Hysterectomy and levonorgestrel-releasing intrauterine system
in the treatment of menorrhagia
– a 10-year randomized comparative trial

Satu Heliövaara-Peippo

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ORIGINAL PUBLICATIONS
List of original publications

The thesis is based on the following original publications, which are referred to in the text by Roman numerals I-IV:

I  
Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: A 10-year randomized controlled trial. Submitted.

II  
The effect of hysterectomy or levonorgestrel-releasing intrauterine system on lower abdominal pain and back pain among women treated for menorrhagia – a five-year randomised controlled trial. Acta Obstetricia et Gynecologica 2009; 88: 1389-1396.

III  

IV  

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<th>Description</th>
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<tr>
<td>BDI</td>
<td>Beck depression inventory</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>EA</td>
<td>Endometrial ablation</td>
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<tr>
<td>ET</td>
<td>Oestrogen therapy</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>5-dimensional EuroQol</td>
</tr>
<tr>
<td>FIE</td>
<td>Feeling of incomplete emptying</td>
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<tr>
<td>GnRH-a</td>
<td>Gonadotrophin-releasing hormone analogue</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>hsCRP</td>
<td>High-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>IDF</td>
<td>Increased daytime frequency</td>
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<tr>
<td>LNG-IUS</td>
<td>Levonorgestrel-releasing intrauterine system</td>
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<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>MBL</td>
<td>Menstrual blood loss</td>
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<tr>
<td>MSS</td>
<td>McCoy sex scale</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life-year</td>
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<tr>
<td>PBAC</td>
<td>Pictorial blood loss assessment chart</td>
</tr>
<tr>
<td>RAND 36</td>
<td>RAND 36-Item health survey</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>STAI</td>
<td>Spielberger state-trait anxiety inventory</td>
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<tr>
<td>SUI</td>
<td>Stress urinary incontinence</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>UI</td>
<td>Urinary incontinence</td>
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<tr>
<td>UISS</td>
<td>Urinary incontinence severity score</td>
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<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
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<tr>
<td>UUI</td>
<td>Urge urinary incontinence</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>VuoKKo</td>
<td>Finnish word shortened from menstruation, intrauterine system and hysterectomy (Vuodot, KIerukka, KOhdunpoisto)</td>
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Abstract

Menorrhagia significantly impairs the quality of life of many women and causes major health care costs. Hysterectomy has been the standard treatment for menorrhagia, with a high satisfaction rate. However, alternative management strategies have gained in popularity and raised questions about the cost, morbidity, health-related quality of life (HRQoL) and possible long-term effects on health associated with treatment modalities. Levonorgestrel-releasing intrauterine system (LNG-IUS) has been advocated as an alternative to surgery.

The VuoKKo trial set out to assess and compare the LNG-IUS and hysterectomy in the treatment of menorrhagia, and it consisted of 236 women, aged 35–49 years, referred for menorrhagia to the five university hospitals in Finland between November 1994 and November 1997. Of these women, 117 were randomized to treatment with hysterectomy and 119 to treatment with LNG-IUS. The follow-up visits took place at 6 months and 1 year after treatment and again 5 and 10 years after randomization. The objective of this present study was to identify and compare the cost-effectiveness and effects on HRQoL, pain, lower urinary tract symptoms (LUTS) and cardiovascular disease (CVD) risk factors of these two treatment modalities during a 10-year follow-up. The continuation rate at 10 years was 94%. Of the 119 women assigned to LNG-IUS, 55 (46%) subsequently underwent hysterectomy over the 10 year period. Of the women assigned to hysterectomy, 109 (93%) underwent hysterectomy. The analyses for HRQoL, cost-effectiveness and pain were performed by intention-to-treat principle and for lower urinary tract symptoms and cardiovascular disease risk factors by actual treatment principle.

HRQoL and other measures of psychosocial well-being (anxiety, depression, sexual function) improved during the first 5 years, but diminished between 5 and 10 years, and the improved HRQoL returned to almost its baseline levels, presumably due to ageing. No significant differences emerged between the LNG-IUS and hysterectomy groups, but the overall costs per participant were substantially lower in the LNG-IUS group ($3423) than in the hysterectomy group ($4937).

Both hysterectomy and LNG-IUS decreased pain. At baseline, 45% of the women in the LNG-IUS group and 38% of the women in the hysterectomy group reported lower abdominal pain, and 64% / 65% of the women reported back pain. At 10 years, 16% (LNG-IUS) and 18% (hysterectomy) of the women reported lower abdominal pain and 38% / 36% reported back pain. In both groups, the pain decreased most during the first 6 months and monthly frequent pain decreased most of all. Lower abdominal pain score (occurrence and intensity combined) decreased in both groups during the 10 years, but back pain score decreased only in the LNG-IUS group.
Women treated by hysterectomy used more often medication for urinary incontinence than women treated by LNG-IUS (12% vs. 1%, p=0.006) during the 10-year follow-up. Moreover, urinary tract infections (34% vs. 14%, p=0.002), feeling of incomplete emptying (19% vs. 9%, p=0.04) and stress urinary incontinence (48% vs. 34%, p=0.04) were more common in women with hysterectomy than in LNG-IUS users.

The CVD risk profile showed that women treated by hysterectomy had higher levels of inflammatory cytokines, tumour necrosis factor α at 5 years (median 108.59 vs. 49.02 pg/ml, p=0.001) and high-sensitivity C-reactive protein at 10 years (median 1.55 vs. 0.78 mg/ml, p=0.04) than women treated by LNG-IUS. No differences between the groups were detected in traditional cardiovascular disease risk factors. Women treated by hysterectomy used more often oestrogen therapy than women treated by LNG-IUS at 5 years (29% vs. 10%, p=0.003) and 10 years (56% vs. 27%, p<0.001) after the treatment.

In conclusion, LNG-IUS is a safe and cost-effective alternative to hysterectomy in the treatment of menorrhagia. Despite 46% of women assigned to LNG-IUS eventually having a hysterectomy, the overall costs were approximately 31% lower in the LNG-IUS group than in the hysterectomy group. Both hysterectomy and LNG-IUS have a favourable effect on HRQoL and pain in menorrhagia patients, but hysterectomy seems to predispose women more to CVD risk factors and LUTS over the long run.
1. Introduction

Heavy cyclical menstrual bleeding over several consecutive cycles is known as menorrhagia. Menorrhagia is a common health problem, affecting nearly one-third of women at some point during their reproductive years and causing distress and ill health in women worldwide (Rees 1987, Shapley et al. 2004).

Hysterectomy has been a preferred treatment option for menorrhagia due to its immediate effectiveness and definitiveness. However, the morbidity and costs associated with hysterectomy cannot be ignored (Fernandez et al. 2003, Hurskainen et al. 2004b). Less invasive treatment options, such as levonorgestrel-releasing intrauterine system (LNG-IUS) and endometrial ablation (EA), are becoming increasingly popular. Of the medical treatment modalities, LNG-IUS is well tolerated and the most effective (Marjoribanks et al. 2006). Both hysterectomy and LNG-IUS have high satisfaction rates among menorrhagia patients (Hurskainen et al. 2004b). Randomized studies comparing LNG-IUS and hysterectomy in the treatment of menorrhagia are few (Matteson et al. 2012). The Finnish Vuokko study carried out in 1994 aimed to compare health-related quality of life (HRQoL) and costs after hysterectomy and LNG-IUS. After 1 and 5 years, both treatments had a similar favourable effect on HRQoL, but the costs associated with treatment were substantially lower in the LNG-IUS group, despite many (20% at 1 year and 42% at 5 years) of the women assigned to this group eventually having to undergo hysterectomy (Hurskainen et al. 2004b). This study was conducted to determine whether the impact of the two treatments on HRQoL and costs remains after 10 years, when the women have aged and most have reached menopause. Moreover, the long-term effect of these treatment options on other aspects of health needed to be elucidated.

Dysmenorrhoea, lower abdominal pain and back pain are common among menorrhagia patients (Molnar et al. 1997, Hurskainen et al. 2001a). Hysterectomy is an efficient treatment for dysmenorrhoea, and in most women chronic pelvic pain decreases after hysterectomy (Learman et al. 2004). Previous studies have shown that also LNG-IUS decreases dysmenorrhoea and chronic pelvic pain (Bahamondes et al. 2007, Anpalagan and Condous 2008, Alhamdan et al. 2010). However, no comparative studies of the impact of these treatments on abdominal pain or back pain in menorrhagia patients exist.

Female urinary incontinence (UI) is an increasingly common complaint (Miner 2004, Kenton et al. 2006). Hysterectomy has been linked to lower urinary tract symptoms (LUTS), including UI, in some, but not all, studies (Brown et al. 2000, van der Vaart et al. 2002, Altman et al. 2007). The long-term
The effect of hysterectomy on LUTS has not been investigated extensively and studies evaluating the impact of hysterectomy on urinary tract infections are lacking.

Cardiovascular diseases (CVDs) are the main cause of death in Western countries. Hysterectomy impairs ovarian function and may cause early menopause (Halmesmäki et al. 2004, Farquhar and Steiner 2005, Moorman et al. 2011). Early menopause, in turn, increases the risk for CVDs (Punnonen et al. 1987, Kharazmi et al. 2007). LNG-IUS seems to have a marginal effect on ovarian function and no effect on menopausal age (Barbosa et al. 1990, Halmesmäki et al. 2004, Halmesmäki et al. 2007a).

Consequently, the aim of this study was to evaluate and compare the effects of LNG-IUS and hysterectomy on HRQoL, pain, LUTS and CVD risk factors in the treatment of menorrhagia and the long-term costs of these two treatment options.
2. Review of the literature

2.1 Menorrhagia

Menorrhagia is subjectively defined as a complaint of heavy cyclical menstrual bleeding occurring over several consecutive cycles (Royal College of Obstetricians and Gynaecologists 1998). Objectively, menorrhagia is a total menstrual blood loss (MBL) of 80ml or more per menstruation (Hallberg and Nilsson 1964). This threshold is derived from population studies showing that average MBL is between 30 and 40 ml, and that 90% of women have blood losses of less than 80ml (Hallberg et al. 1966a, Cole et al. 1971). Moreover, MBL of over 80 ml has been found to be associated with iron deficiency anaemia (Hallberg et al. 1966b). However, half of the women with a subjective complaint of menorrhagia have been shown to have normal levels of MBL when MBL is actually measured (Fraser et al. 1984, Higham et al. 1990, Hurskainen et al. 1998). Thus, factors other than the actual amount of MBL are likely to affect the threshold for seeking care. Perception of menorrhagia is subjective and management usually depends upon what symptoms are acceptable to an individual. In this study, menorrhagia is defined as a complaint of heavy regular menstrual bleeding over several consecutive cycles.

Menorrhagia may be the result of systemic or uterine disorder or iatrogenic causes (Rees 1987, Livingstone and Fraser 2002). Systemic disorders include hypothyroidism and haematological disorders such as bleeding diatheses, e.g. von Willebrand’s disease (Krassas et al. 1999). Local disorders include adenomyosis, fibroids and endometrial polyps (Livingstone and Fraser 2002). Iatrogenic disorders result from medications such as anticoagulant therapy or copper intrauterine device. In half of all cases, no specific aetiology is known and menorrhagia is called essential. Nevertheless, a strong association has been described between family history and essential menorrhagia (Kuzmina et al. 2011). In this study menorrhagia refers to essential menorrhagia.

The pathogenesis of essential menorrhagia is poorly understood. Approximately 50% of menorrhagia patients present no evidence of uterine pathology at hysterectomy (Clarke et al. 1995), suggesting a defect in the cellular process and regulatory mechanism of menstruation. In ovulatory cycles, excessive MBL has been ascribed to abnormal uterine levels of prostaglandins (Hagenfeldt 1987, Livingstone and Fraser 2002). Moreover, endometrial fibrinolytic enzymes and increased fibrinolysis appear to have an important role in menorrhagia (Gleenson 1994). In addition, disturbed angiogenesis and abnormal vascular smooth muscle cells of endometrial spiral arterioles in women with menorrhagia have been associated with an enhanced role of vascular endothelial growth factor and

Assessing MBL is the main problem in the diagnosis of menorrhagia, and several methods to determine the amount of MBL have been developed. MBL can be measured by alkaline haematin extraction method, which is the most accurate measure of MBL, but requires collection of sanitary pads and is difficult in everyday practice (Hallberg and Nilsson 1964, Hurskainen et al. 1998). Total menstrual fluid loss can also be used as an assessment of MBL. Measurement is determined by the difference in weight of tampons or pads before and after use (Reid and Virtanen-Kari 2005). This method does not give accurate information of blood volume because women secrete different amounts of exudates from the uterus and vagina. Haemoglobin concentration measure is widely used in assessment of MBL. When MBL exceeds 80 mL, the incidence of anaemia (haemoglobin less than 120 mg/L) is increased significantly (Hallberg et al. 1966b, Janssen et al. 1995). However, the association is very inaccurate because the amount of iron in food and normal haemoglobin levels in individuals varies.

A simpler measure that is often used is the pictorial blood loss assessment chart (PBAC), by which the amount of MBL is determined visually using a pictorial chart form (Higham et al. 1990, Janssen et al. 1995, Reid et al. 2000). The Finnish Current Care guideline for menorrhagia treatment recommends use of interviews and survey forms for menorrhagia patients to facilitate diagnosis-making and to assess the impact on HRQoL and the amount of MBL (Current Care editorial office 2005, updated 2009). The forms contain a PBAC and a score of over 185 points indicates 75-86% probability for objective menorrhagia. Nevertheless, history and the effect of menorrhagia on the woman’s life are the most important information in the diagnosis, and in practice the treatment of menorrhagia is based on these.

**Epidemiology and impact on life**

Menorrhagia is an important health care problem. An estimated 25 - 30% of women complain of menorrhagia during their reproductive years (Rees 1987, Garry et al. 2004, Shapley et al. 2004). Menorrhagia is one of the most predominant complaints in women referred to gynaecologists accounting for 10 – 20 % of outpatient referrals to gynecology (Coulter et al. 1989, Lethaby et al. 2005). In the UK, 5% of women aged 30-49 years consult their general practitioners each year for menorrhagia (Duckitt and Collins 2007), and according to a Finnish population survey 5% of women aged 25-55 years (50 000 women) annually feel the need for examination or treatment for menorrhagia (Luoto et al. 2004). However, some cultural influences have been found to determine whether or not a woman will seek medical care for menorrhagia, including her status in the society (Kuh and Stirling...
Subjective menorrhagia and likelihood to complain of menorrhagia seem to correlate with lower socioeconomic status, unemployment, abdominal pain, and psychological distress (Kuh and Stirling 1995, Hurskainen et al. 2001a, Shapley et al. 2004). Menorrhagia markedly interferes with daily activities and impairs the quality of life (QoL) of affected women (Coulter et al. 1994, Hurskainen et al. 2001b, NICE 2007, Frick et al. 2009). Moreover, menorrhagia is the most common cause of iron deficiency anaemia among fertile-aged women and causes substantial work loss (Cote et al. 2002, Liu et al. 2007). Menorrhagia creates a major burden in terms of financial costs for women and health care resources for society (Liu et al. 2007, Frick et al. 2009).

2.2 Treatment of menorrhagia

Essential menorrhagia can be treated medically or surgically. Medical treatments include oral medication and LNG-IUS (Table 1). Surgical options include mini-invasive surgery (EA) and hysterectomy (Table 1). The choice of treatment depends on personal choice of the woman, desire for future pregnancy and general health status (Vuorma et al. 2003, Wheeler et al. 2012). In addition, safety, efficacy, cost and availability of different treatment modalities affect which treatment is chosen (Marjoribanks et al. 2006, Wheeler et al. 2012). Guidelines for treatment of menorrhagia were released in Finland in 2005 (Current Care editorial office 2005, updated 2009), and two years later in the UK (NICE 2007). Medical treatment is usually preferred as first-line treatment of menorrhagia by women and professionals (Marjoribanks et al. 2006, Current Care guideline 2005, updated 2009, NICE 2007, Nelson 2010).

