Impact of hysterectomy and levonorgestrel-releasing intrauterine system on ovarian function, bone and sexual health in menorrhagic patients

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To my loved ones
This thesis is based on the following articles, which are referred in the text by their Roman numerals I–IV:


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Abbreviations

AFC................. Antral follicle count
AMH................. Anti-Müllerian hormone
BMD............... Bone mineral density
BMI................. Body mass index
CI.................. Confidence interval
DXA................ Dual-energy x-ray absorptiometry
ET.................. Oestrogen therapy
FSH............... Follicle-stimulating hormone
LH................. Luteinising hormone
LNG.............. Levonorgestrel
LNG-IUS.............. Levonorgestrel-releasing intrauterine system
MBL................. Menstrual blood loss
NS................ Not significant
NSAID............ Non-steroidal anti-inflammatory drug
OR................ Odds ratio
PI................ Pulsatility index
SD................. Standard deviation
SE................ Standard error
SHBG............. Sex hormone binding globulin
TVS............... Transvaginal sonography
VI................ Vascularisation index
VuokKKo............ Finnish word shortened from menstruation, intrauterine system and hysterectomy (Vuodot, Kierukka, Kohdunpoisto)
Abstract

Impact of hysterectomy and levonorgestrel-releasing intrauterine system on ovarian function, bone and sexual health in menorrhagic patients

Karoliina Halmesmäki
THE "VUOKKO" trial consisted of 236 women referred and randomised due to menorrhagia in the five university hospitals of Finland between November 1994 and November 1997. Of these women, 117 were randomised to hysterectomy and 119 to use levonorgestrel releasing intrauterine system (LNG-IUS) to treat this complaint. Their follow-up visits took place six and twelve months after the treatment and five years after the randomisation. The first aim in the primary trial was quality-of-life and monetary aspects, and secondly in the present study to compare ovarian function, bone mineral density (BMD) and sexual functioning after these two treatment options.

Ovarian function seemed to decrease after hysterectomy, demonstrated by increased hot flashes and serum follicle-stimulating hormone concentrations twelve months after the operation. Such an increase was not seen among LNG-IUS users. The pulsatility index of intraovarian arteries measured by two-dimensional ultrasound decreased in the hysterectomy group, but not in the LNG-IUS group. The decrease in serum inhibin B concentrations was similar in both groups, while ovarian artery circulation remained unchanged.

BMD of the women measured by dual x-ray absorptiometry (DXA) at the lumbar spine and femoral neck at baseline and at five years after treatment showed BMD decrease at the lumbar spine among hysterectomised women, but not among LNG-IUS users. In both groups, BMD at the femoral neck had decreased. Differences between the groups were not, however, significant.

Sexual functioning assessed by McCoy’s sexual scale showed that sexual satisfaction as well as intercourse frequency had increased and sexual problems decreased among hysterectomised women six months after treatment. Among LNG-IUS users, sexual satisfaction and sexual problems remained unchanged. Although, the two groups did not differ in terms of sexual satisfaction or sexual problems at one-year and five-year follow-ups, LNG-IUS users were less satisfied with their partners than hysterectomised women.
1. Introduction
HEAVY CYCLICAL menstrual bleeding over several cycles is known as menorrhagia. Menorrhagia influences the lives of nearly one-third of women (Shapley et al. 2004), decreasing quality of life and causing sick days (Jones et al. 2002), and therefore, needs to be treated. Several treatment options exist today, of which hysterectomy and levonorgestrel-releasing intrauterine system (LNG-IUS) are effective and well-known by both physicians and patients (Hurskainen et al. 2001, Hurskainen et al. 2004, Marjoribanks et al. 2006). A Finnish ‘VuoKKo’ study commenced in 1994 aiming to compare quality of life and costs after hysterectomy or after LNG-IUS. It concluded that five years after the randomisation, the treatments had a similar impact on quality of life, but LNG-IUS was 40% less expensive (Hurskainen et al. 2004). The effect of these treatment options on other aspects of health was still to be elucidated. Therefore this study was originated.

Hysterectomy is irreversible and removal of the uterus may have long-term effects on ovarian function, since in hysterectomised women menopausal symptoms seem to appear earlier (Farquhar et al. 2005, Hartmann et al. 1995, Oldenhave et al. 1993, Stadberg et al. 2000). Previous results have, however, been controversial and no definite conclusions could have been drawn (Chalmers et al. 2002, Gallicchio et al. 2006, Virtanen et al. 1993). LNG-IUS, in turn, is considered to have only small effect on ovarian function, as the majority of the cycles are ovulatory (Barbosa et al. 1990, Nilsson et al. 1984). However, if either of the treatments impaired ovarian function, it is possible that other oestrogen dependent alterations, like in bone health and sexual functioning (Gonzalez et al. 2004, Guthrie et al. 2004), would also appear.

Consequently, objective of this study was to evaluate the influence of these two treatment options of menorrhagia on ovarian function, bone mineral density (BMD) and sexual functioning.
2. Review of the literature
2.1 Menorrhagia

2.1.1 Definition

Heavy menstrual bleeding over several consecutive cycles is known as menorrhagia. It is caused by a systemic, local or iatrogenic disorder. Systemic disorders comprise altered thyroid function, and hemorrhagic disease, whereas local disorders include uterine causes, such as adenomyosis, large fibroids or polyps. Iatrogenic disorders result from different medications. In half of all menorrhagia cases, no pathological cause is found, and the excessive bleeding is termed essential menorrhagia. Abnormal uterine bleeding refers to a wide range of gynaecological bleeding problems, such as amenorrhoea, oligomenorrhoea, metrorrhagia and menorrhagia (Rees and Hope, 2006). As the nomenclature is extensive, care should be taken with use of definitions. In this study menorrhagia means cyclic, heavy menstrual bleeding.

Menorrhagia is defined as menstrual blood loss (MBL) of over 80 mL per period. This has been an accepted threshold value, as the average MBL is 30–40 mL per period, and only one out of ten women has an MBL exceeding 80 mL. Furthermore, an MBL of over 80 mL has been found to be associated with iron deficiency anaemia (Oehler and Rees, 2003). However, recently, Warner et al. (2004b) reported that iron status is not compromised and pathological findings do not occur more frequently at an MBL between 50 and 119 mL (Warner et al. 2004b). Moreover, the limit of MBL of 80 mL per period does not take into account the bleeding pattern, or the total amount of menstrual discharge, including transudate (O’Flynn and Britten, 2000). MBL can be measured by alkaline haematin method, which requires collection of sanitary pads (Hallberg and Nilsson, 1964). More practically, MBL can be estimated from the blood sample, because serum haemoglobin and ferritin concentration correlate with MBL to some extent (Hurskainen et al. 1998, Warner et al. 2004a). Menstrual pictoral test can also be used (Wijay et al. 2001). Unfortunately, all the tests have limitations in clinical practice. If MBL measured does not exceed the limit of 80 mL, menorrhagia is a subjective menorrhagia. If it does, menorrhagia is called objective menorrhagia. Unemployment, abdominal pain, perceived inconvenience, anxiety and other psychological distress have been found to correlate with subjective menorrhagia (Hurskainen et al. 2001, Shapley et al. 2003). Objective menorrhagia, by contrast, is associated with decreased serum ferritin concentration, clots in MBL and frequent need during nights to change sanitary pads (Warner et al. 2004a). Objective menorrhagia is also linked to increased duration of bleeding and age (Higham and Shaw, 1999). Age-related menorrhagia may, however, be due to perimenopausal hormonal changes and such uterine pathology as fibroids. Additionally, genetics may play role in menorrhagia (Treloar et al. 1998b). The essential menorrhagia comprises a vast network of different biological and environmental factors.

