A randomized controlled trial of hysterectomy or levonorgestrel-releasing intrauterine system in the treatment of menorrhagia—effect on FSH levels and menopausal symptoms

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BACKGROUND: The purpose of this study was to compare the effects of hysterectomy and a levonorgestrel-releasing intrauterine system (LNG-IUS) on serum FSH levels and menopausal symptoms. METHODS: A total of 236 women referred for menorrhagia to five university hospitals were randomly assigned to treatment with hysterectomy (n = 117) or LNG-IUS (n = 119). Menopausal symptoms were characterized by the Kupperman menopausal distress test. Serum FSH and estradiol levels were measured at baseline and 6 and 12 months after hysterectomy or application of LNG-IUS. Analyses were by intention to treat. RESULTS: After 6 months, there was no difference between the groups, but 12 months after follow-up hysterectomized women had higher FSH levels than women with LNG-IUS (P = 0.005). There was a significant association between FSH levels and treatment modality (P = 0.020). Hot flushes increased significantly in the hysterectomy group (P = 0.02). There was a significant association between hot flushes and both treatment modality and age (P = 0.02 and P = 0.01, respectively). CONCLUSION: Hysterectomy may impair ovarian function shown by rising serum FSH levels and hot flushes. However, these results should be interpreted with caution, and longer follow-up is needed.

Key words: FSH/hot flushes/hysterectomy/levonorgestrel-releasing intrauterine system/menopausal symptoms

Introduction

Hysterectomy is one of the most common surgical procedures performed on women (Coulter et al., 1988; Vuorma et al., 1998). However, studies reporting its long-term effects are rare and provide contradictory results. Some reports show early menopause (Riedel et al., 1986; Menon et al., 1987; Siddle et al., 1987; Oldenhave et al., 1993; Hartmann et al., 1995; Stadberg et al., 2000), a rise in plasma FSH and LH levels (Kaiser et al., 1989; Derksen et al., 1998; Cooper and Thorp, 1999; Muttukrishna et al., 2002) or a transient post-operative decrease in estradiol and progesterone levels (Stone et al., 1975; Vuorento et al., 1992; Dogan et al., 1998; Muttukrishna et al., 2002). On the other hand, some studies report no effect on the levels of gonadotrophins or estradiol and progesterone (Stone et al., 1975; Coppen et al., 1981; Ellsworth et al., 1983; Menon et al., 1987; Feeney et al., 1995; Buekers et al., 2001). The levonorgestrel-releasing intrauterine system (LNG-IUS) has recently been advocated as an effective alternative to hysterectomy in the treatment of menorrhagia (Lähteenmäki et al., 1998; Hurskainen et al., 2001). Studies with LNG-IUS on ovarian function show only a minimal effect (Nilsson et al., 1984; Söderström-Anttila et al., 1997). However, none of the studies has compared hysterectomy and LNG-IUS in terms of the effect on FSH levels or menopausal symptoms.

We performed a randomized controlled trial to compare ovarian function and menopausal symptoms among women with menorrhagia who had been randomized to treatment with hysterectomy or LNG-IUS.
Materials and methods
A detailed description of the original study design has been reported elsewhere (Hurskainen et al., 2001). Of 598 women referred for menorrhagia to the five university hospitals in Finland between November 1994 and November 1997, 236 were eligible for the study and agreed to participate. Women were randomly assigned to treatment with LNG-IUS (n = 119) or hysterectomy (n = 117). The women were 35–49 years old, were menstruating, had completed their family and were eligible for hysterectomy (with no plans for oophorectomy). Women with submucous fibroids, endometrial polyps, urinary or bowel symptoms due to large fibroids or ovarian pathology were excluded. Specific characteristics of the study population have been reported in detail elsewhere (Hurskainen et al., 2001).

LNG-IUS (Mirena, Leiras Co., Turku, Finland) was inserted during the randomization visit. Hysterectomy was performed abdominally, vaginally or laparoscopically at the discretion of the physician. The follow-up visits took place 6 and 12 months after hysterectomy or application of the LNG-IUS.

The study was approved by the Ethics Committees of all university hospitals and STAKES (National Research and Development Center for Welfare and Health).