2.2.1 Levonorgestrel-releasing intrauterine system (LNG-IUS)

Of the medical treatment options, LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) is the most effective in reducing MBL (Marjoribanks et al. 2006, Fraser 2010, Kaunitz and Inki 2012). It has been reported to reduce MBL by 80-97% after three months and to be well accepted by most women (Irvine et al. 1998, Luukkainen 2000). Amenorrhea occurs in 50–75% women with menorrhagia following LNG-IUS insertion (Stewart et al. 2001, Varma et al. 2006). The reduction in bleeding associated with LNG-IUS use has been associated with a significant increase in haemoglobin level (Luukkainen 2000, Kriplani et al. 2007).
LNG-IUS was initially developed for contraception during the 1970s-1980s; it was licensed for contraceptive use in Finland in 1990 (Nilsson et al. 1981a, Luukkainen et al. 1990). The usefulness and effectiveness of LNG-IUS for menorrhagia were soon noted and LNG-IUS was licensed for treatment of menorrhagia in Finland in 1995. Mirena® has been approved by the Food and Drug Administrations in USA and is licenced in 130 countries worldwide for contraception and in 120 countries for a second indication – treatment of menorrhagia (according to information provided by Bayer Oy, 2012). Over 12 million women worldwide use LNG-IUS, but it is impossible to determine how many of them use it for contraception and how many for menorrhagia treatment or hormone replacement therapy.

**Structure of LNG-IUS**

LNG-IUS consists of a 32-mm-long T-shaped polyethylene frame with a hormone reservoir containing 52 mg of levonorgestrel on the stem (Figure 1). Levonorgestrel is the biologically active form of norgestrel (d-norgestrel) and is a synthetic second-generation progestin. The LNG-IUS is approved for up to 5 years’ use. However, there is evidence of effectiveness beyond this period (Faundes et al. 1993, Seeber et al. 2012). Initially, 20 $\mu$g of levonorgestrel / 24 hours is released into the uterine cavity, declining progressively to 11 $\mu$g after 5 years of use (Luukkainen et al. 1990). The concentration of levonorgestrel in the endometrium achieved with LNG-IUS is higher than with much greater daily oral doses of levonorgestrel. The mean systemic plasma level of levonorgestrel with LNG-IUS is less than those achieved with therapeutic oral or parental doses of progestogens and it decreases over time (191±71 pg/ml (mean±SD) in the first year of use, 157±68 pg/ml in the second year of use, 134±41 pg/ml in the third year of use and 133±48 pg/ml in the seventh year of use) (Seeber et al. 2012). Up to 85% of the LNG-IUS cycles are ovulatory (Nilsson et al. 1984, Lähteenmäki et al. 2000).

![Figure 1. Levonorgestrel-releasing intrauterine system (Mirena®). Printed with permission of Bayer Oy.](image)
**Mechanism of action**

The mechanism of action of LNG-IUS on menorrhagia is based on a strong local suppressive action of intrauterine-released levonorgestrel on the endometrium (Silverberg et al. 1986). The endometrium becomes unresponsive to the proliferative effect of ovarian oestrogen (Nilsson et al. 1984, Barbosa et al. 1990). The suppression of the endometrium is associated with a marked reduction in the number of days of bleeding and a reduction of MBL (Pakarinen and Luukkainen 2007). The strong suppression of the endometrium with glandular atrophy, decidualization of the stroma and inactivation of endometrial cells occur in the endometrial epithelium within three months after insertion of the LNG-IUS and remain unchanged during use of LNG-IUS (Silverberg et al. 1986).

**Other health benefits**

Besides contraception and reduction of MBL, LNG-IUS has many other beneficial health effects with important public health implications (Lähteenmäki et al. 2000, Pakarinen et al. 2001, Varma et al. 2006, Fraser 2010, Heikinheimo and Gemzell-Danielsson 2012). LNG-IUS is licensed for intrauterine protection from endometrial hyperplasia or malignant transformation during exogenous oestrogen therapy in perimenopausal and postmenopausal women in 112 countries (according to information provided by Bayer Oy, 2012). In addition, LNG-IUS seems to be an effective treatment for fibroid-related menorrhagia, with a 84-90% decrease of MBL (Soysal and Soysal 2005, Varma et al. 2006). However, information on whether LNG-IUS is associated with decreased fibroid size or no change in fibroid size is inconsistent (Maruo et al. 2003, Varma et al. 2006, Heikinheimo and Gemzell-Danielsson 2012). Several studies have shown a reduction in adenomyosis- and endometriosis-related dysmenorrhoea, menorrhagia and chronic pelvic pain (Varma et al. 2006, Heikinheimo and Gemzell-Danielsson 2012). Furthermore, LNG-IUS might decrease premenstrual symptoms (Leminen et al. 2011).

**Adverse effects**

The most frequent adverse effect (around 10-15% of users) is unscheduled erratic menstrual spotting, which usually occurs during the first 3-4 months following LNG-IUS insertion, but thereafter tends to subside (Irvine et al. 1998, Luukkainen et al. 2001). Irregular bleeding is the most common adverse effect leading to discontinuation of LNG-IUS treatment. Some women experience hormonal side effects, pain and mood changes (Istre and Trolle 2001, Lethaby et al. 2005). An increased incidence of ovarian cysts (10%-20% of users) is reported in women using LNG-IUS (Brache et al. 2002, Inki et al. 2002). The cysts are usually transient and resolve spontaneously (Brache et al. 2002, Inki et al. 2002). In the long term, the effect of the LNG-IUS on the risk of breast cancer (Backman et al. 2005,
Lyytinen et al. 2010) and other cancers remains still largely unclear. Uterine perforation is a rare complication, but expulsion rates seem to be higher among menorrhagia patients than in the general population of LNG-IUS users (Kaunitz et al. 2012). Contraindications for LNG-IUS use are uterine anomaly, active liver disorder and active thromboembolic disease (www.who.int/reproductivehealth).

Table 1. Medical and surgical treatments for essential menorrhagia.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Reduction in menstrual bleeding</th>
<th>Contraceptive?</th>
<th>Potential unwanted outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined oral contraceptives (COCs)</strong>†</td>
<td>Prevents proliferation of the endometrium</td>
<td>up to 50%</td>
<td>Yes</td>
<td>Mood changes, headaches, nausea, fluid retention, breast tenderness, deep vein thrombosis and stroke (rare)</td>
</tr>
<tr>
<td><strong>Oral progestins</strong></td>
<td>Prevents proliferation of the endometrium</td>
<td>12-20% up to 87%</td>
<td>No</td>
<td>Weight gain, bloating, breast tenderness, headaches, acne and mood changes</td>
</tr>
<tr>
<td>(days 15-26)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days 5-26)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injected / depot progestins</strong>*</td>
<td>Prevents proliferation of the endometrium</td>
<td>Amenorrhea or irregular bleeding</td>
<td>Yes</td>
<td>Weight gain, irregular bleeding, premenstrual-like syndrome, loss of bone mineral density</td>
</tr>
<tr>
<td><strong>Levonorgestrel-releasing intrauterine system (LNG-IUS)</strong>†,***</td>
<td>Prevents proliferation of the endometrium</td>
<td>70-95% (full benefit may not be seen for 6 months)</td>
<td>Yes</td>
<td>Irregular bleeding that may last for over 6 months, hormone-related problems such as breast tenderness, acne or headaches and ovarian cysts (generally transient), uterine perforation at time of insertion (rare)</td>
</tr>
<tr>
<td><strong>Tranexamic acid</strong></td>
<td>Antifibrinolytic effect</td>
<td>40-60%</td>
<td>No</td>
<td>Indigestion, diarrhoea and headaches</td>
</tr>
<tr>
<td><strong>Non-steroidal anti-inflammatory drugs (NSAIDs)</strong>, ***</td>
<td>Reduces production of prostaglandins in the endometrium</td>
<td>33-55%</td>
<td>No</td>
<td>Indigestion, diarrhoea, worsening of asthma in sensitive individuals, peptic ulcers</td>
</tr>
<tr>
<td><strong>Gonadotrophin-releasing hormone analogue</strong> (GnRHa)**</td>
<td>Stops production of oestrogen and progesterone</td>
<td>Amenorrhea in 89% of women</td>
<td>No</td>
<td>Menopause-like symptoms (such as hot flashes, increased sweating, vaginal dryness), osteoporosis</td>
</tr>
<tr>
<td><strong>Endometrial ablation</strong></td>
<td>Destruction of the endometrium by loop or rollerball with hysteroscopy or by microwaves or with heated fluid without Hysteroscopy</td>
<td>70-95% Amenorrhea 13-64%</td>
<td>No</td>
<td>Vaginal discharge, increased period pain or cramping (even if no further bleeding), infection, perforation (rare), need for additional surgery, fluid overload during hysteroscopy</td>
</tr>
<tr>
<td><strong>Hysterectomy</strong>*</td>
<td>Surgical removal of the uterus</td>
<td>Amenorrhea</td>
<td>Yes</td>
<td>Infection, intraoperative haemorrhage, damage to other abdominal organs, such as the urinary tract or bowel, thrombosis (rare), death (very rare), urinary tract symptoms</td>
</tr>
</tbody>
</table>

*NICE 2007, **Lethaby et al. 2005, ***Marjoribanks et al. 2006, ****Kaunitz et al. 2009 rare = 1 in 10 000 chance, very rare = 1 in 100 000 chance
2.2.2. Hysterectomy

Hysterectomy is one of the most common surgeries performed on women in the Western world (Farquhar and Steiner 2002). Of the indications for hysterectomy, fibroids are most common (33-55%), followed by bleeding disorders (including both menorrhagia and dysfunctional uterine bleeding) (12-31%) (Vuorma et al. 1998, Mäkinen et al. 2001, Brummer et al. 2009). For menorrhagia, hysterectomy has been the standard treatment owing to its definitive nature, with satisfaction rates of over 95% up to three years after surgery (Lethaby et al. 2000b).

In Finland, over 10 000 hysterectomies for benign reasons were performed annually 10 years ago, but as a result of new treatment guidelines and effective alternatives, the amount has gradually been decreasing, being around 6000 from the year 2007 awards (5873 in 2009 and 6232 in 2010) (Figure 2) (Hospital Discharge Register of the National Institute for Health and Welfare in Finland). In the United Kingdom the number of hysterectomies performed for menorrhagia declined by 64% between 1995 and 2002 since the introduction of LNG-IUS in 1993 and increased use of EA (Reid 2005). Figure 2 shows hysterectomies performed for benign indications and for dysfunctional uterine bleeding (including menorrhagia) as first indication in Finland between 1998 and 2010. Hysterectomy rates are based on the International Classification of Diseases (ICD-10) codes related to dysfunctional uterine bleeding (N92). However, the number of hysterectomies for menorrhagia is difficult to determine as the same women can have a diagnosis of both fibroids and menorrhagia.

The national prospective FINHYST study in 1996 showed abdominal hysterectomy as being most common (58%) (Mäkinen et al. 2001). Minimally invasive methods have since prevailed over abdominal hysterectomy, and in FINHYST study in 2006 the national distribution of hysterectomies by approach was 24% for abdominal hysterectomy, 32% for laparoscopic hysterectomy and 44% for vaginal hysterectomy (Brummer et al. 2009).

Other health benefits

Hysterectomy is an effective treatment for dysmenorrhea, chronic pelvic pain and lower abdominal pain related to endometriosis and adenomyosis (Learman et al. 2004, Luciano and Luciano 2011). Hysterectomy may also decrease the risk of ovarian carcinoma (Chiaffarino et al. 2005) and removes the risk for uterine pathology. Moreover, perimenopausal and postmenopausal women with hysterectomy are able to use oestrogen therapy (ET) without progestin.
Adverse effects and complications

Hysterectomy by any approach has a relatively high incidence of complications, such as haemorrhagia requiring transfusion, wound healing sequelae, bowel, ureter and bladder complications, and infections. Hysterectomy requires a lengthy postoperative recovery period with hospital stay and sick-leave days. A recent large prospective hysterectomy study from Finland showed major complication rates between 2.6%-4.3% and total complication rates between 11.7%-19.2%, with no significant differences between hysterectomy approaches (Brummer et al. 2011).

Previous follow-up studies have shown somewhat higher complication rates (Dicker et al. 1982, Meltomaa et al. 1999). Hysterectomy is irreversible and causes permanent infertility. Hysterectomy also appears to have some adverse long-term effects. Ovarian function seems to be impaired after hysterectomy due to altered vascularity and may cause early menopause (Halmesmäki et al. 2004, 2007a, Farquhar and Steiner 2005). Most studies have, however, shown no negative impact on sexual functioning (Thakar et al. 2002, Kuppermann et al. 2005, Halmesmäki et al. 2007b). An increased risk for development of stress urinary incontinence and pelvic organ prolapse after hysterectomy has been reported in many clinical trials (Altman et al. 2007, Lukanovic and Drazic 2010, Cooper et al. 2011).

Figure 2. Hysterectomies for benign reasons and for bleeding problems in Finland between 1998 and 2010.
2.2.3 Other treatments

Other treatment modalities available for management of essential menorrhagia are oral medical therapy and endometrial resection/ablation (EA). The mechanism, effectiveness and potential unwanted outcomes of menorrhagia treatments are given in Table 1.

Medical treatments

Anti-fibrinolytic drugs, such as tranexamic acid, inhibit fibrinolysis and reduce MBL by about 40–50% (Lethaby et al. 2000a). They are taken only during menstruation and are usually well tolerated.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the production of prostaglandins and leukotrienes and reduce blood loss by 33–55% and also relieve menstrual cramps (Lethaby et al. 2007). NSAIDs need to be taken only during menstruation.

Progestins suppress endometrial growth and activity. Given as a 12-day course, from day 15 to day 26 of the menstrual cycle, oral progestins reduce MBL by 12-20%. Given as a 21-day course, from day 5 to day 26, MBL is reduced up to 87% (Lethaby et al. 2008). Oral progestins are considered unacceptable for long-term use due to high prevalence of hormonal side effects (Irvine et al. 1998). Injected depot progestines leads to amenorrhea or oligomenorrhea, but irregular bleeding and spotting are common and osteoporosis is a harmful side effect (Marjoribanks et al. 2006).

Combined oral contraceptives (COCs) stop ovarian function, inhibit endometrial growth and development and reduce MBL by up to 50% and relieve cramping (Fraser and McCarron 1991). However, a novel COC, estradiol valerate/dienogest, seems to reduce MBL by 60-88% (Fraser and McCarron 2011, Jensen 2011).

Gonadotrophin-releasing hormone analogues (GnRH-as) block the hypothalamic-pituitary axis, decrease gonadotropin levels and reduce gonadal hormone levels to the prepubertal range. The endometrium is almost unexposed to hormone effects that result in amenorrhea. GnRH-as are generally used only for short-term treatment due to the prevalence and severity of side effects such as menopause-like symptoms and osteoporosis (NICE 2007).
Endometrial ablation

In uterus-sparing treatments, the endometrium and underlying basal glands are the target of destruction by various means. In second-generation techniques, which are performed without hysteroscopy and almost exclusively used today, a probe producing microwaves or a deflated balloon filled with heated fluid is moved into the uterus through the vagina and cervix. Compared with hysterectomy, EA has a shorter operation time and hospital stay, quicker recovery and fewer postoperative complications (Dickersin et al. 2008, Munro et al. 2011). However, the effects of EA, hysterectomy and LNG-IUS on QoL are comparable (Marjoribanks et al. 2006, Blumenthal et al. 2011, Matteson et al. 2012). As the endometrium has a marked regeneration capacity, women are likely to continue to experience some degree of menstrual bleeding, and there is no guarantee that bleeding will be reduced to acceptable levels over time (Marjoribanks et al. 2006, Blumenthal et al. 2011, Matteson et al. 2012). Women treated by EA may need re-treatment if menorrhagia persists (Lethaby et al. 2000b, Clegg et al. 2007, Munro et al. 2011).

2.3 Cost-effectiveness of menorrhagia treatments

Alternative treatment options for menorrhagia (surgical and medical) have raised important questions about health outcomes, cost-effectiveness and allocation of resources (NICE 2007, Middleton et al. 2010, Bhattacharya et al. 2011, Blumenthal et al. 2011). Hysterectomy has been a preferred treatment option for menorrhagia due to its definitive nature and high satisfaction rates (Matteson et al. 2012). However, the associated complications and substantial costs cannot be ignored (Fernandez et al. 2003, Halmesmäki et al. 2004, 2007a, Hurskainen et al. 2004b, Matteson et al. 2012). Less invasive alternatives to hysterectomy, such as LNG-IUS and EA, have been increasingly used.