2.1.2 Epidemiology and Impact on Health

Nearly one-third of women have reported suffering from menorrhagia during their reproductive years (Shapley et al. 2004). Menorrhagia decreases quality of life, causes anaemia (Hurskainen et al. 2001) and sick days (Jones et al. 2002). Excessive bleeding is the reason for referral to gynaecological outpatient clinics up to 12 % of cases (Oehler and Rees, 2003). When MBL is measured, however, only 54–53 % of these women actually have an MBL exceeding 80 mL (Hurskainen et al. 2001, Warner et al. 2004a). In population studies the incidence of menorrhagia lies between 9 % and 15 % (Hallberg et al. 1966). Since subjective menorrhagia is at least as common as objective menorrhagia and subjective menorrhagia influences mood, psychosomatic symptoms and sexual functioning similarly to objective menorrhagia (Hurskainen et al. 2001) it is often treated. This emphasises the importance of knowing the long-term consequences of the treatments used.

2.1.3 Treatment

Menorrhagia can be treated either medically or surgically. Medical treatments include anti-fibrinolytic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, oral and subdermal progestogens and LNG-IUS (Marjoribanks et al. 2006). Surgical treatments comprise endometrial destruction either via hysteroscope using electrosurgery or laser or through special intracavitary instrument applying microwave or other forms of energy, or hysterec- tomy (Marjoribanks et al. 2006). Since menorrhagia is a relatively benign condition, less invasive treatment methods should be favoured. The choice of treatment depends on the patient’s personal choice, desire for future pregnancy and general health status.
Medical treatment options for menorrhagia are summarised in Table 1. Briefly, antiplateletolytic drugs, like tranexamic acid, inhibit breakdown of blood clot (hirudinolytic) by preventing activation of plasminogen (Marjoribanks et al. 2006). In menorrhagia patients, endometrial levels of prostaglandins are elevated. NSAIDs inhibit production of prostaglandins and leukotrienes from arachidonic acid by blocking the cyclooxygenase enzyme system (Marjoribanks et al. 2003). Oral contraceptives, in turn, reduce MBL by inhibiting endometrial growth and development (Jyer et al. 2000). LNG-IUS causes endometrial thinning, glandular atrophy, stromal decidualisation and inflammation (Jensen. 2005). The paragraph (2.2) describes the device in more detail. MBL can also be reduced by progestogens. In luteal phase orally and cyclically administered progestogens do not reduce MBL in ovulatory cycles, however. If given from cycle days 5 to 26, MBL is substantially reduced (Lethaby et al. 2003). Long-acting progestogens, such as medroxyprogesterone acetate, can also be administered subdermally. Even though medroxyprogesterone acetate reduces MBL, BMD also decreases significantly (Okt et al. 2001). Medroxyprogesterone acetate cannot, therefore, be recommended for use in reducing MBL (Ora and Critchley. 2005). After discovery of the anti-progestin mifepristone, several compounds with different binding and action properties on the progesterone receptor have been developed (Chabbers-Buff et al. 2005). Selective progesterone receptor modulators, like asaprinil, act on the endometri- um directly and produce amenorrhoea at rates of 63–100% (Chwalisz et al. 2005). Amenorrhoea develops without hypo- oestrogenism, and no negative impact on BMD has been re- ported (Chabbers-Buff et al. 2005).

2.1.3.3 Surgical

Surgical treatments can be divided into the uterus-sparing treatments and hysterectomy. In uterus-sparing treatments, the endometrium and the underlying basal glands are destroyed by various methods. This can be done either with a hysteroscope using electrosurgery or a laser (first-generation endometrial ablation techniques) or with more sophisticated equipment that applies microwaves or thermal energy (second-generation endometrial ablation techniques). Although first-generation endometrial ablation techniques are less invasive than hysterectomy, they require general or spinal anaesthetic, superior surgical skills and often a short stay in hospital (Tapper and Heinonen. 1998). Moreover, risks for uterine perforation, fluid overload and infection exist. Second-generation techniques can be per- formed under regional anaesthesia, and they are quicker and safer procedures than the first-generation techniques. The suc- cess of the procedure is low dependent on surgical skills, and the risk for fluid overload is eliminated. Satisfaction rate and reduction in MBL are similar between the techniques (Garside et al. 2005). As the endometrium has a marked regeneration capacity, a reduction in MBL is only seldom permanent. The need for re-treatment has narrowed the cost gap between uter- us-sparing techniques and hysterectomy; endometrial destruc- tion was only 7% more economical than hysterectomy four years after initial treatment (Marjoribanks et al. 2006) and less effective than LNG-IUS (Busfield et al. 2006). The paragraph 2.3 describes hysterectomy in more detail.

2.2 LNG-IUS-RELEASING INTRAUTERINE SYSTEM (MIRENA®)

LNG-IUS is an intrauterine system that consists of a 21-mm- long T-shaped plastic frame with a reservoir on the stem (Fig- ure 1). The reservoir contains 52 mg of levonorgestrel (LNG), which releases 20 µg of LNG daily. At release is slow, it can be used for five years. LNG-IUS was initially developed for contra- ception, but as it reduces MBL up to 94% after three months of use, its usefulness in treating menorrhagia was soon noted (Lu- sikkainen et al. 1990). Moreover, LNG-IUS is a suitable treat- ment for women with haemorrhagic disorders (Schaeuf et al. 2005). The device also alleviates symptoms related to endome- triosis, adenosomyosis, fibroids and pre-menstrual syndrome. Additionally, it provides endometrial protection for women us- ing oestrogen therapy (ET) (Varma et al. 2006). Mechanism of action is based on changes in the endometrium; thinning, gland- ular atrophy, stromal decidualisation and inflammation. These changes appear already one month after the insertion and are independent of the phase of the menstrual cycle (Jensen. 2005). Among LNG-IUS users the incidence of ovarian cysts increas- es (Ikari et al. 2002), which is probably explained by disturbed follicular rupture (Barbosa et al. 1990). Therefore the cysts al- so resolve spontaneously (Ikari et al. 2002). The most common reason for discontinuation of the therapy is intermittent bleed- ing or spotting. Other reasons include pain and mood changes (Backman et al. 2000).

