score Change Over 5 Years in the 2 Treatment Groups

	Mean Score (95% Confidence Interval)*				
	Baseline†		Change Over 5 Years‡		
Measure	LNG-IUS (n = 119)	Hysterectomy (n = 117)	LNG-IUS (n = 117)	Hysterectomy (n = 115)	*P* Value§
EQ-5D (scale range, 0-1)‖	0.76 (0.70 to 0.80)	0.78 (0.70 to 0.80)	0.08 (0.03 to 0.13)	0.10 (0.05 to 0.15)	.60
Rand-36 (scale range, 0-100)‖					
General health	64 (60.6 to 67.4)	65 (61.0 to 69.0)	3.6 (0.1 to 7.1)	4.4 (1.0 to 7.8)	.80
Physical functioning	83 (79.4 to 86.6)	84 (80.8 to 87.2)	–1.4 (–5.1 to 2.2)	–2.0 (–5.6 to 1.6)	.80
Emotional well-being	67 (63.2 to 70.8)	70 (66.6 to 73.4)	8.4 (4.7 to 12.2)	8.1 (4.9 to 11.4)	.90
Social functioning	72 (67.6 to 76.4)	76 (72.2 to 79.8)	8.7 (4.1 to 13.3)	9.0 (4.5 to 13.6)	.90
Energy	55 (50.6 to 59.4)	57 (53.0 to 61.0)	9.4 (5.3 to 13.6)	10.0 (5.8 to 14.1)	.90
Pain	63 (58.4 to 67.6)	62 (57.6 to 66.4)	12.8 (7.9 to 17.7)	13.4 (7.7 to 19.1)	.90
Role functioning					
Physical	65 (57.7 to 72.3)	66 (58.9 to 73.1)	8.9 (1.3 to 16.4)	10.8 (2.4 to 19.2)	.70
Emotional	61 (53.5 to 68.5)	66 (58.7 to 73.3)	16.2 (8.4 to 24.0)	12.9 (4.0 to 21.8)	.60
General health (VAS scale; scale range, 0-100)‖	73 (69.4 to 76.6)	75 (71.8 to 78.2)	0.4 (–5.1 to 6.0)	4.4 (0.2 to 8.6)	.30
Anxiety (STAI [scale range, 20-80])¶	32 (30.8 to 33.2)	31 (30.0 to 32.0)	–2.4 (–3.5 to –1.3)	–1.9 (–3.1 to –0.8)	.60
Depression (BDI [scale range, 0-39])¶	5.2 (4.2 to 6.2)	4.2 (3.4 to 5.0)	–1.2 (–2.0 to –0.3)	–1.4 (–2.0 to –0.6)	.80
Sexuality (MSS)					
Sexual satisfaction (subscale range, 5-35)#	23.6 (22.4 to 24.8)	23.7 (22.9 to 24.5)	–0.7 (–1.8 to 0.3)	0.2 (–0.9 to 1.4)	.20
Sexual problems (subscale range, 2-14)¶	4.4 (4.0 to 4.8)	4.5 (4.1 to 4.9)	–0.02 (–0.6 to 0.5)	–0.04 (–0.6 to 0.5)	>.99
Satisfaction with partner (subscale range, 3-21)#	11.2 (10.6 to 11.8)	11.6 (11.2 to 12.0)	–0.7 (–1.2 to –0.2)	–0.4 (–1.0 to 0.3)	.30

Abbreviations: BDI, Beck Depression Inventory; EQ-5D, 5-Dimensional EuroQol; LNG-IUS, levonorgestrel-releasing intrauterine system; MSS, McCoy Sex Scale; RAND-36, RAND 36-Item Short-Form Health Survey; STAI, Spielberger State-Trait Anxiety Inventory; VAS, visual analog scale.
*For the current analysis, there was a mean of 5% missing data for health-related quality of life measurement, a mean of 5% for the VAS general health assessment, and a mean of 9% for the STAI, Beck, and McCoy scales. See the "Statistical Analysis" section in the text for methods of handling missing data.
†Baseline values have been reported.[12]
‡By *t* test for paired samples comparing baseline and follow-up scores (see text for presentation of results and *P* values).
§Difference in change between the groups, tested by *t* test for independent samples.
‖Higher scores indicate better health-related quality of life.
¶Higher scores indicate more symptoms or problems.
#Higher scores indicate more satisfaction.

who had bleeding (out of 11 having irregular bleeding and 3 having regular scanty bleeding) contributed samples for MBL. All the other women had only minimal spotting. Blood hemoglobin and serum ferritin concentrations (measured in all participants at baseline and those in the study at 5-year follow-up) were significantly higher in both groups after 5 years, with no substantial difference between the groups (R.H., unpublished data, August 2003).