Effectiveness of interventions

Evaluation of the effectiveness of medical interventions, has traditionally been based on measures of morbidity and mortality. Morbidity is based on changes in symptoms and clinical tests. HRQoL has become an accepted and widely used outcome in clinical research trials, also in menorrhagia, reflecting a patient’s experiences and preferences (Drummond and Jefferson 1996). The term HRQoL includes physical, psychological and social functioning and perception of health status, pain and overall satisfaction with life (Sanders et al. 1998). Measures are normally categorized as generic or
disease-specific. Generic scales allow comparison between different clinical conditions in terms of their impact on HRQoL. Single-value instruments, like EQ-5D (European Quality of Life-5 Dimensions; Euro Qol Group), generate one value for the overall HRQoL by using a weighting of the population’s reference values and can be used in economic evaluation and to calculate of quality-adjusted life-years (QALYs). Those like RAND 36 (RAND 36-Item Health Survey Questionnaire) and Nottingham Health Profile (NHP) produce a HRQoL profile with several dimensions allowing a detailed assessment of several aspects of HRQoL. In addition, two condition-specific outcome measures have been developed for women with menorrhagia, including the Menorrhagia Outcomes Questionnaire (Lamping et al. 1998) and the Multi-attribute Questionnaire (Clark et al. 2002). These measures are rarely used, but they are useful in conjunction with to generic measures because they give a more accurate picture of menorrhagia-related symptoms.

The most commonly used outcomes reflecting the effectiveness of menorrhagia treatments are reduction of MBL and increase in blood haemoglobin concentration. However, MBL values or haemoglobin concentration do not reflect the subjective suffering, as menorrhagia has a strong effect on women's QoL, including both physical and psychological health (Coulter et al. 1994). Also social and working abilities may be disrupted, and women seek help for their menstrual problems mostly because of the deleterious effect on their QoL. In the evaluation of the menorrhagia treatment, RAND 36 is the most commonly used validated HRQoL measurement (Clark et al. 2002). HRQoL measures are well suited for comparison of treatments for research purposes, but if they are used for individual patients’ problems emerge with other health and associated confounding factors. Patient satisfaction is widely used as a primary effectiveness outcome measure in studies of treatment for menorrhagia (Crow et al. 2002).

**Health economics**

Cost-effectiveness analysis is a form of economic analysis that compares the relative costs and outcomes of two or more courses of action. Typically, cost-effectiveness analysis is expressed in terms of a ratio where the denominator is a gain in health from a measure and the numerator is the cost associated with the health gain. A special case of cost-effectiveness is cost-utility analysis, where the effects are measured in terms of QALYs. Cost-effectiveness is typically expressed as an incremental cost per additional QALY gained.
Cost-effectiveness of hysterectomy in the treatment of menorrhagia

The amount and costs of an additional QALY gained by hysterectomy have been calculated in a Finnish prospective trial (Taipale et al. 2009). The amount of QALYs gained until menopause was 0.183 in menorrhagia patients and the cost of additional QALY gained by hysterectomy among was €19415. However, the cost of QALY gained by hysterectomy has been lower in modelling trials and has varied between trials, as the results depends on the method of HRQoL measurement, follow-up time and unit costs of treatments (Table 2).

Costs and effectiveness of LNG-IUS and hysterectomy compared with endometrial ablation

When comparing EA and LNG-IUS in the treatment of menorrhagia, both are effective in reducing MBL and equal in patient satisfaction and HRQoL during 5 years (Marjoribanks et al. 2006, Tam et al. 2006, Kaunitz et al. 2009, Middleton et al. 2010, de Souza et al. 2010, Bhattacharya et al. 2011). Studies have concentrated on short- and medium-term outcomes after hysterectomy and EA, but long-term controlled comparisons of hysterectomy with EA in women with menorrhagia are few (Middleton et al. 2010, Roberts et al. 2011, Bhattacharya et al. 2011, Munro et al. 2011, Matteson et al. 2012). In a recent meta-analysis, second-generation EA was found to be less costly but also provided fewer QALYs than hysterectomy, making hysterectomy the most cost-effective strategy overall (Bhattacharya et al. 2011, Roberts et al. 2011). However, a recent systematic review reported no difference in HRQoL or patient satisfaction between hysterectomy and EA, although hysterectomy had significant better bleeding and pain control (Matteson et al. 2012).

Cost-effectiveness of LNG-IUS compared with Hysterectomy

Overview of previous trials suggests that hysterectomy is successful in the treatment of menorrhagia and that LNG-IUS is the most effective of the medical treatments. However, comparative studies of LNG-IUS and hysterectomy are few (Table 2). The first of the studies was the randomized comparative trial from Finland (VuoKKo-study), which showed that LNG-IUS is more cost-effective than hysterectomy after 1-year and 5-year follow-ups, with no difference in patient satisfaction or HRQoL (Hurskainen et al. 2001b, 2004b). The overall costs at 12 months ($1530 vs. $4222) and 5 years ($2817 vs. $4460) were substantially lower in the LNG-IUS group than in the hysterectomy group, although 42% of the women originally assigned to the LNG-IUS group eventually underwent hysterectomy (Hurskainen et al. 2001b, 2004b).
The majority of studies comparing LNG-IUS and hysterectomy are modelling studies analysed by Markov model or meta-analyses (Table 2). Most of these studies have proposed the LNG-IUS as the most cost-effective treatment option, and it is usually favoured as first-line treatment (Blumenthal et al. 2006, Marjoribanks et al. 2006, Clegg et al. 2007, NICE 2007). An economic modelling study from the UK undertaken for National Institute for Health and Clinical Excellence (NICE) guidelines on menorrhagia, suggested that LNG-IUS generated more QALYs at a lower cost than any other medical or surgical treatment considered (NICE 2007). However, a recent meta-analysis and modelling study using individual patient data on clinical effectiveness and cost-effectiveness of the treatment of menorrhagia found hysterectomy to be more cost-effective, albeit more expensive treatment compared to LNG-IUS or EA (Bhattacharya et al. 2011, Roberts et al. 2011). The paucity of RCTs and the limitations of modelling studies can explain the contradictory findings of the trials. In addition, two review articles of menorrhagia treatments have recently been published. The first article suggests LNG-IUS as the most cost-effective treatment option (Blumenthal et al. 2011) and the second concludes that hysterectomy is the most effective in reducing MBL but found no difference in HRQoL (Matteson et al. 2012). Moreover, hysterectomy was associated with the highest risk for adverse effects and complications, while less invasive treatment options, such as LNG-IUS, carry a significant risk for re-treatment or surgery (Matteson et al. 2012).
Table 2. Summary of trials comparing LNG-IUS and hysterectomy in the treatment of menorrhagia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Assessment tool</th>
<th>Study design</th>
<th>Prices based to</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lähteenmäki et al. 1998</td>
<td>LNG-IUS (n=28)</td>
<td>HRQoL (VAS), Proportion of women cancelling their decision to undergo hysterectomy</td>
<td>Randomized Controlled clinical trial over 1 year</td>
<td>Prices based to 6 months in the control group, but significantly improved in each category (general wellbeing, work performance, physical activity, sexual life and leisure activity) in the LNG-IUS group (p≤0.002), and were maintained to 1 year. At 6 months, 64.3% of the women in the LNG-IUS group and 14.3% in the control group had cancelled their decision to undergo hysterectomy (p&lt;0.001). At 1 year, 57% of the women in the LNG-IUS group had undergone hysterectomy.</td>
<td></td>
</tr>
<tr>
<td>Hurskainen et al. 2001, 2004</td>
<td>LNG-IUS (n=119)</td>
<td>Cost-effectiveness, HRQoL, sexual function, Depression, anxiety, MBL, S-Hb</td>
<td>Randomised Controlled trial over 1 year and 5 years</td>
<td>Finlad 1996 for first year, thereafter</td>
<td>Both LNG-IUS and hysterectomy were associated with a 0.1 increase in HRQoL (EQ-SD) compared with baseline. The total estimated cost (including productivity losses) per woman over 1 year: LNG-IUS=US $1530, Hysterectomy=US $4222. The total (including productivity losses) discounted cost per woman over 5 years: LNG-IUS=US $2817, Hysterectomy=US $4660. LNG-IUS and hysterectomy improved haemoglobin levels significantly and equally.</td>
</tr>
<tr>
<td>Ozdegbemenci et al. 2011</td>
<td>LNG-IUS (n=43)</td>
<td>S-Hb, HRQoL World Health Organization Quality of Life-Short Form, Turkish version (WHOQOL-BREFTR)</td>
<td>Randomized Controlled clinical trial over 1 year</td>
<td>Prices based to 1 year in the control group, but significantly improved in each category (general wellbeing, work performance, physical activity, sexual life and leisure activity) in the LNG-IUS group (p≤0.002), and were maintained to 1 year. At 6 months, 64.3% of the women in the LNG-IUS group and 14.3% in the control group had cancelled their decision to undergo hysterectomy (p&lt;0.001). At 1 year, 57% of the women in the LNG-IUS group had undergone hysterectomy.</td>
<td></td>
</tr>
<tr>
<td>Modelling studies</td>
<td>LNG-IUS</td>
<td>Cost-effectiveness</td>
<td>Markov model over 5 years</td>
<td>Hong Kong year of costs</td>
<td>Cost per QALY gained for base-case analysis:</td>
</tr>
<tr>
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<tr>
<td>You et al. 2006</td>
<td>LNG-IUS</td>
<td>Cost-effectiveness</td>
<td>Markov model over 5 years</td>
<td>Hong Kong year of costs</td>
<td>Cost per QALY gained for base-case analysis:</td>
</tr>
<tr>
<td></td>
<td>Hysterectomy</td>
<td></td>
<td>(Four hypothetical cohorts designed to simulate health care Resource utilization and QALYs)</td>
<td>not specified</td>
<td>LNG-IUS = US $979</td>
</tr>
<tr>
<td></td>
<td>Endometrial destruction</td>
<td></td>
<td></td>
<td>Oral medical treatment=US $1204</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral medical treatment</td>
<td></td>
<td></td>
<td>Endometrial ablation=US $1338</td>
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<td></td>
<td></td>
<td>Hysterectomy=US $1456</td>
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<td>Incremental cost per QALY gained for treatment strategies compared individually with the least costly option (LNG-IUS): Oral medical treatment=Dominated by LNG-IUS Endometrial ablation=Dominated by LNG-IUS Hysterectomy=US $23500</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hysterectomy group was the most effective (4.725 QALYs).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clegg et al. 2007</th>
<th>LNG-IUS followed by endometrial ablation (L-A)</th>
<th>Cost-effectiveness</th>
<th>Markov model over 5 years</th>
<th>UK 2004/2005</th>
<th>The expected 5-year costs of treating menorrhagia per patient:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNG-IUS followed by hysterectomy (L-H)</td>
<td></td>
<td></td>
<td></td>
<td>L-A=UK £828 with 4.14 QALY-expected gain</td>
</tr>
<tr>
<td></td>
<td>Thermal balloon endometrial ablation (TBEA)</td>
<td></td>
<td></td>
<td></td>
<td>L-H=UK £1355 with 4.12 QALY-expected gain</td>
</tr>
<tr>
<td></td>
<td>Microwave endometrial ablation (MEA)</td>
<td></td>
<td></td>
<td></td>
<td>TBEA=UK £1679 with 4.13 QALY-expected gain</td>
</tr>
<tr>
<td></td>
<td>Hysterectomy</td>
<td></td>
<td></td>
<td></td>
<td>MEA=UK £1812 with 4.13 QALY-expected gain</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hysterectomy=UK £2983 with 4.01 QALY-expected gain</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LNG-IUS treatment followed by ablation dominated all of the alternative treatments. Hysterectomy was dominated by the alternative treatments.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>National Institute of Clinical Excellence 2007 (NICE 2007)</th>
<th>LNG-IUS</th>
<th>Cost-effectiveness</th>
<th>Markov model over 5 years</th>
<th>UK 2004</th>
<th>Incremental cost per QALY gained at 5 years compared with LNG-IUS as first-line treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS (compared with no treatment)=£840</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td></td>
<td></td>
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<td></td>
<td>Tranexamic acid=Dominated by LNG-IUS</td>
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<tr>
<td>Combined oral contraceptives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mefenamic acid=Dominated by LNG-IUS</td>
</tr>
<tr>
<td>Surgery</td>
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<td></td>
<td>Combined oral contraceptives=Dominated by LNG-IUS</td>
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<tr>
<td>Surgery</td>
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<td></td>
<td></td>
<td>Surgery=Dominated by LNG-IUS</td>
</tr>
</tbody>
</table>
Bhattacharya et al. 2011 (Middleton et al. 2010) (Roberts el al. 2011)
LNG-IUS Endometrial ablation (EA first generation) Hysterectomy
Cost-effectiveness Individual patient data
(10-year follow-up) (1-year follow-up) UK Rates of dissatisfaction:
Endometrial ablation (EA second generation) Individual patent data of 2814 women)
(2008 LNG-IUS and second-generation EA were similar (18.1% vs. 22.5%, p=0.4)
Hysterectomy Direct and indirect comparisons Markov model
Individual patent data of 2814 women (Four hypothetical cohorts of women with menorrhagia)
Hysterectomy was the most cost-effective treatment. It dominated first-generation EA and, although more expensive, produced more QALYs than second-generation EA and LNG-IUS. The incremental cost-effectiveness ratios for hysterectomy compared with LNG-IUS was £1440 per additional QALY and compared with second-generation EA was £970 per additional QALY.

Systematic reviews with meta-analyses
Marjoribanks et al. 2006 Surgery (hysterectomy or endometrial ablation) Medical therapy (LNG-IUS or medical treatments) 12 parallel group RCTs a total of 1049 women HRQoL, improvement of menorrhagia, safety, acceptability (from 1-year follow-up to-5 year follow-up) Systematic review and meta-analysis (Cochrane database) LNG-IUS provides a better alternative to surgery than oral medication Compared with women with LNG-IUS:
Satisfaction, HRQoL and reduced, MBL are similar in women with endometrial destruction.
Satisfaction and HRQoL are similar, but the reduction in MBL is greater in women with hysterectomy. Also serious complications and higher costs are associated with hysterectomy.

LNG-IUS, levonorgestrel-releasing intrauterinen system. HRQoL, health-related quality of life. S-hb, serum haemoglobin. MBL, menstrual blood loss. QALY, quality-adjusted life-year. EA, endometrial ablation. VAS, visual analogue scale. RCT, randomised controlled trial.
2.4 Lower abdominal pain and back pain in menorrhagia

Menorrhagia and dysmenorrhoea are the most frequent gynaecological complaints of women of reproductive age and often occur simultaneously (Yoo et al. 2011). Elevated prostaglandin synthesis and inflammatory processes play an important role in both conditions and may produce intense uterine contractions with associated vasoconstriction of the small vessels in the uterine wall (French 2005). The painful contractions are often associated with lower abdominal pain and back pain. Dysmenorrhoea, lower abdominal pain and back pain impair QoL, as does menorrhagia, and must be treated. It is therefore important to determine whether menorrhagia treatment cures lower abdominal pain or back pain at the same time. However, sometimes lower abdominal pain and back pain can emerge as an adverse effect of menorrhagia treatment.

Effect of LNG-IUS

The beneficial effect of LNG-IUS on dysmenorrhoea and chronic pelvic pain has been demonstrated in many clinical trials (Jensen et al. 2005, Varma et al. 2006, Anpalagan and Condous 2008, Alhamdan et al. 2010). The mechanism of action of LNG-IUS in treating pelvic pain and dysmenorrhoea is its local progestogenic effect, resulting in changes in a range of molecular mechanisms, associated with excessive uterine contractions and troublesome cramps (Fraser 2010). In addition, LNG-IUS reduces blood flow in the uterine artery and the subendometrial spiral arteries, which can explain the reduction in primary dysmenorrhoea (Anpalagan and Condous 2008). Moreover, LNG-IUS has been shown to be an effective treatment for lower abdominal pain or back pain related to endometriosis or adenomyosis (Maia et al. 2003, Bahamondes et al. 2007). On the other hand, some studies have reported an increase in lower abdominal pain and back pain as an adverse effect of LNG-IUS (Soysal et al. 2002, Lethaby et al. 2005, Kriplani et al. 2007).