2.2.2 Ovarian Function

LNG-IUS releases LNG slowly and continuously. This enables serum concentration of LNG to be relatively steady (Jensen. 2005), varying between 100 and 160 pg/mL (Nilsson et al. 1980) and between 340 and 360 pg/mL (Barbosa et al. 1990). The different outcomes may be explained by small sample sizes and differences in study populations, such as time since device insertion and body-mass index (BMI). These factors influence serum Sex hormone binding globulin (SHBG) concentration, which

**Table 1. Medical Treatment Options for Menorrhagia**

<table>
<thead>
<tr>
<th>Product</th>
<th>Mechanism of action</th>
<th>Reduction in MBL</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifibrinolytic drugs (1)</td>
<td>Inhibition of hirudinolytic action by inhibition of plasminogen</td>
<td>40–50%</td>
<td>Mild nausea and dizziness</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs (2)</td>
<td>Inhibition of prostaglandin production in endometrium</td>
<td>33–55%</td>
<td>Gastrointestinal bleeding, headache</td>
</tr>
<tr>
<td>Oral contraceptives (4)</td>
<td>Inhibition of endometrial growth</td>
<td>up to 50%</td>
<td>Breast tenderness, nausea, headache, weight and mood changes</td>
</tr>
<tr>
<td>Progestogens (1)</td>
<td>Inhibition of endometrial growth</td>
<td>up to 50%</td>
<td>Breast tenderness, nausea, headache, weight and mood changes</td>
</tr>
<tr>
<td>Oral, days 5–26 (3)</td>
<td>Suppression of endometrial growth</td>
<td>51–87%</td>
<td>Breast tenderness, nausea, headache, weight and mood changes</td>
</tr>
<tr>
<td>Selective progesterone receptor modulator (5)</td>
<td>Suppression of endometrial growth</td>
<td>63–100%</td>
<td>Intermittent bleeding, nausia, headache</td>
</tr>
<tr>
<td>LNG-IUS (4)</td>
<td>Suppression of endometrial growth</td>
<td>79–96%</td>
<td>Intermittent bleeding, spotting, pain, hormonal changes, ovarian cysts</td>
</tr>
</tbody>
</table>

* Also an increase of 9–20% has been reported.
1 Marjoribanks et al. 2006
2 Marjoribanks et al. 2003
3 Yee et al. 2000
4 Lethaby et al. 2005
5 Chwalisz et al. 2005

**Figure 1. Levonorgestrel-Releasing Intrauterine System (Mirena®).**

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in turn regulates concentration of free LNG (Ju et al. 1992). However, studies agree that the majority of cycles are ovulatory (Barbo-
as et al. 1990, Nilsson et al. 1984, Xiao et al. 2003). Moreover, among LNG-IUS users average serum estradiol concentra-
tion is 24 ng/mL, reflecting normal ovarian function. There-
fore effect on pituitary gland is not expected either (Xiao et al. 2003) and hormonal side-effects are rare (Balduzzi et al. 2003, Rönnemand and Olund. 1999, Salonen et al. 2004). The ef-
fect of LNG-IUS on ovarian artery blood flow has not been re-
ported, but LNG-IUS may increase pulsatility index (PI) of 
uterine arteries (Javeli et al. 1998). The clinical significance of 
this finding remains to be elucidated.

2.2.3 BONE MINERAL DENSITY (BMD)

As LNG-IUS has only small effect on ovarian function, it has a negligible impact on BMD. This is supported by a study by 
Bahamondes et al. (2005) in which no negative impact on BMD at the midshaft ulna and the distal radius was observed 
after seven years of LNG-IUS use. However, the mean age of 
the patients was 34 years and the fracture risk was not assessed (Bahamondes et al. 2005). Also the effect of LNG-IUS on 
turn-over rate of bone remains to be elucidated. 

Even if relatively little is known about LNG-IUS and bone, the effect of other forms of progestins has been studied to 
some extent. Unfortunately, no clinical studies on oral pro-
genstins and BMD exist. However, according to in vitro stud-
ies, progestins appear to modulate bone remodelling and pro-
tect against bone loss (Thijssen. 2003). Injectable depot medroxyprogesterone acetate use is associ-
ated with reduced BMD at sites containing a larger proportion of 
tubecular bone (e.g. the lumbar spine and the ulnar distali-
 radius). The longer the duration of use, the greater the reductions (Balash 2003, Banks et al. 2001, Berenson et al. 2004, Cromer et al. 2004). Among medroxyprogesterone acetate users, se-
rum concentrations of progestins vary between 0.8 and 10.7 ng/mL (mean 3 ng/mL) (Mathrubutham and Forster. 1981), 
this amount being sufficient to affect ovarian function, induce 
amenorrhea and a hypo-oestrogenic state. When use ceases, the effect of medroxyprogesterone acetate on bone reverses at least partially (Balash 2003, Banks et al. 2001). The progestagen 
contraceptive implant, releases LNG steadily, with the serum concentration of LNG varying be-
tween 1.4 and 3 ng/mL (Stiven et al. 1997). Studies on the 
LNG-releasing rod and BMD show contradictory results. In-
creases (Banks et al. 2001, Di et al. 1999), no change (Banks et al. 2001, Tanenpanichskul et al. 1997) and decreases (Ba-
hamondes et al. 2006, Petitti et al. 2000) in BMD after LNG-
releasing implant have been reported.

2.2.4 SEXUAL FUNCTIONING

Loss of libido, breast tenderness and fatigue may correlate 
with insertion of a subdermal LNG implant (Merik et al. 2003). In 
contrast to implant use, LNG-IUS, with a lower concentration of serum progestin, does not seem to deterio-
rate sexual functioning (Hurskainen et al. 2001, Hurskainen et al. 2004). Moreover, it does not hinder intercourse (Bal-
duzzi et al. 2003). These properties make LNG-IUS a very at-
tractive tool in contraception and treating menorrhagia.

2.3 HYSTERECTOMY

2.3.1 IN MENORRHAGIA

Hysterectomy is the most common surgical operation per-
formed in the Western world (Kozak et al. 2005). In Finland, 
over 10,000 hysterectomies were performed annually a decade 
ago, but thanks to effective alternatives, the number has grad-
tually been decreasing, being 7000 in the year 2005 (http://
www.stakes.fi/info). Even though hysterectomy is effective, 
for hysterectomy. As leiomyomas are a common indication for 
hysterectomy, it is possible that increased oestradiol concentra-
tion after surgery (Cooper and Thorp. 1999, Derksen et al. 1998, Farqui-
hor et al. 2003) and decreased serum inhibin B concentration 
(Nahas et al. 2003) have also been reported. Increased vaso-
motor symptoms and vaginal dryness have frequently been 
found (Hartmann et al. 1995, Oldenhave et al. 1993, Siddle et al. 1987, Stadberg et al. 2000). Hysterectomy is also associ-
ated with increased use of oestradol therapy (ET) (Berlin and 
Therefore the debate on the effect of hysterectomy on ovari-
an function continues.