Questionnaire
All women completed a questionnaire including information on body mass index (BMI), smoking, method of contraception and menopausal symptoms at the randomization visit and 6 and 12 months after the treatment. The Kupperman test of menopausal distress was used to measure menopausal symptoms (Kupperman et al., 1959). It is a 10-item questionnaire of hot flushes, sweating, insomnia, nervousness, melancholia, vertigo, weakness, pain, headache and palpitation. The scores range from 0 to 3 (none, mild, moderate and severe). The Kupperman index was calculated as reported (Kupperman et al., 1959).

Laboratory investigations
Serum FSH and estradiol levels were measured at baseline and 6 and 12 months later. Baselines of all the blood samples were measured at the early follicular phase (period days 1–7). FSH levels were measured by an immunofluorometric method (Wallac, Turku, Finland). Serum estradiol concentrations were measured from a subgroup of 100 women at Helsinki University Central Hospital by using a $^{125}$I-RIA kit (DPC Corporation, Los Angeles, CA).

Statistical analysis
All analyses were performed according to the intention-to-treat principle unless otherwise indicated. Student’s t-test for independent samples and Wilcoxon test were used to test differences in main outcomes between the groups pre- and post-treatment. Changes in outcome measures within the groups were tested by paired sample t-test and signed rank test. A multiple regression model was used to test association between FSH levels and explaining factors and between Kupperman test variables and explaining factors. The variable of the Kupperman test was added in dichotomized form, and potential explaining factors either in continuous (BMI and age) or dichotomized form (treatment modality, smoking and sterilization). Probability values ≤0.05 were considered significant.

Results
Selected characteristics of the study populations are shown in Table I. After the first year, 107 women randomized to the hysterectomy group had had a hysterectomy (20% abdominally, 28% vaginally and 52% laparoscopically). Bilateral oophorectomy had been performed in five (4%) women. Five patients withdrew from the study and five patients did not want to undergo hysterectomy for personal reasons. Six (5%) women used estrogen replacement therapy (ERT).

After the first year, the LNG-IUS was in situ in 81 (68%) women randomized to the LNG-IUS group. Twenty-four women (20%) had undergone hysterectomy including two (2%) oophorectomies. Ten women had their LNG-IUS removed and three were lost to follow-up. Five (4%) of the women used ERT.

In the hysterectomy group, serum FSH increased from 8.4 ± 0.6 IU/ml (mean ± SEM) to 9.2 ± 1.0 IU/ml at 6 months and to 13.8 ± 1.9 IU/ml at 12 months post-operatively. The corresponding figures in the LNG-IUS group were 8.7 ± 0.8, 8.4 ± 1.1 and 9.2 ± 1.0 IU/ml, respectively (Figure 1). Within the groups, the increase of serum FSH was significant after 12 months (P = 0.001). Serum FSH was significantly higher in the hysterectomy group at the 12 month follow-up visit (P = 0.005). Surgical technique did not influence FSH levels (data not shown). Regression analysis showed significant association between FSH levels and age (P = 0.001) and treatment modality (P = 0.020). We also analysed the results by age by looking separately at women <43 years old versus those ≥43 years old. Among younger women, FSH decreased (−1.9 ± 0.5 IU/ml) in the LNG-IUS group and increased

### Table I. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Hysterectomy</th>
<th>LNG-IUS</th>
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<tr>
<td></td>
<td>(n = 117)</td>
<td>(n = 119)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>43.1 (3.5)</td>
<td>43 (3.2)</td>
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<tr>
<td>Parity*</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.0)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)*</td>
<td>26.6 (5.1)</td>
<td>25.1 (4.5)*</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>65 (55%)</td>
<td>66 (56%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>28 (25%)</td>
<td>34 (32%)</td>
</tr>
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</table>

Data are the mean (SD)* or the number of women.
In the hysterectomy group, estradiol levels (mean 30 ± 0.02 pg/ml in the LNG-IUS group and 28 ± 0.02 pg/ml in the hysterectomy group) at 12 months follow-up.

At baseline, the Kupperman index scores on menopausal symptoms showed no difference between the groups except that headache was more common in the LNG-IUS group at 12 months follow-up (Table II). No difference was shown between the groups, however, due to limitations of the study designs, no firm conclusions can be drawn from these studies.