Effect of hysterectomy

Hysterectomy is an effective treatment for dysmenorrhoea; most women with chronic pelvic pain improve after the procedure (Learnman et al. 2004). However, in some women pain persists or develops after surgery (5-32%) (Brandsborg et al. 2007, 2008). Pain may be caused by bowel spasm, which hysterectomy does not treat. The mechanisms of chronic postoperative pain are poorly understood, but nerve damage during surgery or a continuous inflammatory response, or both, may lead to an altered pain perception (Brandsborg et al. 2008). Chronic pelvic pain may also be explained by adhesions after hysterectomy. Moreover, increased back pain after hysterectomy is reported in some studies (Carlson et al. 1994, Ceausu et al. 2006, Wijnhoven et al. 2006).
2.5 Lower urinary tract symptoms

Lower urinary tract symptoms (LUTS), particularly urinary incontinence (UI) are major health problems and have significant effects on women’s QoL (Miner 2004, Kenton and Mueller 2006, Gimbel et al. 2007). Daily living, hygiene, emotional and psychological health and lifestyle are changed because of incontinence (Imamura et al. 2010). UI of varying degree affects the lives of 20% of middle-aged women and 40% of elderly women (Thomas et al. 1980, Mäkinen et al. 1992a, Hunskaar et al. 2004, Milsom 2009). The new joint report of the International Urogynaecological Association and the International Continence Society on the terminology of female pelvic floor dysfunction from the year 2010 classified LUTS into six groups: urinary incontinence symptoms, sensory symptoms, bladder storage symptoms, voiding and postmicturition symptoms, lower urinary tract pain and lower urinary tract infection. The most common types of urinary problems are stress urinary incontinence (SUI) (complaint of involuntary loss of urine on effort or physical exercise, or on sneezing or coughing), urgency urinary incontinence (UUI) (complaint of involuntary loss of urine associated with urgency) and mixed urinary incontinence (complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing) (Haylen et al. 2010). The most prevalent type of incontinence is SUI in women under 55 years of age. At later ages, mixed urinary incontinence becomes the most common type of incontinence (Hunskaar et al. 2004).

**Effect of LNG-IUS**

Only one trial has evaluated the effect of LNG-IUS on LUTS. A nationwide cohort study from Sweden compared incidence of UI symptoms among women using LNG-IUS, oral contraceptives or no contraception (Iliadou et al. 2009). No difference was present between women with LNG-IUS and those with no contraception, but oral contraception users had significantly reduced risk for UI. Women with oral contraception or no contraception were significantly younger and had had fewer pregnancies than LNG-IUS users, but the results remained unchanged after adjustment. There is no evidence that LNG-IUS has an effect on LUTS or urinary tract infections (UTIs). However, as LNG-IUS seems to cause vaginal flora disturbance and may increase the rate of vulvovaginal infections (Haukkamaa et al. 1986, Donders et al. 2011), the rate of UTIs may also be increased. On the other hand, increased vaginal discharge can prevent dryness of the vagina and may affect the occurrence of LUTS.
Effect of hysterectomy

LUTS and lower urinary tract dysfunction have been reported to be more prevalent in women who have undergone hysterectomy. Most of the studies have shown an increased risk for both UUI and SUI after hysterectomy (Brown et al. 2000, van der Vaart et al. 2002, Altman et al. 2007). A 60% increase in risk for UI is described, but only in women aged over 60 years, as the development of UI after hysterectomy usually takes many years (Brown et al. 2000).

Development of LUTS could be explained by damage occurring during surgery to the innervation and supportive tissues of the pelvis or by changes in urethral pressure dynamics due to distorted pelvic organ anatomy (Prior et al. 1992, DeLancey 1997). As hysterectomy changes the anatomy and function of pelvic organs it may also increase the risk of UTIs. However, long-term studies of the effect of hysterectomy on UTIs are lacking. Some studies have evaluated the effects of different surgical approaches. LUTS appear to be more common following vaginal hysterectomy than abdominal hysterectomy (Lakeman et al. 2010, 2011). A possible explanation is that a difference exists in damage of the pelvic innervation between the approaches. However, some studies have reported an increased risk for UI after hysterectomy, irrespective of surgical approach (Altman et al. 2007).

2.6 Cardiovascular disease risk factors

Cardiovascular disease (CVD) is the leading cause of death for women. Approximately 10 000 women in Finland (www.stat.fi) and 8.6 million women worldwide (World Health Organization 2004) die of CVDs annually. The potential differences in risk factors and clinical profile of CVD in women have been extensively studied (Stramba-Badiale et al. 2006). Smoking, diabetes, hypertension, abdominal obesity, metabolic syndrome and associated insulin resistance, increased levels of serum lipids and inflammation are the main risk factors for CVD among women.

Inflammatory serum markers

The pathogenesis of atherosclerosis can be considered as inflammatory process in which inflammation plays a fundamental role at all stages from inception and development to thrombotic complications (Libby 2002, Lind 2003). Elevated levels of serum inflammatory markers among patients with CVDs,
as well as apparently healthy women, have proven to predict future adverse vascular events and deaths. A number of inflammatory biomarkers have been used as risk indicators of CVDs. Such mediators include C-reactive protein (CRP), tumour necrosis factor α (TNF-α), fibrinogen, various adhesion molecules, selectins and cytokines (Libby 2002, Blankenberg et al. 2003, Lind 2003).

CRP is a classical acute-phase protein produced mainly by the liver in response to pro-inflammatory cytokines. CRP is a mediator of immune responses against various pathogens and damaged cells of the host (Casas et al. 2008). Modestly elevated baseline CRP levels have been associated with a long-term risk of coronary heart disease in general populations, and use of CRP as part of a global coronary risk assessment strategy in adults without known CVD has been suggested (Danesh et al. 2004). The pathogenic and clinical significance of the association between CRP and CVD is controversial (Casas et al. 2004). The term “high-sensitivity” CRP (hsCRP) is used to refer to measurement of CRP using immunoassay methods with sufficient sensitivity to quantify CRP throughout its normal range (in contrast to acute-phase responses).

TNF-α is produced by several types of cells, especially by macrophages. Most organs of the body appear to be affected by TNF-α and it has a variety of functions, including growth-stimulating properties and growth-inhibitory processes, beneficial immune responses and a role in local immune responses (Locksley et al. 2001). TNF-α is involved in the pathogenesis of atherosclerosis by impairing endothelial function. In addition, TNF-α has been shown to impair insulin signalling (Kleinbongard et al. 2011). Increased plasma TNF-α can predict risk of CVD (Libby 2002).

Effect of LNG-IUS

The effects of LNG-IUS on serum lipids and lipoproteins have been studied in women of reproductive age (Nilsson et al. 1981b, Morin-Papunen et al. 2008) and in women with menorrhagia (Kayikcioglu et al. 2006). An association between use of LNG-IUS and reduced levels of both total and HDL cholesterol, yet an unaltered HDL/total cholesterol ratio, has been demonstrated among fertile-aged women (Morin-Papunen et al. 2008). However, two other studies found no effect on serum lipid levels (Nilsson et al. 1981b, Kayikcioglu et al. 2006). The use of LNG-IUS was not associated with changes in blood pressure or elevated levels of serum CRP (Morin-Papunen et al. 2008), but an association with increased levels of serum glucose in women with menorrhagia was seen (Kayikcioglu et al. 2006).
Effect of hysterectomy

Hysterectomy may be accompanied by responses that predispose women to CVD (Luoto et al. 1995, Howard et al. 2005). Hysterectomy impairs ovarian function and may cause early menopause (Halmesmäki et al. 2004, 2007a, Farquhar and Steiner 2005). Early menopause, in turn, may induce low-grade inflammation in the body and increase the risk for CVD (Abu-Taha et al. 2009). A recent population-based cohort study from Sweden revealed that hysterectomy in women aged 50 years or younger substantially increases the risk for CVD later in life, and oopherectomy further adds to the risk of both coronary heart disease and stroke (Ingelsson et al. 2011). Some studies have shown an association between hysterectomy and high blood pressure (Luoto et al. 1995, Kharazmi et al. 2007), and unfavorable lipid profile (Zhang et al. 2005).
3. Objectives of the study

The main objective of this thesis was to compare LNG-IUS and hysterectomy in the treatment of menorrhagia in the long term to obtain new knowledge for clinical decision-making and patient counselling as well as in implementing primary or special health care. More specifically, the aim was to assess the cost-effectiveness and other health effects of these two treatment modalities, as menorrhagia is a very common problem, requiring treatment.

Specific objectives were to compare the effect of LNG-IUS and hysterectomy on:

1. quality of life and cost-effectiveness (Study I)
2. lower abdominal pain and back pain (Study II)
3. lower urinary tract symptoms (Study III)
4. cardiovascular disease risk factors (Study IV)

in the treatment of menorrhagia.
4. Patients and methods

4.1 Study protocol and study population

A total of 598 women referred for menorrhagia to the five University Hospitals in Finland between November 1994 and November 1997 were assessed by a study gynaecologist, and 184 (31%) of the women were excluded because of predefined exclusion criteria (Figure 3) (Hurskainen et al. 2001b). During the first visit all eligible women were informed of the different treatment modalities for menorrhagia and the purpose of the trial. By the second visit, 178 (43%) of these women decided not to participate for the following reasons: treatment preference (hysterectomy n=71, LNG-IUS or some other medical treatment n=37, EA n=3), refusal of any treatment (n=28), still planning pregnancy (n=11), did not want randomization (n=5), or other reason (n=23) (Figure 3). The women excluded or not participating did not differ from the study group in terms of sociodemographic factors, age, employment status or occupation. All 236 women included were aged 35-49 years (mean 43.1 and median 43.0 years), were menstruating, had completed their family size and were eligible for hysterectomy and LNG-IUS.

Hysterectomy was performed abdominally, vaginally or laparoscopically by (or supervised by) an experienced gynecologist. The mean waiting time for the operation was 6.7 months (range 12 days to 21 months). The LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) was inserted during the randomization visit on cycle day one to seven.

Randomization was performed separately for each centre in randomly varying clusters using numbered, opaque, sealed envelopes. Of the 236 women, 107 were randomized in Helsinki, 44 in Kuopio, 22 in Oulu, 21 in Tampere and 42 in Turku. The follow-ups took place 6 and 12 months after the treatment and again 5 and 10 years after the randomization. The trial profile is shown in Figure 3. A questionnaire was completed by the gynecologist during each follow-up visit and another by the participant at home before randomization and before each follow-up visit.

This study is a continuation of the 1- and 5-year follow-ups and is based on the same study protocol and study population (Hurskainen et al. 2001b, Hurskainen et al. 2004b).

The trial has been registered in clinicaltrials.gov with the identifier NCT00966264.
Figure 3. The trial profile.
**Ethics**

All participants gave their written informed consent. The study protocol was approved by the Ethics Committees of all university hospitals and STAKES (National Research and Development Centre for Welfare and Health) in Finland. Ethics reference no. 249/E8/04; date of approval: 26 August 2004 (ethics approval granted by the Institutional Review Board of the Helsinki University Hospital).

**4.2 Outcomes**

The questionnaire of participants contained information on body mass index (BMI), smoking, parity, age at menarche, deliveries, marital status, level of education, employment, smoking, chronic diseases, regular use of medication, physical and hormonal symptoms, HRQoL instruments, instruments of psychosocial well-being, health care use, sick-leave days and travel costs. Gynaecologists completed a form that included information on abortions, gynaecological infections, menstrual cycle, duration of menorrhagia, contraception, operations and treatments for menorrhagia as well as findings of physical examination. In addition, the questionnaire contained information about LNG-IUS-associated bleeding problems, reasons for discontinuation and details and complications of surgery. Data on all performed hysterectomies and use of LNG-IUS were confirmed from medical records and the Hospital Discharge Registry of the Finnish National Institute for Health and Welfare.

**4.2.1 Health-related quality of life and other psychosocial well-being**

HRQoL and other measures of psychosocial well-being were measured at baseline and at each follow-up visit by questionnaires containing HRQoL instruments. The 5-Dimensional EuroQol (EQ-5D) was selected as the primary measure of effectiveness because it provides a single numeric score for HRQoL, is universally used and has been validated in the Finnish general population. The EQ-5D includes five 3-level dimensions: morbidity, self-care, usual activities, pain, and mood. The score index, ranging from 0 to 1, was calculated from relative weights for the dimensions obtained from a Finnish population survey. The validated Finnish version of the RAND 36-Item Short-Form Health Survey (RAND-36) was also used to measure HRQoL. The RAND-36 includes eight multi-item dimensions: general health, physical functioning, mental health, social functioning, vitality, pain and physical and emotional role functioning. Each subscale ranges from 0 to 100, higher scores indicating...
better HRQoL. The reference values of healthy and chronically ill women were obtained from two large population surveys (Ohinmaa and Sintonen 1996, Aalto et al. 1999). The general health assessment was recorded using an EQ-5D visual analogue scale (EQ-5D VAS), ranging from 0 to 100. Anxiety was measured by the validated Finnish version of the Spielberger State-Trait Anxiety Inventory (STAI), ranging from 20 to 80 (Spielberger et al. 1970). Depression was measured using the 13-item version of Beck’s Depression Inventory (BDI; scale 0-39) (Beck et al. 1974). Sexually related factors were assessed by the McCoy Sex Scale (MSS) as modified by Wiklund (McCoy and Davidson 1985, Wiklund et al. 1993). The MSS comprises three subscales: sexual satisfaction (5 items, subscale 5-35), sexual problems (2 items, subscale range 2-14) and satisfaction with partner (3 items, subscale 3-21). On the scales, more anxiety, more depression, more sexual satisfaction, more sexual problems and more satisfaction with partner are indicated by higher scores.

4.2.2 Costs and cost-effectiveness

Data on direct costs, including use of hospital services (operations, inpatient days, other procedures, outpatient visits), and on indirect costs, including sick-leave days as productivity losses, were obtained from medical records and questionnaires. Information on other visits to doctors for menorrhagia, Papanicolaou tests and out-of-pocket costs (medication and travelling) related to menorrhagia were obtained from questionnaires. The costs of hospital services were obtained from the 10-year period, whereas the costs of health care out of hospital, out-of-pocket costs, and indirect costs (sick-leave days) were obtained from first and fifth study years (Hurskainen et al. 2004b) and again from the period during 5-10 years.

A pricing system based on diagnostic related groups used by Helsinki University Hospital was used for pricing the hospital procedures. The first year costs were based on 1996 price levels, the costs over 1-5 years on 2001 price levels and the costs over 5-10 years on 2006 price levels. The currency conversion had its basis in purchasing power parities in 1996 (US $1 = FIM 5.89) (Organization for Economic Co-operation and Development 1993) and in 2002 when Finland implemented the euro (FIM 1 = EUR €0.168). The unit cost of hysterectomy included one preoperative visit, the actual operation, and 1-5 inpatient days ($1864 in 1996, $2055 in 2001, $3187 in 2006). If a longer stay in hospital was needed, additional days were priced according to the average bed day price ($247 in 1996, $297 in 2001, $363 in 2006). The cost of primary health-service care was calculated from the unit costs of these services in the City of Helsinki Occupational Health Care Centres. The productivity loss per sick-leave day was defined as the average daily gross wage of women in Finland, including social security ($71 in 1996, $85 in 2001, $142 in 2006). The costs were discounted by the commonly
recommended rate of 3% per year (Drummond and Jefferson 1996) to the 1996 level (average year for treatment decisions).

Uncertainty was assessed in the model parameters by sensitivity analysis. We tested results based on higher discount rate (5%, which is another commonly used discount rate) (Drummond and Jefferson 1996), lower estimate of productivity loss (one-third of average wage rate) (Koopmanschap and Rutten 1994), and different prices of hysterectomy due to different pricing systems applied in other countries. Furthermore, the results were tested using a lower hysterectomy rate \( n = 25, 21\% \) in the LNG-IUS group.