2.3.3 BMD

The effect of hysterectomy on BMD remains controversial. 
Some studies show a positive association between hysterecto-
y and ovarian conservation (Cheng et al. 2003, Foroum et al.
2001, Graeving et al. 2001, Johansson et al. 1995, Topp craftin-
en et al. 1995), some no change (Carranza-Lisa et al. 2002, Krits-Silverstein et al. 2004, Ranv et al. 1995, Shilbash. 2003) and 
still others a decrease in BMD (Durac Simoes et al. 1995, 
may, however, be increased after hysterectomy (Torgerson et al.
1996, van der Voort et al. 2001). The association of hysterecto-
y with increased BMD may be linked to the underlying reason 
for hysterectomy. As leiomysomas are a common indication for 
hysterectomy, it is possible that increased oestradol concentra-
tion among women with leiomysomas preserves BMD (Randell 
et al. 2006). Decreased BMD after hysterectomy has, in turn, 
been explained by altered ovarian function after surgery (Cooper and Thorp. 1999, Derksen et al. 1998, Oldenhave et al.
1993). The effect of ovarietomy on BMD is clearer. Ovarietomy 
results in surgical menopause and deprivation of ovarian ster-
oids. This, in turn, produces a BMD loss comparable to that of 
menopausal transition. Moreover, ovarietomy may be an 
independent risk factor for fractures (Balash 2003, Joho-
son et al. 1993, Tudor-Locke and McColl. 2008). Post-men-
opausally, factors other than ovarietomy may be more im-
portant in determining fracture risk (Krits-Silverstein et al.
2004, Shilbash. 2003). For as women ages, fracture risk is al-
so affected by visual acuity, neuromuscular disorders and co-
orrelation, low physical activity and medical disorders (NIH 
Consensus Development Panel on Osteoporosis Prevention, 
Diagnosis, and Therapy. 2001).

2.3.4 SEXUAL FUNCTIONING

Hysterectomy has been postulated to impair sexual func-
tioning since it disrupts nerve supply of the genital tract and 
changes pelvic anatomy (Kilkki et al. 1983, Maas et al. 2003, 
McPherson et al.). In addition, hysterectomy may impair ovari-
an function and cause early menopausal symptoms, 
including vaginal dryness (Cooper and Thorp. 1999, Derksen 
et al. 1998, Faquhar et al. 2003, Hartmann et al. 1995, Na-
bas et al. 2003, Oldenhave et al. 1993, Siddle et al. 1987, Stad-
berg et al. 2000). However, results from randomised control-
led studies comparing different operation techniques do not 
support the theory of the deteriorating effect of hysterectomy 
on sexual function (Elliot et al 2003, Kuppermann et al.
et al. 2005, Thakar et al. 2002, Zobb et al. 2004). Also observa-
tional studies support this (Virtanen et al. 1995). Randomised 
controlled studies comparing hysterectomy with uterus-spar-
ting treatment modalities are few, but no negative impact on 
sexual functioning has been reported (Alexander et al. 1996, 

2.4 OVARIAN FUNCTION

In the foetal ovaries seven million oocytes are present and are 
due to apopotic demise their number decreases significantly be-
ning only one million at birth and half a million at puberty. Ap-
proximately 600 oocytes from the original seven million pool 
will ovulate during the fertile life span (see Veide and Pearson. 2002). During each menstrual cycle, 10-20 antral follicles es-
cape apopitosis and start to grow in consequence of increasing 
serum FSH levels and usually one follicle emerges as a domi-
nant follicle (McGee and Huscho. 2000). All growing follicles secrete ovarian and inhibit B, the latter which inhibits pi-
notary FSH secretion (Mottukrishna et al. 2002). Increased 
circulating oestradiol concentrations trigger the onset of the 
luteinising hormone (LH) surge from the pituitary gland re-
sulting in ovulation (Mesinis. 2006). Remnants of the Graafian foli-
Menstrual cycle.

The follicular phase starts with ovulation. The Graafian follicle forms and matures, releasing estrogen and inhibin A. If the egg is not fertilized, the corpus luteum forms and secretes progesterone, leading to luteal phase. If fertilization occurs, the corpus luteum persists, releasing progesterone and hCG, which maintains the uterus. If fertilization does not occur, the corpus luteum regresses, and menstruation occurs.

The menstrual cycle is regulated by the hypothalamic-pituitary-ovarian axis. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the ovaries to produce estrogen and progesterone, respectively. Estrogen feedback inhibits the release of GnRH, LH, and FSH.

The menstrual cycle length varies from 21 to 35 days. Hormonal changes during the menstrual cycle are influenced by age, genetics, and lifestyle factors.

2.4.1 General factors

Variation in cycle length may be explained by variations in age, genetics, and lifestyle. Women with a BMI > 25 kg/m^2 may have a shorter menstrual cycle compared to normal weight women. Smoking can also affect menstrual cycle length, with smokers having a shorter cycle than non-smokers. Increase in parity and smoking can lead to earlier menopause.

2.4.2 Behavioural factors

A high BMI has a significant influence on reproductive function. Women with a BMI > 25 kg/m^2 have longer cycles. Cycles are characterized by longer follicular phases and shorter luteal phases. Ovulation is also delayed (Gosman et al. 2006, Santoro et al. 2004). Variation in cycle length may be explained by altered hormone levels (Freeman et al. 2005, Callichiis et al. 2005, Gracia et al. 2005, Lambert-Messerlian and Harkow 2006, Santoro et al. 2004). In post-menopausal obese women (BMI > 30 kg/m^2), serum inhibin B, oestradiol and LH concentrations are elevated (Freeman et al. 2005, Gracia et al. 2005). In addition, excess adipose tissue increases peripheral aromatisation of androgen to oestrogen. Furthermore, serum concentration of SHBG is diminished, resulting in an increased amount of bioavailable testosterone and oestradiol (Gosman et al. 2006).

Approximately 20% of Finnish women of reproductive age smoke tobacco (www.stat.fi/til/tup/2004). At least cadmium, nicotine and cotinine of tobacco smoke affect ovarian function (Myllyniemi et al. 2005). The inhibins are dimeric peptides secreted by the ovary. Inhibin A is secreted by a dominant follicle and the corpus luteum whereas inhibin B is secreted by granulosa cells of the developing pool of antral follicles. Serum inhibin B concentration on cycle day 3 indirectly estimates ovarian reserve, as it reflects the amount of inhibin B produced by granulosa cells of antral follicles (Muttukrishna et al. 2002). Excess smoking may lead to decreased inhibin B concentration, which affects the recruitment of primordial follicles, leading to a decrease in fertility.

2.4.3 Ovarian circulation

The premenopausal ovary, blood flow is relatively constant on the non-dominant side (Valentin. 1997). On the dominant side, circadian and cyclic variations in blood flow exist. The blood flow is lowest in the morning and tends to increase throughout the day (Zaidi et al. 1996). The circadian cycle of blood flow increases at the luteal phase and the corpus luteum is intensively vascularised (Valentin. 1997). Menopausal transition decreases diastolic ovarian artery blood flow so that after final menstrual period in 55% of women no diastolic blood flow is detectable. In post-menopause no diastolic ovarian artery flow is present in 82.5% of women. The use of ET does not improve ovarian artery flow. In postmenopausal intraovarian arterities, no signal at all was found (Kurjak and Kupecic. 1995). The increase in resistance to flow may be due to increased amounts of fibroblasts and connective tissue (Valentin. 1997).

2.4.4 Measuring ovarian function

Ovarian function relies on ovarian reserve, which is determined by the size of the ovarian follicle pool and the quality of the oocytes it contains. In clinical practice, ovarian reserve is useful to measure by age, serum FSH, inhibin B, and anti-Müllerian hormone (AMH) concentration or by antral follicle count (AFC) (Nikolaou and Templeton. 2004; Piltonen et al. 2005, van Rooij et al. 2005) and both reproducibility of the measurement and cyclically constant levels support the use of AMH in estimating ovarian reserve (Fanchin et al. 2005).