Cost Analysis

The costs of health care, out-of-pocket costs (ie, medication, travel), and productivity losses (ie, sick leave days) are provided in TABLE 2. The discounted total cost per participant was $2817

Table 2. Total (Direct and Indirect) Cost of Menorrhagia in the LNG-IUS and Hysterectomy Groups*

Cost Component	Unit Cost, US $		LNG-IUS		Hysterectomy	
	1996	2001	No.	Cost, US $	No.	Cost, US $
Cost Components						
LNG-IUS						
First LNG-IUS	185	165	117	21 675	2	331
Reinserted LNG-IUS	185	165	58	9691		
Hysterectomy	1864	2055	50	98 167	109	203 601
Extra inpatient days	247	297	20	5695	45	11 097
Relaparoscopy	1502	1569	1	1569		
Readmissions because of complication						
Infection (inpatient days)	247	297	10	2668	35	8631
Urinary retention (inpatient days)	247				3	740
Occlusion (inpatient days)	247	297	12	3569	17	4886
Secondary hemorrhagia (operation)	1527				2	3054
Laparoscopy because of pain	1475				1	1475
Suture of ileum, with 11 days in intensive care					1	11 000
Laparotomy because of occlusion					1	3102
Nephrostoma, with 2 inpatient days					1	1273
Ureterneocystostomia and oophorectomy, with 8 inpatient days					1	5494
Curettage/hysteroscopy	542	798	6	4275		
Thermoablation		1225	1	1225		
Laparoscopic oophorectomy for ovarian cyst	1475	1503	5	7429	3	4508
Outpatient visits (controls and complications)†	110	124	652	74502	600	68 140
Health care use out of hospital						
Visits to general practitioner at health center	46	58	29	1480	8	366
Visits to private physician	27	40	2	54	1	27
Visits to private gynecologist	42	53	30	1563	14	729
Papanicolaou test		31	83	2537	39	1192
Out-of-pocket costs						
Medication				656		1017
Travel				398		861
Summary of Health Care Costs						
Direct costs						
Total health care costs				237 153		331 525
Discounted total costs per participant (95% CI)‡				1892 (1352-2189)		2787 (2312-3133)
Indirect costs						
Sick leave days	71	85	1484	115747	3050	220 459
Discounted productivity losses per participant (95% CI)‡				925 (725-1232)		1873 (1650-2096)
Total costs				352 900		551 984
Total costs per participant (95% CI)				2966 (2362-3679)		4718 (4072-5238)
Discounted total costs‡				335 172		545 272
Discounted total costs per participant (95% CI)‡				2817 (2222-3530)		4660 (4014-5180)

Abbreviations: CI, confidence interval; LNG-IUS, levonorgestrel-releasing intrauterine system.
*Baseline values have been reported.[12] All costs are menorrhagia-related. To facilitate ease of comprehension, decimal values for the unit costs (eg, $185.26 and $165.37 for 1996 and 2001 LNG-IUS costs) are not provided, which, when multiplied, resulted in the summary values given herein. Also, costs may reflect a combination of 1996 and 2001 unit costs depending on the year in which interventions occurred (see "Methods" section). For some cost components a unit cost is not provided because the cost given reflects total management cost for the condition.
†"Controls" indicate planned follow-up visits at 6 months, 1 year, and 5 years as per study design. For women having hysterectomy, there was also a planned visit 4 weeks after hysterectomy. The other visits were due to complications.
‡Discounted by 3%.

Table 3. Results of Sensitivity Analysis

Variable Used in Analysis	Total Cost per Participant, US $	
	LNG-IUS	Hysterectomy
Base case*	2817	4660
Discount rates for costs		
No discounting	2939	4688
Discount rate 5%	2759	4640
Productivity loss (indirect cost)		
Lower estimate†	2188	3411
Health care use (direct cost)		
Estimated use‡	2932	4708
Cost of hysterectomy (direct cost)		
Lower estimate§	2738	4313
Mean 1996 US hysterectomy cost‖	3186	6640

Abbreviation: LNG-IUS, levonorgestrel-releasing intrauterine system.
*Discounted by 3%.
†One third of the average wage rate.
‡Estimated costs of Papanicolaou tests, physician appointments out of hospital related to menorrhagia, and out-of-pocket costs due to menorrhagia of 3 years added to base case.
§Twenty percent lower than base case.
‖Mean cost of hysterectomy in the United States in 1996 was $3995.[26]

(95% confidence interval [CI], $2222-$3530) in the LNG-IUS group and $4660 (95% CI, $4014-$5180) in the hysterectomy group. Both the discounted direct cost and the discounted productivity losses (indirect cost) were significantly lower in the LNG-IUS group vs the hysterectomy group (direct cost: $1892 [95% CI, $1352-$2189] vs $2787 [95% CI, $2312-$3133], respectively; productivity losses: $925 [95% CI, $725-$1232] vs $1873 [95% CI, $1650-$2096]). Because the difference in quality-adjusted life-years showed no statistical difference between the groups, no incremental cost-utility ratio was calculated.