The additional QALYs gained by the treatments were calculated by using 12-month, 5-year and 10-year values of EQ-5D, assuming that HRQoL would have remained at a baseline level without treatment. The incremental cost per additional QALY gained was calculated for both treatments using the number of QALYs gained and the total cost of menorrhagia treatment per participant.

### 4.2.3 Lower abdominal pain and back pain

Lower abdominal pain and back pain were recorded at baseline and at each follow-up visit using Likert-scale questions on frequency of lower abdominal pain and back pain during the last six months in Study II. The scores ranged from 1 to 4 (1 indicating never or rarely, 2 indicating monthly, 3 indicating weekly and 4 indicating nearly every day). The intensity of pain during the last six months was recorded by a visual analogue scale, range from 1 to 7 (1 indicating no pain and 7 indicating the worst possible pain). To evaluate the change in pain after treatment, we determined the pain score by multiplying the frequency of pain by the intensity of pain (range from 1 to 28). The scores were compared between 6 months and baseline, 12 months and 6 months, 5 years and 12 months, 5 years and baseline, 10 years and 5 years and 10 years and baseline.

### 4.2.4 Lower urinary tract symptoms

Lower urinary tract symptoms (LUTS), including stress urinary incontinence (SUI), urge urinary incontinence (UUI), increased daytime frequency (IDF), dysuria and feeling of incomplete emptying (FIE) (yes/no) were enquired about for the previous six months, at baseline and at each follow-up visit. SUI was defined as involuntary leakage on effort or exertion, UUI as involuntary leakage accompanied by or immediately preceded by urgency, IDF as patients opinion that she voided too often by day, dysuria as burning during urination and FIE as the feeling experienced by the individual
after passing urine (Blaivas et al. 1997, Abrams et al. 2003). To assess the severity of UI and the impact of UI on everyday life, the Urinary Incontinence Severity Score questionnaire (UISS) was used. The UISS questionnaire has been designed by the Finnish Gynaecological Society’s urogynaecologic working group (Mäkinen et al. 1992b, Stach-Lempinen et al. 2001), and it consists of 10 questions with a three-point scoring system (0 = not at all, 1 = sometimes, 2 = often). On a scale ranging from 0 to 20 (0-100%), the higher scores indicate severe symptoms. The number of UTIs was questioned at baseline and each follow-up visit. The questionnaire completed by gynaecologists included information on surgical procedures for UI as well as on microbiologically confirmed UTIs. Surgery for UI was also confirmed from medical records. The records for the use of medication for UI were obtained from the Registry of Purchased Drugs of the Finnish Social Insurance Institution, which keeps a registry of all purchased prescription-only medicines.

4.2.5 Cardiovascular disease risk factors

At the 10-year follow-up visit, blood pressure, waist circumference and the serum concentrations of total cholesterol, high- and low-density lipoprotein cholesterol and triglycerides were measured. The weight was self-reported and the BMI was calculated. The levels of serum hsCRP and TNF-α were determined at baseline, 5 years and 10 years (the methods described below). Data on the use of medication for the treatment of diabetes, hypertension, ischaemic heart disease and hypercholesterolaemia as well as ET use were obtained from the Social Insurance Institution of Finland.

4.2.6 Laboratory investigations

Menstrual blood loss (MBL) was measured before randomization and before each follow-up visit using the alkaline haematin method (Hurskainen et al. 1998). At 10 years, none of the women provided MBL samples.

Blood haemoglobin concentrations were measured using a Coulter Counter T660 (Coulter Electronics Ltd., London, England). The blood samples were taken during menstrual days 1-7 at baseline and at follow-up visits.

Serum concentrations of total cholesterol, HDL-cholesterol and triglycerides were measured using enzymatic colorimetric test using Roche Diagnostics Cholesterol CHOD-PAP method, HDL-C plus 3rd generation method, and Triglycerides GPO-PAP method (Hitachi Modular PP-analyzer, Hitachi Ltd.,
Tokyo). Serum concentration of LDL-cholesterol was calculated according to the Friedewald equation.

Serum TNF-α concentration was determined by commercial ELISA kits (Duoset, Genzyme Diagnostics, Cambridge, USA) according to the manufacturer’s instructions. The lower detection limit was 10 pg/ml.

Serum CRP levels were quantified using an immunofluorometric CRP kit (Innotrac Diag, Turku, Finland). The sensitivity of the assay is 0.05 mg/l, with an assay range of 0.05-50 mg/l. As CRP values >10 μg/ml may be more consistent with acute inflammation, the data were also analysed after excluding these high values (baseline n=4, 5 years n=11, 10 years n=11).
4.3 Analysis

4.3.1 Study groups

In Studies I and II, all analyses were performed by intention-to-treat principle. In Study II, the data were analysed also by actual treatment, and in studies III and IV all analyses were performed by actual treatment, as 55 (46%) of the women randomized to LNG-IUS had had a hysterectomy during the 10-year follow-up (Figure 4). The actual treatment groups at 5 years consisted of 159 women who had had a hysterectomy (hysterectomy group) and 77 women without a hysterectomy (LNG-IUS group) (58 of these 77 women had LNG-IUS in situ still at 5 years). Correspondingly, the actual treatment group at 10 years consisted of 164 women who had had a hysterectomy and of 71 women without a hysterectomy (45 of these 71 women had LNG-IUS in situ still at 10 years). Data of treatment modality at 10 years were missing for one woman. The baseline characteristics were tested separately for original study groups and for actual treatment groups (Table 3.)

<table>
<thead>
<tr>
<th>Table 3. Baseline characteristics of the study population at baseline and at 10 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>43.1 (SD 3.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>26.6* (SD 5.1)</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>2.1 (SD 1.0)</td>
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<tr>
<td>Smoker</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>38 (32%)</td>
</tr>
<tr>
<td>Menstrual blood loss (ml)</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>130 (SD 116)</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>LNG-IUS (n = 119)</td>
</tr>
<tr>
<td>Elementary</td>
</tr>
<tr>
<td>Lower secondary</td>
</tr>
<tr>
<td>Upper secondary</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
</tbody>
</table>

*p=0.02, ** p=0.03
Total number of women in actual treatment analysis is 235, as the data of treatment modality at 10 years were missing for one woman. Actual treatment analyses compare women with hysterectomy with all other women.
Figure 4. Treatment modalities of the patients examined in study. At 10 years data were missing for one women.
4.3.2 Statistics

The data were analysed by SPSS 14.0, SPSS 15.0, SPSS 16.0 and SPSS 17.0 versions for Windows and STATA 11.1. The target of 115 patients for each treatment group was set by power calculations based on HRQoL measured by EQ-5D standard deviation (SD) of 19% (derived from a Finnish 34-49-year-old female population (Ohinmaa and Sintonen 1998) and $\alpha$-level of 0.05 (Hurskainen et al. 2001b). The study had 80% power to detect a 7.5% difference between the groups. In Studies III and IV, the power calculation was based on a sample size of 164 patients in the hysterectomy group and 71 patients in the LNG-IUS group, and an $\alpha$-level of 0.05. Study III had an 80% power to detect a 15% difference in the incidence of LUTS. Study IV had an 80% power to detect a 15% difference in the CVD risk factors.

Chi-square test or Fisher’s exact test was used to test the differences in the dichotomized variables between the groups pre- and post-treatment. Student’s t-test for independent samples was used to analyse the differences in continuous variables with normal distribution and Mann-Whitney U-test for variables not following normal distribution. Changes within the group, before and after the treatment, were tested by Student’s t-test for dependent samples when parameters followed normal distribution and by Wilcoxon signed-rank test when parameters were not normally distributed.

Either multivariate logistic or linear regression model was used to test factors associated with change in variables or contributing factors. In this analysis, the potential contributing factors were added either in continuous or in dichotomized form. In addition, all confounding factors were tested one by one in a univariate regression model. In Study IV Pearson’s correlation was used to evaluate the correlation between the levels of hsCRP and TNF-$\alpha$.

To assess the total change trajectories of HRQoL and psychosocial outcomes over the 10-year follow-up period, we applied random-intercept multilevel longitudinal modelling by pooling all four measurement times (baseline and 1-year, 5-year and 10-year follow-ups) in a single analysis. The method does not require full data for all measurement times, so all participants and their available person-observations of the four measurement times were included in this analysis.

Odds ratios were calculated to approximate the relative risk (RR) with 95% confidence intervals. P-values <0.05 were considered significant.
5. Results

5.1 Clinical characteristics and findings (Studies I – IV)

The mean age of the study population 10 years after the treatment was 53.1 years (median 53.0 years, range 46–59 years, 77% of the women > 51 years of age), thus most women had reached menopause.

Selected baseline characteristics of the study population, including the intention-to-treat population, the actual treatment population and the 55 women who were originally randomized to treatment by LNG-IUS but eventually underwent hysterectomy, are shown in Table 3. The groups were comparable except that BMI (intention-to-treat) and unemployment (actual treatment) were slightly higher in the LNG-IUS group.

The 10-year continuation rate was 94% (Figure 3).

5.1.1 LNG-IUS arm

After 10 years, 55 (46%) of the 119 women randomized to treatment by LNG-IUS had had a hysterectomy, 44 (37%) had LNG-IUS in situ, 18 had no LNG-IUS or hysterectomy, one had died and one woman had missing data (Figure 4). Of the hysterectomies, 13 (24%) were performed vaginally, 10 (18%) abdominally, and 32 (58%) laparoscopically. Eight women had bilateral salpingo-oophorectomy with hysterectomy. Intraoperative or postoperative complications occurred in 15 (27%) of the 55 women who had had a hysterectomy; these included postoperative pelvic infection (n=9, 16%), strong abdominal pain (n=3, 5%), wound infection (n=2, 4%), heavy perioperative bleeding (n=1, 2%), ileus (n=1, 2%), postoperative bleeding (n=1, 2%), postoperative fever (n=1, 2%), and urinary retention (n=1, 2%). No major complications (pulmonary embolism, re-operation or visceral damage; bladder, bowel or ureter injury) occurred. Reasons for LNG-IUS removals and hysterectomies during the first 5 years were intermenstrual bleeding (n=42), heavy bleeding (n=19), hormonal symptoms (n=18), abdominal pain (n=6), depression (n=2), recurrent thromboembolic disease (n=1) and benign ovarian cyst (n=1). Some of the women reported more than one reason, and one woman wanted hysterectomy without any specific indication. The reasons for removal of LNG-IUS after 5 years were menopause (n=8) and breast cancer (n=3). All five women who had had a hysterectomy after 5 years had fibroids with bleeding problems as the main indication. Three of these women also reported pressure symptoms.
At 12 months, 41 (51%) of the 81 women with LNG-IUS in situ reported amenorrhea or oligomenorrhea and 26 (32%) reported irregular or intermenstrual bleeding. Correspondingly at 5 years, 43 (75%) of the 57 women with LNG-IUS reported amenorrhea or oligomenorrhea and 11 (19%) reported irregular or intermenstrual bleeding. At 10 years, 40 (91%) of the 44 women with LNG-IUS in situ reported amenorrhea or oligomenorrhea, one (2%) reported irregular or intermenstrual bleeding and none reported heavy menstrual bleeding.

5.1.2 Hysterectomy arm

Of the 117 women randomized to hysterectomy, 109 (93%) had a hysterectomy, eight had no hysterectomy and one of them had LNG-IUS in situ after 10 years (Figure 4). Of the 109 hysterectomies, 30 (28%) were performed vaginally, 22 (20%) abdominally and 57 (52%) laparoscopically. All hysterectomies were performed between baseline and 5 years. Intraoperative or postoperative complications, including wound infection (n=12, 11%), infected pelvic haematoma (n=6, 5%), urinary retention (n=4, 4%), severe abdominal pain (n=3, 3%), ileus (n=2, 2%), postoperative bleeding (n=2, 2%), postoperative fever (n=2, 2%), wound rupture (n=2, 2%), peritonitis (n=1, 1%), ureter lesion (n=1, 1%) and vesicovaginal fistula (n=1, 1%), occurred in 37 (34%) women. Major complications occurred in three women (3%). During the 10-year follow-up eight women had bilateral salpingo-oophorectomy. Seven of the eight women with no hysterectomy reported amenorrhea or oligomenorrhea. One had LNG-IUS in situ. One woman reported normal menstrual bleeding.

5.1.3 Laboratory results

At baseline, the mean MBL was 130ml (SD 116) in the LNG-IUS group and 128ml (SD 116) in the hysterectomy group (Table 3). At 12 months, the mean MBL among LNG-IUS users was 13ml (SD 23.5, range 1-92). Only four women at 5 years (mean MBL 17 ml, SD 11.3, range 8-32 ml) and none of the women at 10 years contributed their MBL samples. There was significant increase in blood haemoglobin concentration in both study groups, with no significant differences between the groups (Figure 5).
5.2 Health related quality of life and psychosocial well-being outcomes (Study I)

The baseline EQ-5D scores of subjects in HRQoL were significantly lower than the mean scores of same-aged Finnish women (Ohinmaa and Sintonen 1996). The RAND-36 scores were also significantly lower in women with menorrhagia than in healthy Finnish women of the same age, corresponding to the score of women with chronic illness (Aalto et al. 1999).

HRQoL (by EQ-5D and RAND-36) and psychosocial well-being improved significantly during the first 5 years (Figures 6 and 7). The improvement was most striking during the first year, reaching the best HRQoL values 12 months after the treatment. After the 12-month follow-up, HRQoL decreased gradually. Nevertheless, 5 years after the treatment, HRQoL and other psychosocial measures were still significantly better than baseline, with no significant difference between the study groups (Hurskainen et al. 2004b). During the period 5-10 years most of the measures of HRQoL and psychosocial well-being decreased significantly.
Between baseline and 10 years, EQ-5D scores remained at baseline level, with no difference between the groups. Of the dimensions measured by the RAND-36, emotional well-being and social functioning improved in the LNG-IUS group (p=0.01) and energy increased in both groups (LNG-IUS p=0.01, hysterectomy p=0.03). General health assessed by VAS was impaired in both groups (p=0.01, p<0.001). Of other psychosocial well-being markers, sexual satisfaction (p=0.01, p=0.01) and satisfaction with partner (p<0.001, p=0.01) decreased and sexual problems increased (p<0.001, p=0.02) in both groups. In addition, anxiety decreased in the LNG-IUS group (p<0.001). No significant differences were found between the groups over periods of baseline-10 years or 5-10 years.

The multilevel models suggested fairly steep initial improvement of HRQoL within the first year after baseline, but then less steeply declining levels during the rest of the follow-up period (Figures 6 and 7). Despite this decline, the average levels of HRQoL tended to be higher after 10 years than at baseline, albeit not significantly. There were no significant differences in trajectories of HRQoL and psychosocial outcomes between LNG-IUS and hysterectomy groups over 10 years.
Figure 6. HRQoL trajectories in hysterectomy and LNG-IUS groups.
95% confidence intervals are shown only for hysterectomy group for reasons of clarity.
The differences between the groups is not significant if the confidence interval exceeds the average of the LNG-IUS group.
(Range).
Figure 7. Psychosocial wellbeing trajectories in hysterectomy and LNG-IUS groups.
95% confidence intervals are shown only for hysterectomy group for reasons of clarity.
The differences between the groups is not significant if the confidence interval exceeds the average of the LNG-IUS group.
(Range).

5.3 Costs and cost-utility outcomes (Study I)

The discounted total cost of treatment of menorrhagia per participant over 10 years was $3423 in the LNG-IUS group and $4937 in the hysterectomy group (direct cost $2291 vs. $3036, indirect cost $1133 vs. $1900) (Table 5). Both the discounted direct cost and the discounted indirect cost were significantly lower in the LNG-IUS group than in the hysterectomy group. The discounted total costs per participant between 5 and 10 years were $606 in the LNG-IUS group and $277 in the hysterectomy group. Only the costs related to menorrhagia treatment were included in the analysis (Table 4).