Ovarian volume, circulation and AFC decrease with ageing (Bastos et al. 2006, Ng et al. 2003, Pan et al. 2002). Therefore these parameters may correlate with ovarian reserve (Bukulmez and Heineman. 2001, Kline et al. 2005; Wallace and Kelsey. 2004). However, discrepancy between outcomes exists (Bukulmez et al. 2004).

Serum FSH concentration on cycle day 3 indirectly estimates ovarian reserve, as it reflects the amount of inhibin B produced by granulosa cells of antral follicles (Muttukrishna et al. 2002). Patients with low serum FSH concentration have better ovarian reserve than women with high serum FSH concentration (>15 IU/L) (Bukulmez and Heineman. 2001). Unfortunately, in serum FSH concentrations, marked inter-individual and inter-cyclic variation exist, reducing their reliability in clinical practice (Fanchin et al. 2005). Increased serum oestradiol concentration on day 3 is thought to be responsible for shortening of the follicular phase as women get older (Bukulmez and Heineman. 2001). However, since women aged 24–50 years have similar serum oestradiol concentrations, it cannot be used to identify women with reduced ovarian reserve (Bukulmez and Arici. 2004). Interestingly, aging also decreases ovarian capacity to produce androgen (Piltonen et al. 2004).

The inhibins are dimeric peptides secreted by the ovary. Inhibin A is secreted by a dominant follicle and the corpus luteum whereas inhibin B is secreted by granulosa cells of the developing pool of antral follicles. Serum inhibin B concentrations can therefore be used as a direct marker of ovarian reserve (Laven and Fauser. 2004). A decrease in serum inhibin B concentration precedes the rise in serum FSH concentration (Ozolins et al. 2005), and in women with diminished ovarian reserve, serum inhibin B concentration is decreased, even when serum FSH concentration is still normal (Laven and Fauser. 2004).

Ovarian granulosa cells also produce another dimeric glycoprotein, AMH, which initially inhibits the recruitment of primordial follicles into the pool of growing follicles and later decreases the responsiveness of growing follicles to cyclic FSH stimulation (Gruejirs et al. 2003). Serum AMH concentration correlates relatively well with AFC (Fanchin et al. 2003, Piltonen et al. 2005, van Rooij et al. 2005) and both reproducibility of the measurement and cyclically constant levels support the use of AMH in estimating ovarian reserve (Fanchin et al. 2005).

Ovarian volume, circulation and AFC decrease with ageing (Bastos et al. 2006, Ng et al. 2003, Pan et al. 2002). Therefore these parameters may correlate with ovarian reserve (Bukulmez and Heineman. 2001, Kline et al. 2005; Wallace and Kelsey. 2004). However, discrepancy between outcomes exists (Bukulmez et al. 2004).
2.5 BMI AND WOMEN’S HEALTH

Normal ovarian function is essential for peak bone mass accrual and regulation of bone remodelling (Balasch. 2003). The onset of menarche correlates inversely with premenopausal BMI; the earlier the onset of menstruation, the greater the woman’s bone mass (Tudor-Locke and McColl. 2000). This is due to early and continued exposure to endogenous oestrogen during accelerated bone growth (Balasch. 2003). Cyclic regularity, reflecting normal weight, is also important. Women with anovulatory menses due to low body weight and inappropriate nutrient availability annually lose approximately 4.2% of their BMD. Reduced bone mineral content correlates with duration of amenorrhea and severity of oestrogen deficiency (Norellöv. 2002). BMI at the lumbar spine seems to be the most vulnerable to menstrual irregularities (Pongchayakul et al. 2005). Among women complaining of subjective menorrhagia, however, BMI at the distal radius is 7% higher than among women reporting light menstrual flow (Tudor-Locke and McColl. 2000). The effect of parity on BMD remains unclear. During pregnancy bone metabolism alters and favours growth, but evidence to date that parity decreases BMD is insufficient (Balasch. 2003, Tudor-Locke and McColl. 2000). As BMD among parous women seems to be higher than among nulliparous women (Foroum et al. 2001, Peterson et al. 2005) the ability to conceive may actually reflect normal ovarian function. This, in turn, is seen as higher BMD (Balasch. 2003, Tudor-Locke and McColl. 2000). Calcium is lost to milk during lactation, and therefore, lactation doubles the daily loss of calcium. Moreover, lactation is associated with hypo-oestrogenism, which causes increased bone resorption (Balasch. 2003). Thus, six months of weaning reduces BMD at the lumbar spine by approximately 2.8%. This decrease is, however, transient, with recovery occurring after resumption of menses (Åkesson et al. 2004, Tudor-Locke and McColl. 2000). In premenopausal women, bone loss at the lumbar spine is approximately 0.13% annually and at the femoral neck bone mass can even be gained at yearly rate of 0.52%. At late perimenopause, the corresponding losses are 0.92% and 0.71% at the time of final menstrual period, bone loss accelerates even more, and thus these figures are now 2.48% and 1.74%. After menopausal transition, bone loss slows down and annual figures are 0.74% and 0.50% (Guérthie et al. 1998). Therefore, an extended reproductive period reflected by late onset of menopause provides a longer protective hormonal environment for bone. Late onset of menopause correlates with reduced hip fracture risk in older women (Balasch. 2003, Tudor-Locke and McColl. 2000). Postmenopausal women with low BMI are at increased risk of low BMD and rapid bone loss (Lane. 2006). Accelerated bone remodelling during menopausal transition can be reduced by ET. Only a small amount of ET is needed for this effect; osteoclast inhibition of 0.33 mmol/L is sufficient to preserve BMD at lumbar spine (Guérthie et al. 2004). The effect appears rapidly after commencement the therapy and wears off rapidly after discontinuation (Banks et al. 2004).

2.5.2 MEASURING BONE MINERAL DENSITY

BMD can be measured by several means. Dual x-ray absorptiometry (DXA) is a good standard for measuring BMD and it can be used to measure bone mineral content in an entire skeleton, especially at sites most vulnerable to fractures (e.g. lumbar spine, femoral neck). The technique gives with low radiation exposure a two-dimensional estimate of BMD (areal density, g/cm2) (Briot and Roux. 2005). Quantitative ultrasound can be used to assess BMD at the heel. As information on bone structure is acquired, its use has gained interest. BMD parameters of quantitative ultrasound are associated independently with fracture risk at the femoral neck, but cannot be used to monitor response to treatment (Bonne and Nicolson. 1998, Briot and Roux. 2005). Quantitative computed tomography can be used to measure BMD at the lumbar spine and at peripheral sites. At the lumbar spine, quantitative computed tomography has an accuracy comparable with that of DXA, but has the advantage of giving a volumetric BMD. Moreover, quantitative computed tomography is able to distinguish cortical bone from trabecular bone and is therefore more sensitive to changes in BMD. Due to its sensitivity, quantitative computed tomography can be used to follow BMD over time and to follow response to the therapy. Although, effective, the main disadvantages compared with DXA are high exposure to radiation, high costs and need to calibrate the equipment (Lane. 2006). Osteoporosis can also be diagnosed from radiography, although with low sensitivity. Radiography allows subclinical vertebral fractures and diminished bone mineral content to be detected (Pavlou et al. 2005). Even if osteoporotic vertebral fracture is a strong independent risk factor for another osteoporotic fracture (Lane. 2006), radiographs provide, however, an extremely rough estimate of BMD (Pavlou et al. 2005). Biochemical markers of bone turnover can be measured from serum or urine, and they reflect the dynamic process of bone turnover. Osteoblasts release bone formation markers, such as bone-specific alkaline phosphatase and osteocalcin. Osteoclasts, in turn, secrete breakdown products of collagen. Moreover, an osteoclast-specific isoform of tartarate-resistant acid phosphatase is a promising marker in predicting vertebral fractures. In addition to estimating fracture risk, bone turnover markers can be used to monitor response to treatment and assist in selection of patients for treatment. However, in the diagnosis of osteoporosis, they are not useful (Briot and Roux. 2005, Lane. 2006).