The robustness of our findings was tested using different estimates of discount rate, cost of hysterectomy, wage rate, and health care use (visits to private physicians, Papanicolaou tests, and medications). The sensitivity analyses showed that these variables had no significant effect on the difference in cost (TABLE 3). The serious adverse events in 2 women in the hysterectomy group caused extra costs due to 11 inpatient days in the intensive care unit involving suture of the ileum and 10 inpatient days involving nephrostoma or ureterneocystostomia and oophorectomy. However, if these costs are distributed among all women in the hysterectomy group, the net effect is only $128 per woman.

COMMENT

We showed that in the treatment of menorrhagia, the health-related quality-of-life outcomes associated with the LNG-IUS and hysterectomy were similar. Although 42% of the women assigned to the LNG-IUS group subsequently underwent hysterectomy, the overall direct and indirect costs after 5 years were still approximately 40% lower in the LNG-IUS group. In general, women were equally satisfied with the LNG-IUS and with hysterectomy.

All 5 university hospitals in Finland participated in the study. The dropout rate was very low (1%), showing high commitment of the participating women and absence of compliance bias. The characteristics of the study population did not differ from those in other studies of menorrhagia. Our inclusion criteria followed general clinical guidelines, suggesting that selection bias was unlikely. Moreover, the use of different techniques of hysterectomy reflected current practice in true clinical settings. Although not all women referred for menorrhagia complaints were included, those not participating either did not provide consent or were unable to meet the eligibility criteria. We thus suggest that the study group represents women who were true candidates for both treatment options and that the findings are generalizable.

The complication rate of hysterectomy was high when compared with register studies[28,29] but in the same range when compared with cohort studies.[30,31] The LNG-IUS discontinuation rate also was relatively high. However, this is in line with other recent studies also showing a relatively high discontinuation rate after 2 years (34%),[32] or after 4 to 5 years (50%).[33] Success or failure of treatment with hysterectomy or the LNG-IUS is multifactorial and difficult to predict in an individual case. Our subanalyses suggest that lower baseline scores in HRQL predict poorer continuation rate with the LNG-IUS. It is possible that women in the LNG-IUS group having hysterectomy had lower tolerance for adverse effects of the LNG-IUS because of psychosocial problems.

There is some controversy as to whether the results of an economic analysis performed in 1 country can be generalized to other countries. Also, the relative price of hysterectomy likely correlates with the likelihood of its use as a treatment choice. We therefore performed sensitivity analyses for discounting rate, productivity loss, health care use, and cost of hysterectomy. The results revealed no significant effect on cost, but the higher price of hysterectomy made use of the LNG-IUS even more attractive. We have also reported the estimates separately so that readers can judge the relevance of the trial to their local clinical settings.

Randomized health economic trials of menorrhagia are rare. Five reports from 3 randomized trials have compared costs of endometrial resection vs hysterectomy.[6,34-37] These trials showed that although endometrial resection has less health care cost than hysterectomy, the cost disparity narrowed over a prolonged follow-up primarily because of the retreatment of women who underwent endometrial resection. After 4 months, the cost of resection was 53% of hysterectomy, whereas after 2 and 4 years the costs accounted for 71%[37] and 93%,[6] respectively. This study is the first long-term randomized outcomes and cost trial comparing medical and surgical treatments of menorrhagia. The find-

ings after the first year suggested that the decision to treat menorrhagia with hysterectomy rather than with the LNG-IUS was approximately 3 times more expensive.[12] After 5 years, treatment with the LNG-IUS was still 40% less expensive than hysterectomy.

It has been suggested that introduction of endometrial ablation has increased the overall rate of expensive surgical procedures.[38] In England, hysterectomy rates have increased despite the growing popularity of endometrial ablation.[38] In Finland, the use of endometrial ablation is low but the LNG-IUS is widely accepted (Finnish Social Insurance Institution, unpublished data, January 2001). The national hysterectomy rate has declined by about 13% since 1998 (Finnish Hospital Discharge Register, unpublished data, 2001), suggesting that the use of the LNG-IUS is already changing clinical practice.

Because menorrhagia is often a reason for seeking medical attention, it is important to consider the outcomes and costs of various treatment options to provide the most appropriate care. The LNG-IUS may improve HRQL at relatively low cost, undoubtedly enhances patient choice, and may reduce surgery-related costs.

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