The total cost per participant using a higher or lower discount rate, higher or lower hysterectomy cost, or lower estimate of productivity loss (sensitivity analysis) was again lower in the LNG-IUS group than in the hysterectomy group (Table 5). The total cost per participant in the LNG-IUS group with a lower hysterectomy rate (n = 30) and a higher LNG-IUS continuation rate (n = 67) was $308 lower than the base case (Table 5).

LNG-IUS produced 0.45 QALYs and the incremental cost per additional QALY gained was $7607. Hysterectomy, by contrast, resulted in 0.51 QALYs at a cost of $9680 per additional QALY.
Table 4. Total costs of menorrhagia in the LNG-IUS and hysterectomy groups during the 10-year follow-up.

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Unit Cost, US$</th>
<th>LNG-IUS</th>
<th>Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG-IUS First</td>
<td>185</td>
<td>165</td>
<td>117</td>
</tr>
<tr>
<td>LNG-IUS Re-inserted</td>
<td>185</td>
<td>165</td>
<td>216</td>
</tr>
<tr>
<td>Hysterectomy (includes 1-5 inpatient days)</td>
<td>1864</td>
<td>2055</td>
<td>3187</td>
</tr>
<tr>
<td>Extra inpatient days</td>
<td>247</td>
<td>297</td>
<td>363</td>
</tr>
<tr>
<td>Re-laparoscopy</td>
<td>1502</td>
<td>1669</td>
<td>1</td>
</tr>
<tr>
<td>Re-admissions due to complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection (inpatient days)</td>
<td>247</td>
<td>297</td>
<td>10</td>
</tr>
<tr>
<td>Urinary retention (inpatient days)</td>
<td>247</td>
<td>297</td>
<td>12</td>
</tr>
<tr>
<td>Occlusion (inpatient days)</td>
<td>247</td>
<td>297</td>
<td>84 (26)</td>
</tr>
<tr>
<td>Secondary haemorrhagia (operation)</td>
<td>1527</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy due to pain</td>
<td>1475</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suture of fleum (with 11 days in intensive care)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparotomy due to occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrostoma (2 inpatient days)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ureterectomy and oophorectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curatage/Hysteroscopy</td>
<td>542</td>
<td>798</td>
<td>823</td>
</tr>
<tr>
<td>Thermoablation</td>
<td>1225</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic oophorectomy for ovarian cyst</td>
<td>1475</td>
<td>1503</td>
<td>5</td>
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<tr>
<td>Abdominal salpingo-oophorectomy for ovarian cyst</td>
<td></td>
<td>3187</td>
<td></td>
</tr>
<tr>
<td>Outpatient visits (controls* and complications)</td>
<td>110</td>
<td>124</td>
<td>253</td>
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<tr>
<td>Health care use out of hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to general practitioner at health centre</td>
<td>46</td>
<td>58</td>
<td>82</td>
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<tr>
<td>Visits to private physician</td>
<td>27</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>Visits to private gynaecologist</td>
<td>42</td>
<td>53</td>
<td>112</td>
</tr>
<tr>
<td>Papanicolaou test</td>
<td>31</td>
<td>20</td>
<td>263</td>
</tr>
<tr>
<td>Medication (Out-of-pocket costs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travel (Out-of-pocket costs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick-leave days</td>
<td>71</td>
<td>85</td>
<td>142</td>
</tr>
<tr>
<td><strong>Summary of health care costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Direct costs</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total health care costs</td>
<td>300893</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discounted total health care costs per participant**</td>
<td>2291</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indirect costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discounted productivity losses per participant**</td>
<td>1133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>449868</td>
<td>595376</td>
<td></td>
</tr>
<tr>
<td>Total costs per participant</td>
<td>3780</td>
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<td></td>
</tr>
<tr>
<td>Discounted total costs**</td>
<td>407355</td>
<td>577573</td>
<td></td>
</tr>
<tr>
<td>Discounted total costs per participant**</td>
<td>3423</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Controls indicate planned follow-up visits at 6 months, 1 year, 5 years and 10 years. For women having hysterectomy, there was also a planned visit 4 weeks after hysterectomy, **Discounted by 3%.
Table 5. *Sensitivity analysis.*

<table>
<thead>
<tr>
<th>Variable used in analysis</th>
<th>Total cost per participant, US $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNG-IUS</td>
</tr>
<tr>
<td><strong>Base case</strong>*</td>
<td>3423</td>
</tr>
<tr>
<td><strong>Discount rates for costs</strong></td>
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<tr>
<td>No discounting</td>
<td>3780</td>
</tr>
<tr>
<td>Discount rate 5%</td>
<td>3247</td>
</tr>
<tr>
<td><strong>Productivity loss (indirect cost)</strong></td>
<td></td>
</tr>
<tr>
<td>Lower estimate**</td>
<td>2668</td>
</tr>
<tr>
<td><strong>Cost of hysterectomy</strong></td>
<td></td>
</tr>
<tr>
<td>Lower estimate***</td>
<td>3324</td>
</tr>
<tr>
<td>Mean hysterectomy cost in the US in 1996****</td>
<td>3861</td>
</tr>
<tr>
<td>Laparoscopic hysterectomy cost in the US in 2007 *****</td>
<td>4876</td>
</tr>
<tr>
<td><strong>Number of hysterectomies in the LNG-IUS group</strong></td>
<td></td>
</tr>
<tr>
<td>(n = 30)****</td>
<td>3115</td>
</tr>
</tbody>
</table>

*Discounted by 3%, **One-third of the average wage rate, ***20% lower than base case.
****Mean cost of hysterectomy in the US in 1996 was $3995 (Dorsey et al. 1996).
*****Approximate cost of laparoscopic hysterectomy in the US in 2007 ($6973) (Sarlos et al. 2011).
******Without cost of 25 hysterectomies between 12 months and 5 years, and with cost of 25 added LNG-IUS at 5 years and 25 added LNG-IUS at 10 years.
5.4 Lower abdominal pain and back pain (Study II)

Lower abdominal pain

Lower abdominal pain was common before the treatment. At baseline, 45% of the women in the LNG-IUS group (8% nearly every day, 15% weekly and 21% monthly) and 38% of the women in the hysterectomy group (5% nearly every day, 9% weekly and 22% monthly) reported lower abdominal pain. Lower abdominal pain decreased in both study groups during the 10 years after the treatment (p<0.001), but the decline was most evident during the first 6 months (p<0.001) (Figure 8). After the first year, more women in the LNG-IUS group (30%) than in the hysterectomy group (14%) suffered from lower abdominal pain (p=0.02). Between baseline and 10 years, monthly abdominal pain decreased most (LNG-IUS: from 21% to 7%, p<0.001, hysterectomy: from 22% to 8%, p<0.001), but also the daily and weekly pain decreased significantly in the both study groups. At 10 years, 38% of the women in the LNG-IUS group and 35% of the women in the hysterectomy group experienced less often abdominal pain than before treatment. However 5% and 10% of the women, respectively, had lower abdominal pain more often than before treatment.

Lower abdominal pain score (which combined occurrence and intensity of pain) showed no significant differences between the study groups at baseline (Figure 10). No significant changes were noted between baseline and 6 months, but between 6 and 12 months lower abdominal pain score decreased in both groups (p=0.05 and p=0.02), with no significant difference between the groups. Overall, between baseline and 10 years, lower abdominal pain score decreased in the LNG-IUS group (mean -3.8, p=0.005) and in the hysterectomy group (mean -2.7, p=0.01), with no significant difference between the groups. At 10 years, 70% of the women in LNG-IUS group and 73% of the women in hysterectomy group experienced lower pain scores than at baseline, and correspondingly, 12% and 20% of the women had higher pain scores.

The multivariate model adjusted by age, BMI, ET and unemployment showed an association between LNG-IUS use and a decrease in lower abdominal pain score between baseline and 10 years (p=0.04). The route of hysterectomy (vaginal, abdominal or laparoscopic) did not explain the changes in pain after hysterectomy.

The actual treatment analysis showed only minor differences relative to the intention-to-treat analysis. Lower abdominal pain score decreased more among LNG-IUS users than among women with hysterectomy between 6 months and 5 years. All of the other results were in line with the intention-to-treat analysis.
Before the treatment, back pain was common; 64% of the women in the LNG-IUS group (21% nearly every day, 10% weekly, 33% monthly) and 65% of the women in the hysterectomy group (11% nearly every day, 13% weekly, 41% monthly) reported back pain (Figure 9). After the treatment, occurrence of back pain decreased in both groups. At 10 years, 40% of the women in the LNG-IUS group and 42% of the women in the hysterectomy group reported back pain. The decrease in back pain was most striking during the first 6 months, but still after 10 years the occurrence of back pain was significantly lower than at baseline in both study groups (p<0.001), with no significant difference between the

Figure 8. Occurrence of lower abdominal pain in the LNG-IUS group (a) and hysterectomy group (b) during the 10- year follow-up. *Difference between the groups (p=0.02).

Back pain

Before the treatment, back pain was common; 64% of the women in the LNG-IUS group (21% nearly every day, 10% weekly, 33% monthly) and 65% of the women in the hysterectomy group (11% nearly every day, 13% weekly, 41% monthly) reported back pain (Figure 9). After the treatment, occurrence of back pain decreased in both groups. At 10 years, 40% of the women in the LNG-IUS group and 42% of the women in the hysterectomy group reported back pain. The decrease in back pain was most striking during the first 6 months, but still after 10 years the occurrence of back pain was significantly lower than at baseline in both study groups (p<0.001), with no significant difference between the
groups. Monthly pain decreased most in both groups (LNG-IUS: from 33% to 17%, p<0.001 and hysterectomy: 41% to 10%, p<0.001). Daily back pain decreased in the LNG-IUS group (from 21% to 14%, p=0.01) and increased in the hysterectomy group (from 11% to 25%, p<0.001). At 10 years, 29% of the women in the LNG-IUS group and 19% of the women in the hysterectomy group experienced back pain less often and 13% and 25% of the women, respectively, experienced back pain more often.

Figure 9. Occurrence of back pain in the LNG-IUS group (a) and in the hysterectomy group (b) during the 10-year follow-up. *Difference between the groups (p=0.02).
Before the treatment, back pain score was higher in the LNG-IUS group (mean 10.18) than in the hysterectomy group (mean 8.44) \((p=0.02)\) (Figure 10). Between baseline and 10 years, back pain score decreased in the LNG-IUS group (mean -1.2, \(p=0.2\)) and increased in the hysterectomy group (mean +1.8, \(p=0.06\)), with a significant difference emerging between the study groups \((p=0.02)\). At 10 years, 52% of the women in LNG-IUS group and 33% of the women in hysterectomy group experienced lower pain scores than at baseline. The corresponding proportions of women with higher pain scores were 34% and 56%.

The multivariate model adjusted by age, BMI, ET and unemployment showed an association between LNG-IUS use and a decrease in back pain score between baseline and 10 years \((p=0.02)\). The route of hysterectomy did not explain the changes in back pain.

The results by actual treatment were in line with intention-to-treat analyses.

**Figure 10.** Lower abdominal pain score (mean) and back pain score (mean) in the LNG-IUS group and in the hysterectomy group during the 10-year follow-up. (Scale range 1-28). *Difference between the groups \((p=0.02)\).
5.5 Lower urinary tract symptoms (Study III)

The baseline incidences of LUTS categorized by 10-year actual treatment group are given in Table 6. No significant differences were present between the groups. None of the women had undergone surgery for urinary incontinence (UI) before treatment. During the 10-year follow-up, three of the hysterectomized women and one LNG-IUS user underwent a tension-free vaginal tape procedure. Re-operation by the transobturator vaginal tape procedure was performed on one woman with hysterectomy. None of the women had used medication for UI before treatment. During the 10 years women with hysterectomy used significantly more anticholinergics and duloxetine for UI than LNG-IUS users (Table 7).

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hysterectomy (n = 164)</td>
</tr>
<tr>
<td>Urinary tract infection (UTI)*</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Urge urinary incontinence (UUI)</td>
<td>32 (20%)</td>
</tr>
<tr>
<td>Stress urinary incontinence (SUI)</td>
<td>65 (40%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>13 (8%)</td>
</tr>
<tr>
<td>Increased daytime frequency (IDF)</td>
<td>51 (31%)</td>
</tr>
<tr>
<td>Feeling of incomplete emptying (FIE)</td>
<td>26 (16%)</td>
</tr>
</tbody>
</table>

* Self-reported.

No significant differences between the study groups.
Table 7. Use of medication for urinary incontinence in the 10 years after hysterectomy or treatment with LNG-IUS.

<table>
<thead>
<tr>
<th></th>
<th>Hysterectomy</th>
<th>LNG-IUS</th>
<th>Difference between the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticholinergic medicines</td>
<td>Duloxetine</td>
<td>Total</td>
</tr>
<tr>
<td>Baseline to 5 years</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Baseline to 5 years</td>
<td>8 (5%)</td>
<td>0</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Baseline to 10 years</td>
<td>10 (6%)</td>
<td>6 (4%)</td>
<td>16</td>
</tr>
</tbody>
</table>

Analysed by actual treatment.

During the follow-up LUTS increased more among women with hysterectomy. Between baseline and 12 months, IDF decreased in the hysterectomy group (p<0.001) and SUI decreased in the LNG-IUS group (p=0.006) (Table 8). Between 12 months and 10 years, UUI, SUI, dysuria and IDF increased among women treated by hysterectomy (p<0.001, p=0.002, p=0.02, p=0.002) and IDF increased in the LNG-IUS group (p=0.007). At 10 years, SUI was more common in hysterectomized women than in treated with LNG-IUS (p=0.04). Correspondingly, FIE was more common among women with hysterectomy at 5 years (p=0.04). At 10 years, the mean UISS score in the LNG-IUS group was 3.2 (16%) (SD 2.8) and in the hysterectomy group 4.0 (20%) (SD 3.8) (p=0.09).

Between 5 and 10 years, lower urinary tract infections (UTIs) were more common in women with hysterectomy than in women with LNG-IUS (Figure 9); 34% and 14 %, respectively, reported at least one UTI (p=0.002). The corresponding proportions for microbiologically confirmed UTIs were 20% and 9% (p=0.02).

The multivariate model adjusted by bilateral oophorectomy, age, parity, BMI, ET use and smoking showed an association between UTIs and hysterectomy between 5 and 10 years (p=0.004) and between FIE and hysterectomy at 5 years (p=0.03).
Table 8. Incidence of urinary symptoms at baseline and at each follow-up after hysterectomy or LNG-IUS insertion.

<table>
<thead>
<tr>
<th>Lower urinary tract symptoms</th>
<th>LNG-IUS</th>
<th>Hysterectomy</th>
<th>Difference between the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Total</td>
<td>%</td>
</tr>
<tr>
<td>Urge urinary incontinence</td>
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<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>20</td>
<td>119</td>
<td>17</td>
</tr>
<tr>
<td>6 months</td>
<td>12</td>
<td>105</td>
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<td>12 months</td>
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<td>94</td>
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<td>5 years</td>
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<td>10 years</td>
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<tr>
<td>Stress urinary incontinence</td>
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<td>Randomization</td>
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<tr>
<td>10 years</td>
<td>23</td>
<td>68</td>
<td>34</td>
</tr>
<tr>
<td>Dysuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>10</td>
<td>119</td>
<td>8</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>105</td>
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<tr>
<td>12 months</td>
<td>7</td>
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<td>5 years</td>
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<td>10 years</td>
<td>4</td>
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</tr>
<tr>
<td>Increased daytime frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>30</td>
<td>119</td>
<td>25</td>
</tr>
<tr>
<td>6 months</td>
<td>23</td>
<td>105</td>
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<tr>
<td>12 months</td>
<td>13</td>
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<td>5 years</td>
<td>13</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td>10 years</td>
<td>18</td>
<td>68</td>
<td>26</td>
</tr>
<tr>
<td>Feeling of incomplete emptying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>20</td>
<td>115</td>
<td>17</td>
</tr>
<tr>
<td>6 months</td>
<td>10</td>
<td>105</td>
<td>10</td>
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<tr>
<td>12 months</td>
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<tr>
<td>5 years</td>
<td>4</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>10 years</td>
<td>6</td>
<td>68</td>
<td>9</td>
</tr>
</tbody>
</table>

Analysed by actual treatment.
Total number of observations is lower than the number of study participants, as some women did not answer all of the questions.
Figure 10. Proportion of women with at least one urinary tract infection after treatment with LNG-IUS or hysterectomy.