2.6 SEXUALITY

2.6.1 WOMEN’S SEXUALITY

Of sexually active women aged 40–80 years, approximately 70–80% are relatively satisfied with their sexual functioning (Addis et al. 2006, Laumann et al. 2006, Tomic et al. 2006) and only 9% experience distress from decreased sexual functioning (Leblum et al. 2006). Nevertheless, up to 50% of women may experience sexual dysfunction to some extent (Addis et al. 2006, Laumann et al. 1999). Ageing and a negative attitude towards ageing decreases sexual well-being (Addis et al. 2006, Avis et al. 2005, Beazle et al. 2004, Gonzalez et al. 2004, Guérthie et al. 2004, Laumann et al. 2006, Tomic et al. 2006). Moreover, ageing is associated with menopause. Identifying, which of the changes in sexual functioning are related to ageing and, which to menopause is difficult. During menopausal transition serum oestrogen and testosterone concentrations decline, affecting sexual desire, sexual response and urogenital health (Palacios et al. 2002). Particularly sexual response and dyspareunia are influenced (Dementstein and Lehri. 2004, Lathe et al. 2006). Dyspareunia is often caused by vaginal dryness, which in turn has an effect on sexual satisfaction (Laumann et al. 2006, Tomic et al. 2006). ET can be used to overcome sexual problems (Gonzal- et al. 2004, Wiklund et al. 1993b), but full symptom relief seldom occurs (Brunner et al. 2005). Among post-menopausal women, testosterone therapy has also been attempted to improve sexual functioning (Adh. 2006). However, as the role of testosterone during menopausal transition remains to be fully elucidated (Aziz et al. 2005), testosterone therapy cannot yet be recommended for improving sexual functioning (Adh. 2006, North American Menopause Society. 2005).

2.6.2 MEASURING SEXUAL FUNCTIONING

Sexual functioning is made up of several factors, including physical pleasure, emotional satisfaction, arousal, desire, frequency of intercourse and pain during intercourse. Therefore, standardised, multi-dimensional instruments to measure sexual functioning are needed. Uni-dimensional tools are not specific enough to identify the dysfunctional factor. Several methods to measure sexual functioning exist, but only a few are multi-dimensional and have been validated (Jones et al. 2002). Multi-dimensional self-assessed questionnaires validated in Europe with over one hundred mentally healthy women include McCoy’s Sexual Scale, the Brief Index of Sexual Functioning for Women, the Derogatis Interview for Sexual Functioning, the Female Sexual Function Index, the Medical Outcome Study – Sexual Problems Scale, the Sexual Function Questionnaire and Quality of Sexual Function. McCoy’s Sexual Scale was developed in the 1980s (McCoy and Davidson. 1985). It has since been modified by Wiklund (1993), and the test has been validated especially in Scandinavia (Wiklund et al. 1992, Wiklund et al. 1993a, Wiklund et al. 1993b). The scale contains ten items, comprising the three domains of sexual satisfaction, sexual problems and partner satisfaction. A disadvantage of this scale is that the questionnaire does not evaluate sexual functioning in general, but only within the last 30 days (McCoy and Dav- ison. 1985). The Brief Index of Sexual Functioning for Women differs from McCoy’s Sexual Scale by comprising seven domains, which form a composite score (Taylor et al. 1994). The Deroga- tis Interview for Sexual Functioning, in turn, has a concur- rent validity and reliability with Change in Sexual Functioning Questionnaire (Clayton et al. 1997, Keller et al. 2006, Me- ton and Derogatis. 2002). Both the instruments are composed of an
3. Objectives of the study

Interview process and self-assessed questionnaire. The interview process allows flexibility that is not offered by questionnaires only. However, it also requires an interviewer and takes time, which make it slow and costly (Derogatis. 1997). The Female Sexual Function Index has 19 items and it is validated to detect especially problems with arousal, response to therapy and epidemiology of arousal problems. It does not, however, take into account issues related to personal distress (Wiegand et al. 2005). The Medical Outcome Study—Sexual Problems Scale contains only four items, but has an advantage of having a response option “did not have sexual activity”. However, due to its narrowness it has recently been expanded to cover sexual functioning more widely (Kuppermann M. et al. 2004, Kuppermann M. et al. 2005). The Sexual Function Questionnaire contains seven domains, but since domains have only moderate reproducibility, the instrument is sensitive to temporal changes (Quirk et al. 2002). A novel Quality of Sexual Function can be used in both genders. This makes the instrument useful when relational and gender-specific tools are needed. The scale consists of 32 items and eight general questions. Validity and reproducibility are under further study (Heinemann et al. 2005).

A variety instruments are available for assessing sexual functioning. It is unlikely that a single instrument can yield a comprehensive view of sexual functioning. Moreover, as the literature reflects a proliferation of different instruments, the use of reliable and valid tools becomes increasingly important to enable reasonable comparisons between studies (Jones le. 2002).
3. Objectives of the Study

Since menorrhagia affects one third of reproductive age women (Shapley et al. 2004) and needs to be treated (Jones et al. 2002), it is important to know whether the most efficient treatment is either surgical or medical (Marjoribanks et al. 2006). The overall objective of this thesis was to evaluate the effect of the two treatment options of menorrhagia, hysterectomy and LNG-IUS, on ovarian function, BMD and sexuality. The studies had the following objectives:

- The effect of hysterectomy or LNG-IUS on ovarian function by measuring menopausal symptoms, serum FSH and inhibin B levels, and intraovarian blood flow (Studies I and II).
- The effect of hysterectomy or LNG-IUS on BMD (Study III).
- The effect of hysterectomy or LNG-IUS on sexuality (Study IV).
4. Patients and methods
4.1 Study protocol and patients

In the primary ‘VuoKKo’ study (Hurskainen et al. 2001) there were 598 women referred for menorrhagia to the five university hospitals in Finland between November 1994 and November 1997. Of the 598 women, 184 (31%) were excluded because of the following predefined exclusion criteria shown in Figure 3. During the first visit all eligible women (n=414) were informed of the different treatment modalities for menorrhagia and the purpose of the trial. Of these women, 178 (43%) decided not to participate due to the following reasons: treatment preference, refusal of any treatment, were still planning pregnancy, did not want randomisation, or for some other reason. The women excluded or declining to participate did not differ from the final study group in terms of sociodemographic factors, age, employment status or occupation. A total of 236 women were enrolled into the present study. These women were 35–49 years old, had completed their family size and were eligible for hysterectomy. The women completed a questionnaire, including information on BMI, smoking, parity, age at menarche, number of deliveries, method of contraception, marital status, level of education and employment. As the women completed the questionnaire, they were randomised to either a hysterectomy or a LNG-IUS group. In addition, alcohol use, daily medication and occurrence of impressive negative life changes were recorded. Moreover, patients reported their daily calcium intake (mg), physical activity (hours/week x intensity), history of fractures and lactose malabsorption for Study III. Physical activity intensity was categorised as follows: 1) no sweating or laboured breathing 2) some sweating or laboured breathing and 3) heavy sweating and greatly laboured breathing. Table 2 shows selected characteristics of the study population. In 25 patient characteristics tested, only BMI differed between the treatment groups (Hurskainen et al. 2001).