Subsequent studies have shown that both menopausal hormone profile and climacteric symptoms develop earlier after hysterectomy compared with controls without hysterectomy (Riedel et al., 1986; Menon et al., 1987; Siddle et al., 1987; Kaiser et al., 1989; Oldenhave et al., 1993; Hartmann et al., 1995; Derksen et al., 1998; Cooper and Thorp, 1999; Stadberg et al., 2000). The younger the age at hysterectomy, the more severe were the symptoms (Siddle et al., 1987; Kaiser et al., 1989; Oldenhave et al., 1993). However, it has been difficult to rule out selection bias since none of the studies have been randomized. Even if control groups were included, confounding factors have been difficult to rule out (Siddle et al., 1987; Kaiser et al., 1989). Our results are in accordance with these studies suggesting that hysterectomy impairs ovarian function. In the current randomized study, the effect of key confounding factors such as age, parity, BMI, smoking and history of sterilization could be eliminated.

The mechanism by which simple hysterectomy impairs ovarian function remains unclear. According to one theory,
diminished arterial blood flow leads to increased intercellular congestion and oedema, which may result in stromal cell hyperplasia, thickening of the tunica albuginea, a significant decrease in follicular reserve of the ovaries, and endocrinological disturbances (Souza et al., 1986). Ovaries produce less inhibins which is seen as a rise in the FSH level (Muttukrishna et al., 2002). The vascular theory is also supported by reports suggesting ovarian dysfunction after uterine artery embolization (Payne et al., 2002; Tulandi et al., 2002).

Another theory suggests an interaction between the endometrium and the ovaries. Accordingly, the balance between ovaries and endometrium is changed, which may affect the ovary–pituitary gland axis. This may explain the report of the rise of serum FSH level after both hysterectomy and endometrial ablation (Derksen et al., 1998).

In the current study, the effect of hysterectomy on menopausal symptoms and hormonal changes was compared with that in women using LNG-IUS. In LNG-IUS users, low serum concentrations of LNG have only a weak effect on ovarian function; after the first year of use, 85% of all menstrual cycles are ovulatory according to serum progesterone concentrations (Nilsson et al., 1984). Ovaries of LNG-IUS users respond similarly to gonadotrophin stimulation compared with non-users. Oocyte maturation remains unaffected (Söderström-Anttila et al., 1997) and systemic side effects are rare (Barbosa et al., 1990; Ronnerdag and Odlind, 1999). In this study, the FSH levels in the serum increased 4% among LNG-IUS users. An equal rise in FSH is seen among women of similar age with normal reproductive health (Burger et al., 1997; Erdem et al., 2002).

Cooper and Thorp (1999) reported that smoking increases serum FSH levels twice as much as hysterectomy. Our study does not support this. Regression analysis revealed no correlation between smoking and serum FSH levels. Probably smoking must be heavy to affect FSH. As only 12% smoked >10 cigarettes per day in our study, it has no effect on FSH levels. Blood samples for the measurement of FSH 6 and 12 months after the treatment were not adjusted according to the menstrual cycle in either group since many of the patients had amenorrhea or irregular light bleeding. This may have introduced a systematic bias to the detection of the increased FSH levels, although this is unlikely since this was the case in both groups. The Kupperman test of menopausal distress was developed to measure symptoms in menopausal women. Among the premenopausal women included in the study, the Kupperman index may have been too insensitive to show minor differences between the groups. Some of the symptoms measured, such as vertigo, headache or muscle pain, probably have origins other than menopause. The study is limited by the relatively small number of patients, short duration of follow-up and the single hormone assays. Rising serum FSH levels in the hysterectomy group occurred mainly during the last 6 months of follow-up, showing that it is important to expand the observation period.

In summary, the present study suggests that hysterectomy may impair ovarian function, as seen by rising FSH levels and increasing incidence of menopausal symptoms. Since hysterectomy is a common treatment modality for a benign disease, it is important to remember that the long-term effects of hysterectomy may include impaired ovarian function.

References


Submitted on May 29, 2003; accepted on September 26, 2003