UI, urinary tract infection.
Analysed by actual treatment.
Women with bilateral oophorectomies excluded.
Difference between groups: * p=0.002, ** p=0.02.
5.6 Cardiovascular disease risk factors (Study IV)

At baseline, no differences existed in the use of medications for diabetes, hypertension, ischaemic heart disease and hypercholesterolaemia between the study groups (Table 9). Between baseline and 10 years, medication for hypertension and hypercholesterolaemia increased in both groups (p<0.001), with no difference between the groups, but use of diabetes medication increased only in women with hysterectomy (p=0.008) (from 1.7% to 6.7%) (Table 11).

The traditional CVD risk factors (total cholesterol, high- and low-density cholesterol, blood pressure and waist circumference) were analysed at 10 years; no significant differences emerged between the groups. BMI increased significantly in both groups (LNG-IUS: +1.8kg/m2, hysterectomy: +2.2kg/m2, p<0.001), with no difference between the groups.

Table 9. Use of medication for hypertension, diabetes, hypercholesterolaemia and ischaemic heart disease.

<table>
<thead>
<tr>
<th></th>
<th>LNG-IUS n (%)</th>
<th>Hysterectomy n (%)</th>
<th>Change between the groups p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22 (18.9%)</td>
<td>15 (12.6%)</td>
<td>0.21</td>
</tr>
<tr>
<td>5 years</td>
<td>28 (37.8%)</td>
<td>48 (30.2%)</td>
<td>0.25</td>
</tr>
<tr>
<td>10 years</td>
<td>30 (42.2%)</td>
<td>71 (43.2%)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6 (5.1%)</td>
<td>2 (1.7%)</td>
<td>0.17</td>
</tr>
<tr>
<td>5 years</td>
<td>6 (7.9%)</td>
<td>4 (2.5%)</td>
<td>0.05</td>
</tr>
<tr>
<td>10 years</td>
<td>6 (8.4%)</td>
<td>11 (6.7%)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Hypercholesterolaemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>5 years</td>
<td>5 (6.8%)</td>
<td>11 (6.9%)</td>
<td>0.96</td>
</tr>
<tr>
<td>10 years</td>
<td>15 (21.1%)</td>
<td>26 (15.8%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Ischemic heart disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0%)</td>
<td>1 (0.8%)</td>
<td>0.32</td>
</tr>
<tr>
<td>5 years</td>
<td>0 (0%)</td>
<td>2 (1.3%)</td>
<td>0.33</td>
</tr>
<tr>
<td>10 years</td>
<td>1 (1.4%)</td>
<td>4 (2.4%)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Number of women in treatment groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>119</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>77</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>71</td>
<td>164</td>
<td></td>
</tr>
</tbody>
</table>

Analysed by actual treatment. Use of medication derived from the Social Insurance Institution of Finland.
Oestrogen therapy (ET) was used by 8 women (10%) in the LNG-IUS group and by 52 women (33%) in the hysterectomy group at 5 years (p< 0.001). At 10 years, ET was used by 19 women (27%) in the LNG-IUS group and by 97 women (59%) in the hysterectomy group (p< 0.001). When the 16 women with bilateral oophorectomy were excluded, the correspondingly numbers were 8 (10%) vs. 42 (29%) at 5 years (p=0.003) and 19 (27%) vs. 83 (56%) at 10 years (p<0.001) (Figure 11).

**Figure 11. Proportion of women using oestrogen therapy after treatment with LNG-IUS or hysterectomy.**

Analysed by actual treatment.

Women with bilateral oophorectomies (n=16) excluded.

Difference between the groups: * p=0.003, ** p<0.001.
Inflammatory serum markers

No significant differences between study groups were noted in the levels of hsCRP and TNF-α at baseline. The levels of hsCRP did not change during the first 5 years (Figure 12). At 10 years, hsCRP levels were higher among women with hysterectomy than among LNG-IUS users (p=0.04). At 5 years, women with hysterectomy had higher levels of TNF-α than women with LNG-IUS (p=0.001). In both groups, TNF-α levels decreased after 5 years (Figure 10). Multivariate analysis (with potential explaining factors of age, ET use, BMI, smoking, social status and oophorectomy) showed an association between hysterectomy and levels of TNF-α at 5 years (p=0.003), whereas hsCRP was associated with age (p=0.04) and BMI (p<0.001).

Figure 12. Serum levels (median) of hsCRP (µg/ml) and TNF-α (pg/ml) at baseline and at 5 and 10 years after treatment by LNG-IUS or hysterectomy.
Analysed by actual treatment. Differences between groups *p=0.04, **p=0.001.
6. Discussion

6.1 Methodological considerations

This study is the only long-term randomized trial comparing LNG-IUS and hysterectomy in the treatment of essential menorrhagia. Power analysis was based on the main outcome measure (HRQoL), and all five university hospitals in Finland were included. A wide range of outcome measures was used to determine the effect of LNG-IUS and hysterectomy on HRQoL, costs, pain, LUTS and CVD risk factors. Most of the instruments used were validated and HRQoL was estimated by exceptionally many instruments. The costs of the treatments included both health care and productivity losses and were calculated with a number of variables.

The randomization was successful, with similar subject characteristics in both arms. The only differences between the study groups at baseline were slightly higher BMI and back pain score in the LNG-IUS group. The dropout rate even at the 10-year follow-up was low (6%), suggesting a high commitment of both participating women and doctors and a good study protocol. Thanks to this, compliance bias is presumably absent in this study. As the inclusion criteria followed general clinical guidelines, selection bias was unlikely as well. Over half of the women referred for menorrhagia to the university hospital were excluded from the study. They either declined to participate or failed to meet the criteria of either of the two treatment modalities. Therefore it is assumed that the study population represents women who are candidates for both treatment modalities and that results are generalized.

The duration of follow-up in this study was exceptionally long. The mean age of menopause in Finland was 50 years in 1997 and 51 years in 2007 (Pakarinen et al. 2010). The mean age of the study population 10 years after the treatment was 53.1 years, meaning that most women had reached menopause and menorrhagia was no longer a problem. The 10-year follow-up thus covers the entire treatment of menorrhagia.

The discontinuation and hysterectomy rates in the LNG-IUS arm are in line with previous studies (Marjoribanks et al. 2006, Matteson et al. 2012). However, our data were collected from women referred to university hospitals for menorrhagia and meeting the criteria for hysterectomy. Had the LNG-IUS treatment been initiated already in primary health care, the number of hysterectomies in the LNG-IUS arm would likely have been much smaller. Women who were prepared for hysterectomy seemed to poorly tolerate the bleeding problems with the LNG-IUS during the first months.
The total complication rate of hysterectomy in this study was relatively high (total complications 32%, major complications 2%) compared with complication rates in Finland in general (total complications 11.7-19.2%, major complications 2.6-4.3%) (Brummer et al. 2011). However, only this study included strong postoperative abdominal pain to the complications. The approach of hysterectomy in this study (vaginal hysterectomy (VH) 26%, abdominal hysterectomy (AH) 20%, laparoscopic hysterectomy (LH) 54%) differed from the normal distribution of approaches in Finland in 1996 (VH 18%, AH 58%, LH 24%) and in 2006 (VH 44%, AH 32%, LH 24%). The high rate of laparoscopic hysterectomies can be explained by the indication of essential menorrhagia for hysterectomies, usually without uterine prolapse or large fibroids.

The hysterectomies performed in the LNG-IUS group are part of the treatment flow also in normal clinical work. This is why intention-to-treat analyses reflect well the results of the decision to start treatment of menorrhagia either with hysterectomy or LNG-IUS. However, to even better show the effect of hysterectomy or LNG-IUS, analyses were conducted by actual treatment in Studies III and IV. The strength of evidence in these studies may be lower as the power of randomization was lowered. However, the baseline characteristics of the 55 women originally randomized to LNG-IUS group and who subsequently had hysterectomy did not differ from those of the other women. Another limitation in the Studies III and IV was that in the actual treatment analysis women who had had hysterectomy were compared with all other women, although only 45 women still had LNG-IUS in situ at 10 years. One woman was excluded from the actual treatment analysis at 10 years due to missing data about treatment modality. This inaccuracy in actual treatment groups can weaken the strength of the results in actual treatment analysis.

The questionnaires were sent home by post, allowing the patients sufficient time to respond. Some of the women did not respond to all of the questions. This would have introduced a systematic recall bias had it not been but was avoided by randomization and sophisticated statistical methods in HRQoL analyses. Overall, the response rate was high, also lowering the bias. Because the reliability of questionnaires may not be the best possible, other data sources were also used. The records for use of medication were obtained from the registry of purchased drugs of the Finnish Social Insurance Institution, which keeps a registry of all purchased prescription-only medicines. Data on special reimbursements of diseases were confirmed from the registry of special reimbursements of medicines of the Finnish Social Insurance Institution. Data on all performed hysterectomies and use of LNG-IUS as well as on complications and surgery for UI were confirmed from medical records and the Hospital Discharge Registry of the Finnish National Institute for Health and Welfare. The registries in Finland have proven to be reliable (Suoyrjö et al. 2007).
Some limitations in the calculation of cost-utility exist. Firstly, the EQ-5D values were measured at baseline and at 1 year, 5 years and 10 years, not annually. Secondly, the cost-utility calculation was based on the baseline values of EQ-5D (not on values of reference group) because we had no randomized study group without treatment and there was no difference in HRQoL between the LNG-IUS and hysterectomy groups. Despite this uncertainty in the QALY calculations, cost-utility values of both treatment modalities were convincing. If we had had a reference group, it is expected that the amount of QALYs gained would have been increased and the cost of QALY gained would have been decreased, as the HRQoL tends to decrease with age (Ohinmaa and Sintonen 1996, Aalto et al. 1999).

6.2 Cost-effectiveness of LNG-IUS and hysterectomy in the treatment of menorrhagia

Hysterectomy reduced MBL and improved HRQoL, but was the most expensive treatment option and was also associated with a several of complications. In most women, LNG-IUS was effective in reducing MBL; however, in the 10-year follow-up 55 (46%) of the women randomized to LNG-IUS had undergone hysterectomy. Bleeding problems were the most common reasons for hysterectomy or discontinuation of LNG-IUS use.

Health related quality of life

Menorrhagia has deleterious effect on the QoL of many women. The results of our study are in accordance with previous reports showing significant improvement in HRQoL, anxiety and depression after treatment of menorrhagia (Marjoribanks et al. 2006, Middleton et al. 2010, Blumenthal et al. 2011). At baseline, EQ-5D and RAND-36 scores of the study population were significantly lower than the mean scores of age-matched Finnish women, and similar to the scores of women with chronic illness (Ohinmaa and Sintonen 1996, Aalto et al. 1999). HRQoL and other measures of psychosocial well-being improved in both groups, with no significant differences between the study groups. The multilevel model showed that study groups followed very similar trajectories, but the trajectories of women in the LNG-IUS group moved slightly below the trajectories of women in the hysterectomy group, which mostly resulting from small baseline differences combined with non-significant differences in change between baseline and 12-month follow-up.
The impact of the treatment of menorrhagia on HRQoL was strongest after one year, yet the 5-year values were still significantly better than baseline values. Between 5 and 10 years, the HRQoL decreased, presumably explained by the effect of ageing, not by the effect of the treatment of menorrhagia. Only five women needed more treatment for bleeding problems after 5 years; all others were satisfied with their menstruation. The majority of women had reached menopause, and 90% of the women in the LNG-IUS group were in amenorrhoea already at 5-year follow-up. The reference values of HRQoL, obtained from two large Finnish population surveys, are known to decrease with ageing (Ohinmaa and Sintonen 1996, Aalto et al. 1999). The finding of impaired in sexual functioning during ageing is also in line with previous studies showing declining sexuality after menopause (McCoy and Davidson 1985, Dennerstein et al. 2003).

Ten years after treatment, most of the HRQoL values were still above or at the same level as baseline, in contrast to HRQoL reference values of same-aged, women decreasing with age (Ohinmaa and Sintonen, Aalto et al 1999). This difference between our results and reference values appears to be related to treatment of menorrhagia. However, the HRQoL values of the study population at 5 and 10 years were still lower than reference values, but the difference was smaller than at baseline (Ohinmaa and Sinotnen 1996, Aalto et al. 1999). Because menopause and ageing have a marked influence on HRQoL, the only way to clarify the real effect of menorrhagia treatments on HRQoL is a randomized study group of menorrhagia patients without treatment. Such a study design is not, however, ethical. Our results support the findings of previous studies that the maximum HRQoL benefits of menorrhagia treatments are achieved during the first year and are generally maintained up to 5 years (Blumenthal et al. 2011). However, no study of the impact of LNG-IUS on HRQoL has continued beyond 5 years.

**Cost-effectiveness**

LNG-IUS has previously been shown to be cost-effective at 1-year and 5-year follow-ups (Hurskainen et al. 2001b, 2004b). Now we have shown that LNG-IUS remains cost-effective after 10 years. Although 46% of the women assigned to the LNG-IUS group eventually underwent hysterectomy, the discounted direct and indirect costs in the LNG-IUS group remained substantially lower than in the hysterectomy group 10 years after treatment. The decision to start the treatment with LNG-IUS was approximately 31% less expensive than treatment with hysterectomy. Most (91%) of the hysterectomies in the LNG-IUS group were performed during the first 5 years and 44% during the first year. Only five women had a hysterectomy between 5 and 10 years. Had the costs of all gynaecological treatments (including oestrogen therapy and medication for urinary incontinence) been included in to the analysis, the difference of costs between the study groups would probably have been...
even more pronounced. On the other hand, the cost-saving of sanitary products after treatment of menorrhagia or amenorrhoea can be substantial.

During the 10-year period, the incremental cost per additional QALY gained was significantly lower than the commonly accepted threshold value of $50,000 both in the LNG-IUS group ($7607) and in the hysterectomy group ($9680), demonstrating the cost-effectiveness of both treatment modalities for menorrhagia (Birch and Gafni 2004). In a recent Finnish prospective trial investigating utility and costs of hysterectomy with benign indications, the cost of an additional QALY gained by hysterectomy among menorrhagia patients was higher (€19,415=$19,620) than in this study (Taipale et al. 2009). However, the follow-up of the study was only six months and the HRQoL was assumed to continue at 6-month level until menopause. Moreover, HRQoL was measured by the 15D HRQoL questionnaire, which may show lower HRQoL effects than EQ-5D.

Our results are consistent with many modelling studies and reviews that suggest LNG-IUS to be the most cost-effective treatment option for menorrhagia (Clegg et al. 2007, NICE 2007, Blumenthal et al. 2011, Matteson et al. 2012). A modelling study from UK undertaken to inform National Institute for Health and Clinical Excellence guidelines on menorrhagia, showed that LNG-IUS generated more QALYs at a lower cost than any other medical or surgical treatment (NICE 2007). The most recent review concluded that hysterectomy is the most effective treatment in reducing MBL, but found no difference in HRQoL (Matteson et al. 2012). Hysterectomy was associated with the highest risk for adverse effects and complications, while less-invasive treatment options, such as LNG-IUS, carried significant risk for re-treatment or surgery (Matteson et al. 2012). By contrast, a recent systematic meta-analysis and modelling study using individual patient data of clinical effectiveness and cost-effectiveness of the treatment of menorrhagia found hysterectomy to be the most cost-effective, albeit the most expensive, treatment compared with EA or LNG-IUS (Bhattacharya et al. 2011, Roberts et al. 2011). The lack of RCTs comparing LNG-IUS and hysterectomy and the problems and limitations of modelling studies can explain the different results of the trials.

The Finnish Current Care guideline of menorrhagia treatment (Current Care editorial office 2005, updated 2009) conclude that the appropriate treatment of menorrhagia improves patients’ QoL, and that medical treatment, including a LNG-IUS, should usually be tried before surgical treatment. The National Institute for Health and Clinical Excellence guideline on menorrhagia is consistent with Finnish Current Care guideline and suggests LNG-IUS to be more cost-effective than any other medical or surgical treatment considered (NICE 2007).
6.3 Effect of LNG-IUS and hysterectomy on lower abdominal pain and back pain

Lower abdominal pain is often associated with menorrhagia (Yoo et al. 2011). This finding was also made here; 42% of the women reported lower abdominal pain before treatment, 22% reporting pain monthly, 12% weekly and 7% nearly every day. Monthly lower abdominal pain, presumably related to the menstrual cycle, was present in one of five women at baseline; it nearly halved during the follow-up, as did monthly back pain.