Randomisation was performed separately for each centre in randomly varying clusters using numbered, opaque, sealed envelopes. Of the 236 women, 107 were randomised in Helsinki, 44 in Kuopio, 22 in Oulu, 21 in Tampere and 42 in Turku. The follow-up visits took place 6 and 12 months after the initial treatment, and 5 years after the randomisation process. The gynaecologist and patient filled in a questionnaire at each visit. The trial flow chart is illustrated in Figure 3. At the 12 month follow-up the drop-out rate was 3% (Hurskainen et al. 2001) and at the five year follow-up, it was 1% (Hurskainen et al. 2004).

All women gave their written informed consent. The Ethics Committees of all five university hospitals and STAKES (National Research and Development Centre for Welfare and Health), Finland, approved the study protocol.

All 236 women were included in Studies I and IV. In these Studies, the LNG-IUS users had higher BMI than the hysterectomised women. This difference was not noted in Studies II and III. Serum concentration of inhibin B and bone mineral density (Studies II and III, n=54 for hysterectomy group and n=53 for LNG-IUS group) were measured only in women enrolled in the University Hospital of Helsinki. For Study II ovarian blood flow was measured in 60 patients (n=28 in LNG-IUS group and n=32 in hysterectomy group) (Figure 4).

4.2 Treatment of Menorrhagia

With Hysterectomy or LNG-IUS

Each hysterectomy was performed either abdominally, vaginally or laparoscopically by (or supervised by) an experienced gynaecologist and patient filled in a questionnaire at each visit. The trial flow chart is illustrated in Figure 3. At the 12 month follow-up the drop-out rate was 3% (Hurskainen et al. 2001) and at the five year follow-up, it was 1% (Hurskainen et al. 2004).

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<table>
<thead>
<tr>
<th>TABLE 2. Baseline Characteristics of the Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hysterectomy</strong> (n=117)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Serum FSH (IU/L)</td>
</tr>
<tr>
<td>Menarche (y)</td>
</tr>
<tr>
<td>Parity</td>
</tr>
<tr>
<td>Tubal Iigation</td>
</tr>
<tr>
<td>Living with partner</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>High school</td>
</tr>
<tr>
<td>College</td>
</tr>
<tr>
<td>University</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
</tbody>
</table>

Data are given by means ± SD or n (%).
Menopausal symptoms were recorded by using Kupperman’s symptom (Kupperman et al. 1959).

As randomisation and after 6- and 12-month periods serum samples to measure parameters of ovarian function were drawn. The randomisation samples were drawn on cycle days 1–7. Later the women were either hysterectomised or on the LNG-IUS, and therefore menstruation could not be used to evaluate the time of the cycle, and serum oestradiol and progesterone concentrations were measured. The hormone concentration limits during the cycle and intra- and inter-assay coefficients are shown in Table 3. A similar amount of women were in the luteal phase in the Study II (n = 3) in the hysterectomy group and n = 4 in the LNG-IUS group). An immunoafluorometric method (Wallac, Turku, Finland) was used to measure serum FSH concentrations and 125I-RIA kits (DPC Corporation, Los Angeles, CA, USA) to measure serum oestradiol and progesterone concentrations. In Study III, women were categorised to be menopausal if their serum FSH concentration exceeded 40 IU/L, or they used or had used ET. This cut-off point was chosen to reduce the effect of cyclic variation in serum FSH levels. Enzyme-linked immunosorbent assay (ELISA from Diagnostic System Laboratories, Inc., Webster, TX, USA) was applied to measure serum inhibin B concentrations. For inhibin B concentration, the limit of detection was 7 ng/L. Inhibin B concentrations between 0.01 and 7 ng/L were assigned a value of 3.5 ng/L (mean). Inhibin B concentrations over 300 ng/L, were excluded from the analysis in accordance with the manufacturer’s instructions (one in the hysterectomy group at baseline and one in the LNG-IUS group at one year).

An experienced gynaecologist measured ovarian and intraovarian artery circulation (n = 60) by transvaginal ultrasound (TVS) at randomisation, and at 6 and 12 months. To reduce the effect of circadian variation on results, TVS was always performed between 10.00 and 12.00 by using a 5.5 MHz broadband probe (ATL, HDI 3000, Bothell, WA, USA) (Zaidi et al. 1995). A colour Doppler was used for imaging ovarian and intraovarian arteries. The pulsatility index (PI) was measured from representative flow velocity waveforms of vessels, including three cardiac cycles, by the following formula: PI = (A – B)/mean, where A is the peak systolic Doppler shift frequency and B is the end-diastolic shift frequency over the cardiac cycle (Gosling 1976). For statistical analysis, a mean of the left and right intraovarian artery PIs was calculated. In the hysterectomy group the measurements were successful in 28 at randomisation, 20 at 6 months, and 13 at 12 months. Respectively, in the LNG-IUS group the corresponding numbers were 18, 12 and 16. If a unilateral ovarian cyst was present (n = 4 in the hysterectomy group and n = 12 in the LNG-IUS group), only the value from the cyst-free side was used. Temporal variability and reproducibility of the PI was tested in ten patients by measuring variables three times at 10-min intervals (Takay and Jooppila 1996).

### Table 3. The Used Range of Hormone Concentrations During the Menstrual Cycle and the Assay Coefficients

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Follicular phase</th>
<th>Ovulation</th>
<th>Luteal phase</th>
<th>Menopause</th>
<th>Intra-assay Coefficient (%)</th>
<th>Inter-assay Coefficient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (IU/L)</td>
<td>1 – 10</td>
<td>12 – 25</td>
<td>1 – 8</td>
<td>&gt;30</td>
<td>3.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Inhibin B (ng/L)</td>
<td>75 – 95</td>
<td>100 – 165</td>
<td>5 – 20</td>
<td>&lt;5</td>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>1 – 7</td>
<td>17 – 17</td>
<td>14 – 62</td>
<td>&lt;3</td>
<td>3.7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

1. [www.hubbell.fr](http://www.hubbell.fr)