Both LNG-IUS and hysterectomy decreased pain among menorrhagic women. In both groups, the main decrease in frequency of pain occurred during the first 6 months and was maintained for up to 10 years. At the 12-month follow-up, lower abdominal pain was more common in the LNG-IUS group. This finding is in line with pain measures by the RAND-36 instrument showing that women with hysterectomy suffered less pain at 12-month follow-up (Hurskainen et al. 2001b), but no longer at the five-year-follow up (Hurskainen et al. 2004b). The greatest decrease in pain shortly after initiation of the treatment may be partly explained by women’s expectations since outcomes are influenced by subjective experiences. On the other hand, the main decrease in the pain score (occurrence and intensity of pain combined) occurred between 6 months and 5 years.

Some of the women in both groups experienced more lower abdominal pain and back pain after the treatment than before the treatment. This finding is consistent with previous trials showing that in most cases both LNG-IUS (Jensen et al. 2005, Varma et al. 2006, Anpalagan and Condous 2008, Alhamdan et al. 2010) and hysterectomy (Learman et al. 2004) reduce pain, but in some women lower abdominal pain and back pain increase after hysterectomy (Wijnhoven et al. 2006, Brandsborg et al. 2007, 2008) or after insertion of LNG-IUS (Lethaby et al. 2005, Kriplani et al. 2007). According to a review article, chronic pain is reported by 5–32% of women after hysterectomy (Brandsborg et al. 2008). However, surgery did relieve pain in the majority of women, and pain as a new symptom was reported in 1–14.9% of women and increased pain in 2.9–5% of women with pre-operative pelvic pain. Pre-operative pain was associated with a higher risk of having pelvic pain at follow-up. The prevalence of chronic pain was similar irrespective of the technique of hysterectomy, a finding supported by this study. A Danish nationwide study reported that 15% of women hysterectomized for benign reasons develop chronic pelvic pain after hysterectomy (Brandsborg et al. 2007). In a non-randomised prospective study among women with menorrhagia, 38.3% reported back pain as a side effect after 3 months’ use of LNG-IUS. However 77.5% of the women reported relieved dysmenorrhea at 3 months, and after 2 years’ use of LNG-IUS none of the women had dysmenorrhea (Kriplani et al. 2007). The results of this study agree with previous findings showing a decrease in lower abdominal pain in 38-70% and in back pain in 28-52% of women in the LNG-IUS group, and, correspondinglyly in 35-73%
and 19-33% of women in the hysterectomy group. The correspondingly figures for an increase in abdominal pain and back pain were 5-12% and 13-34% in women with LNG-IUS and 10-20% and 25-56% in women with hysterectomy.

Women in both groups experienced more back pain than lower abdominal pain. Moreover, back pain increased (not significantly) in both groups between 5 and 10 years. Presumably much of the back problems were associated with other causes of back pain, such as menorrhagia, which become more common with age. However, back pain, mostly daily back pain, increased more in the hysterectomy group than in the LNG-IUS group. A possible explanation for the increased pain after hysterectomy could be adhesions and bowel problems caused by hysterectomy. Moreover, the risk of failure of the pelvic floor, leading to vaginal prolapse, increases after hysterectomy (Mant et al. 1997). These kinds of changes in anatomy may cause lower abdominal pain, back pain and spastic pelvic symptoms after hysterectomy. The increase in back pain may be partly explained by age-related changes in bones and muscles, possibly associated with hormonal changes, as hysterectomy seems to have a more deleterious effect on ovaries than does LNG-IUS (Halmesmäki et al. 2006).

Overall, in the long run, LNG-IUS seems to be as beneficial as hysterectomy for lower abdominal pain and for back pain even more beneficial.

6.4 Effect of LNG-IUS and hysterectomy on lower urinary tract symptoms

After the treatment, women treated with hysterectomy had more LUTS, including SUI, FIE and UTIs, than women treated with LNG-IUS. Women with hysterectomy also used also more medication for UI than LNG-IUS recipients. In both groups, the incidence of LUTS decreased during the first year and increased thereafter being close to baseline levels at 10 years. The marked decrease during the first year post-treatment may be explained by improved QoL and by women’s expectations (Hurskainen et al. 2004b). The subsequent increase in symptoms may be explained by ageing, as age is a known risk factor for LUTS, particularly UI (Brown et al. 2000). The prevalence of UI and pelvic floor dysfunction increases after 60 years of age (Brown et al. 2000, Luber et al. 2001), and it is assumed that LUTS are more pronounced in an older study population.
The findings of the effect of hysterectomy on lower urinary tract function have been contradictory in previous studies. The duration of follow-up likely plays an important role in the evaluation of outcomes (Samuelsson et al. 2000, Neumann et al. 2004). A population–based cohort study showed that hysterectomy increases SUI surgery, irrespective of surgical technique (Altman et al. 2007). Another population-based study found an increased risk for urge urinary incontinence (UUI) after hysterectomy (van der Vaart et al. 2002), and a review article concluded that hysterectomy increases the likelihood of UI in the long term (Brown et al. 2000). On the other hand, a RCT comparing hysterectomy and EA found no increased risk of UI after hysterectomy in a 2-year follow-up (Bhattacharya et al. 1996). Thakar et al. (2002) concluded in their randomized trial that neither total nor subtotal hysterectomy adversely affected pelvic organ function at 12 months. Findings of studies with a longer follow-up (Brown et al. 2000, van der Vaart et al. 2002, Altman et al. 2007) are in line with our results showing increases in LUTS after hysterectomy, whereas studies with a short follow-up have been unable to demonstrate an increase in UI after hysterectomy (Bhattacharya et al. 1996, Thakar et al. 2002, Neumann et al. 2007). The incidence of LUTS in hysterectomized women in our study was somewhat lower than in the trial of Thakar et al (2002), which compared total abdominal hysterectomy and subtotal abdominal hysterectomy.

Considering the increase in the use of medication for UI among hysterectomized women and some more surgery for UI, it can be assumed that without medication these women would have been even more symptomatic. Most of the medicines used for UI were anticholinergics. Thus, the finding of no differences in UUI and UISS between the study groups may be biased as a result of medication, and it can speculated that UUI in particular would have been more pronounced among women treated with hysterectomy.

It is possible that women in the LNG-IUS group with more LUTS could have had more hysterectomies than women without LUTS. We controlled for this by comparing the incidence of LUTS at baseline between the AT groups. No differences were found indicating that the threshold for hysterectomy was not lower among women with LUTS. Although 20% of the women with hysterectomy and 11% of the women with LNG-IUS reported UUI at baseline, the difference was not significant. Thus, the grouping did not explain the increased LUTS among hysterectomized women.

An interesting and unprecedented observation was the association between UTIs and hysterectomy in long term. Women with hysterectomy had significantly more UTIs than LNG-IUS users at 10 years. This finding was confirmed by the multivariate model, where treatment modality was the only explaining factor for UTIs. Anatomical changes following hysterectomy may predispose women to UTIs and pelvic floor dysfunction. Although the risk for post-surgical UTI after hysterectomy is well known (Mäkinen et al. 2001, Cadkova et al. 2008), no long-term exist on hysterectomy and UTIs. However, the association between UTIs and UI is established (Moore et al. 2008), and this study
showed a link between UTIs and UUI, and between UTIs and FIE. Hence, the increased risk for UTIs after hysterectomy may develop via increased UI and incomplete emptying. A potential explanation for increased UTIs and SUI in women with hysterectomy may be impaired ovarian function and earlier menopause causing mucosal atrophy in the vagina and urethra. It is also possible that the local progestin effect of LNG-IUS in the mucosa of the bladder and urethra protects against UTIs in LNG-IUS users. Thus, whether the difference in the incidence of LUTS between the treatment groups is due to a predisposing effect of hysterectomy or a protective effect of LNG-IUS is unclear.

6.5 Effect of LNG-IUS and hysterectomy on CVD risk factors

Women treated with hysterectomy had higher levels of TNF-α and hsCRP than women treated with LNG-IUS at 5 and 10 years after treatment. The results suggest that hysterectomy may be accompanied by responses that predispose women to CVD, consistent with previous findings (Howard et al. 2005, Ingelsson et al. 2011). An increased risk may result from an earlier menopause in women with hysterectomy, which may induce low-grade inflammation in the body (Farquhar and Steiner 2005, Halmesmäki et al. 2007a, Abu-Taha et al. 2009).

Interestingly, but not surprisingly, ET was significantly more often used by women treated with hysterectomy than by LNG-IUS users at 5 years (29% vs. 10%) and 10 years (56% vs. 27%) after treatment. Women with bilateral oophorectomy were excluded from the analysis. This finding strengthens the link between hysterectomy and earlier menopause. The effect of ET on the risk of CVD varies with age at the time of initiation of treatment. ET has a protective effect in younger women, but in older women it increases the risk (Manson et al. 2007, Rossouw et al. 2007). However, as the women in our trial were relatively young (average age at end of study 53.1 years), the effect of ET use on CVD risk may have been protective rather than predisposing. Previous data have demonstrated increased levels of hsCRP, but not TNF-α, among women receiving either oestrogen alone therapy (Kwok et al. 2009) or combination therapy with progestin (Eilertsen et al. 2008). This could in part explain the observed higher levels of hsCRP in the hysterectomy group, although multivariate regression analysis did not find an association between ET and hsCRP levels. In line with previous studies, a higher concentration of hsCRP was associated with BMI (Bochud et al. 2009) and age (Werner et al. 2000), but not with smoking or social status. The hsCRP concentrations in the groups observed in this study are consistent with those reported for healthy women (Ridker et al. 2000,
Woloshin and Schwartz 2005). The LNG-IUS was not associated with changes in serum hsCRP levels, which is also in line with earlier findings (Kayikcioglu et al. 2006).

Use of diabetes medication increased during the follow-up period in the hysterectomy group. Although the number of women was low and the results are unlikely to be clinically significant, this is an interesting finding, as increased levels of hsCRP are known to predict type 2 diabetes in humans, and TNF-α causes insulin resistance in animal models (Hotamisligil 1999, Bochud et al. 2009). After adjusting for confounding factors (classic CVD risk factors), TNF-α levels were fully explained by treatment modality and not by BMI. The significant increase in of TNF-α level 5 years after hysterectomy may therefore reflect a low-grade inflammatory status of the body after hysterectomy, and therefore being one of the key factors mediating increased CVD risk after hysterectomy.

The number of women receiving medication for hypercholesterolaemia, hypertension or ischaemic heart disease increased in both groups during the follow-up period, in accord with an age-related increase in serum cholesterol and blood pressure (Amery et al. 1978). No difference was present between the treatment groups in the use of medication for these conditions, which is consistent with the lack of differences between the groups in the levels of serum cholesterol or blood pressure. The finding of the neutral effects of LNG-IUS on blood pressure, cholesterol and hsCRP supports earlier research (Nilsson et al. 1981, Kayikcioglu et al. 2006, Morin-Papunen et al. 2008), strengthening the presumption that LNG-IUS does not have an adverse effect on cholesterol, unlike oral progestins (Graff-Iversen and Tonstad 2002).
7. Summary and conclusions

In conclusion, this study shows that treatment of menorrhagia with LNG-IUS or hysterectomy improves HRQoL significantly and similarly. The results highlight the importance of menorrhagia treatment. The cost of starting treatment of menorrhagia with LNG-IUS was 31% less than the cost of starting with hysterectomy, establishing LNG-IUS as the more cost-effective treatment option. However, both LNG-IUS and hysterectomy had a commendable cost-utility value when the cost of gained QALYs was calculated. Both hysterectomy and LNG-IUS decreased lower abdominal pain, which is often associated with menorrhagia, but LNG-IUS seemed to have more beneficial effect on back pain. Compared with treatment by LNG-IUS, hysterectomy increased the risk for LUTS in the long run. Women treated with hysterectomy were more exposed to incomplete bladder emptying and UTIs. They were also more likely to develop SUI and to need more medication for UI. Women treated with hysterectomy used more ET reflecting earlier menopause, than women with LNG-IUS or without treatment. Hysterectomy seemed to correlate with increased levels of TNF-α and hsCRP relative to LNG-IUS or no treatment, suggesting that women undergoing hysterectomy may have an increased risk for future cardiovascular events.

Menorrhagia is one of the most common reasons for women seeking medical care, and treatment is frequently needed. When making treatment decisions for menorrhagia, costs, effectiveness and potential long-term risks and benefits of the treatments should be weighed. This study confirms that LNG-IUS should be the first choice in the treatment of menorrhagia. LNG-IUS should be tried at an early stage and before planning hysterectomy.
8. Summary in Finnish

Tässä kymmenen vuoden seurantatutkimuksessa verrattiin hormonikierukan ja kohdunpoiston kustannusvaikuttavuutta runsaiden kuukautisten hoidossa. Lisäksi tutkimuksessa arvioitiin hoitomuotojen vaikutusta elämänlaatuun ja psykososiaaliseen hyvinvointiin, alavatsa- ja selkäkipuihin, alempien virtsateiden oireisiin sekä sydän- ja verisuonisairauksien riskitekijöihin.


Ennen hoitoa alavatsakipuja oli 45%:lla hormonikierukkaryhmän ja 38%:lla kohdunpoistoryhmän naisista ja selkäkipuja yli puolella (64% vs. 65%). Molemmat hoitomuodot vähensivät kipuja merkittävästi. Kymmenenvuotiskäynnillä alavatsakipua valittiin enää 12% hormonikierukkaryhmän ja 15% kohdunpoistoryhmän naisista ja selkäkipua 40% / 42% naisista. Molemmissa ryhmissä kivut vähenevät eniten ensimmäisen kuuden kuukauden aikana ja kuukausittain ilmenevät kipu vähensi eniten. Kun kivun voimakkuus yhdistettiin esiintymistieteyteen, alavatsakipu väheni molemmissa ryhmissä, mutta selkäkipu vain hormonikierukkaryhmässä.

Hoitomuotojen vaikutusta alempien virtsateiden oireisiin sekä sydän- varisuonisairauksien riskitekijöihin tutkittiin toteutuneen hoitomuodon mukaan. Kohdunpoistolla hoidetuilla naisilla oli
enemmän ponnistusvirtsinkarkailua (48% vs. 34%, p=0.04) ja he käyttivät enemmän lääkkeitä (12% vs. 1%, p=0.006) virtsinkarkailun hoitoon kuin hormonikierukalla hoidetut naiset. Heillä ilmeni myös enemmän rakon tyhjenemisongelmia (19% vs. 9%, p=0.04) ja virtsatieinfektiot olivat yleisempiä (34% vs. 14%, p=0.002) kuin kierukkaryhmässä.

Sekä verenpainetauti että hyperkolesterolemia lisääntyivät molemmissa hoitotyöryhmissä, mutta diabeteslääkkeiden käyttö lisääntyi vain kohdunpoistotyöryhmässä. Painoindeksi nousi samankaltaisesti hormonikierukalla (+1.8 kg/m2) ja kohdunpoistolla (+2.2 kg/m2) hoidetuilla naisilla. Lisäksi havaittiin, että naiset joillain kohtu oli poistettu käytettävät merkitsevästi enemmän estrogeenihoitoa kuin hormonikierukalla hoidetut naiset viisi vuotta (29% vs. 10%, p=0.003) ja kymmenen vuotta (56% vs. 27%, p<0.001) hoidon jälkeen. Kohdunpoistolla hoidetuilla naisilla todettiin seerumissa korkeammat sydän- ja verisuonisairauksien riskiä kuvaavien tulehduksellisten merkkiaineiden pitoisuudet (TNF-α ja hsCRP). Tulokset vahvistavat käsitystä, että kohdunpoisto heikentää munasarjojen toimintaa ja saattaa tämän seurauksena lisätä sydän- ja verisuonisairauksien riskiä.

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