2. Groome et al. 1996.
5. Results

ET use. Only for Study II, oophorectomy status and ET use were taken into an account. In Study I for serum FSH concentrations data were also analysed by age (younger than 43 years vs. older than 43 years). In Study II, women who were originally randomised to the LNG-IUS group but hysterectomised (n=12), or those whose LNG-IUS was removed (n=3) were excluded. Also excluded were women randomised to the hysterectomy group, but not operated on (n=2). Moreover, all oophorectomised women or women on ET were excluded (n=4). Thus, 46 women were included in the analyses for the hysterectomy group and 36 women for the LNG-IUS group. Students’ t-test for independent samples was used to analyse the differences in variables with normal distribution and Mann-Whitney U-test for variables with non-normal distribution. Differences in categorical variables were tested by the X²-test. Changes in end point parameters between the groups were tested by the Student’s t-test for independent samples. Changes within the group, in pre-treatment and in post-treatment, were tested by the Student’s t-test for dependent samples when parameters followed normal distribution and by the Wilcoxon signed-rank test, when parameters were not normally distributed. A univariate linear regression model was used to test factors associated with change in variables and contributing factors. The potential contributing factors were added either in continuous (e.g. changes in variables of study, BMI and age) or in dichotomised form (e.g. treatment modality, parity, sterilisation and smoking). Variables showing a significant correlation were also tested in a multivariate regression model. Moreover, in Studies II and IV, a multivariate model was generated adjusting for the outcome variable (treatment modality, serum FSH concentration (IU/L), age, BMI and smoking for Study II and treatment modality, BMI, ET, living with partner and smoking for Study IV). P-values <0.05 were considered significant.
Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Hysterectomy</th>
<th>P-value within the groups</th>
<th>LNG-IUS</th>
<th>P-value</th>
<th>P-value between the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupperman index</td>
<td>-3.04 ± 7.96</td>
<td>NS</td>
<td>-3.12 ± 8.38</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>0.21 ± 0.97</td>
<td>0.02</td>
<td>0.03 ± 0.74</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0.14 ± 0.99</td>
<td>NS</td>
<td>0.1 ± 1.08</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0.84 ± 0.85</td>
<td>&lt;0.0001</td>
<td>1.06 ± 0.95</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-0.38 ± 0.97</td>
<td>&lt;0.0001</td>
<td>-0.24 ± 1.08</td>
<td>0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Palpitations</td>
<td>-0.22 ± 0.9</td>
<td>0.01</td>
<td>-0.19 ± 0.85</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Melancholy</td>
<td>-0.14 ± 0.67</td>
<td>0.03</td>
<td>-0.12 ± 0.54</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Weakness</td>
<td>-0.41 ± 0.93</td>
<td>&lt;0.0001</td>
<td>-0.37 ± 0.89</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>0.53 ± 0.75</td>
<td>&lt;0.0001</td>
<td>0.85 ± 0.93</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>Vertigo</td>
<td>-0.21 ± 0.95</td>
<td>0.03</td>
<td>-0.3 ± 0.83</td>
<td>0.0002</td>
<td>NS</td>
</tr>
<tr>
<td>Pain in muscles</td>
<td>-1.22 ± 0.98</td>
<td>&lt;0.0001</td>
<td>-0.9 ± 0.99</td>
<td>&lt;0.0001</td>
<td>0.03</td>
</tr>
</tbody>
</table>

5.1 Ovarian Function (Studies I and II)

At the 12-month follow-up, hot flashes increased significantly among hysterectomised women, but not among the LNG-IUS users. On the other hand, pain and headache were more common in the LNG-IUS group (Table 4). Serum FSH increased more among hysterectomised women than among LNG-IUS users (Figure 5). A decrease in serum inhibin B concentration was evident in both treatment groups six months after the treatment (Figure 6). Blood flow in the ovarian artery remained unchanged (Figure 7), but intraovarian artery blood flow decreased in the hysterectomy group (Figure 8). The difference was significant between the groups both at 6 months (P = 0.0001) and at 12 months (P = 0.004).

Hysterectomy Group

During the one-year follow-up the Kupperman score did not change. However, insomnia, palpitations, melancholy, weakness, vertigo, pain in muscles, nervousness, and headache improved, but hot flashes worsened (Table 4). In regression analysis hot flashes associated with hysterectomy (OR 3.5, CI 1.27–9.50) and age (OR 1.24, CI 1.04–1.42). Serum FSH increased both among older (>43 years) and younger (<43 years) women (Table 5). The mean serum oestradiol level was 0.28 nmol/L (SE 0.02) in the hysterectomy group and did not differ from the correspond-
**TABLE 5. SERUM FSH CONCENTRATIONS (IU/L) BY STUDY GROUP AND AGE**

<table>
<thead>
<tr>
<th>Age ≤ 43 years</th>
<th>Age &gt; 43 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>LNG-IUS</td>
<td>IU/L ± SE</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>IU/L ± SE</td>
</tr>
<tr>
<td>Daily calcium intake (mg)</td>
<td>1107 ± 495</td>
</tr>
<tr>
<td>Physical activity (hours/week x intensity)</td>
<td>7.3 ± 9.0</td>
</tr>
<tr>
<td>Alcohol consumption (doses/week)</td>
<td>27 (50%)</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>15 (28%)</td>
</tr>
<tr>
<td>Occasional use of oral corticosteroids</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>History of fracture*</td>
<td>6 (11%)</td>
</tr>
</tbody>
</table>

*Data are given by means ± SD or n (%).

**TABLE 6. MULTIVARIATE REGRESSION MODEL OF INHIBIN B CONCENTRATIONS AND INTRAOVARIAN ARTERY BLOOD FLOW**

Change in inhibin B concentration

<table>
<thead>
<tr>
<th>Standardised coefficients</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment modality</td>
<td>-0.38</td>
<td>-4.30 to 0.10</td>
</tr>
<tr>
<td>Serum FSH concentration (IU/L)</td>
<td>-0.60</td>
<td>-3.44 to 1.09</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>-5.65 to 5.25</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28</td>
<td>-1.10 to 0.30</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.02</td>
<td>-2.80 to 2.48</td>
</tr>
</tbody>
</table>

Change in intraovarian artery blood flow

<table>
<thead>
<tr>
<th>Standardised coefficients</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment modality</td>
<td>0.49</td>
<td>0.02 to 0.35</td>
</tr>
<tr>
<td>Serum FSH concentration (IU/L)</td>
<td>0.17</td>
<td>-0.01 to 0.02</td>
</tr>
<tr>
<td>Age</td>
<td>0.23</td>
<td>-0.02 to 0.08</td>
</tr>
<tr>
<td>BMI</td>
<td>0.28</td>
<td>-0.06 to 0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.06</td>
<td>-0.46 to 0.35</td>
</tr>
</tbody>
</table>

**TABLE 7. STUDY POPULATION CHARACTERISTICS RELATED TO BMD (STUDY III).**

<table>
<thead>
<tr>
<th></th>
<th>Hysterectomy</th>
<th>LNG-IUS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily calcium intake (mg)</td>
<td>110.7 ± 49.5</td>
<td>98.2 ± 31.2</td>
<td>NS</td>
</tr>
<tr>
<td>Physical activity (hours/week x intensity)</td>
<td>7.3 ± 9.0</td>
<td>8.3 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol consumption (doses/week)</td>
<td>27 (50%)</td>
<td>29 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;2</td>
<td>13 (28%)</td>
<td>14 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;5</td>
<td>22 (22%)</td>
<td>9 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>11 (20%)</td>
<td>12 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>7 (15%)</td>
<td>8 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Occasional use of oral corticosteroids</td>
<td>6 (11%)</td>
<td>3 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of fracture*</td>
<td>6 (11%)</td>
<td>6 (11%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are given by means ± SE or n (%).

**5. RESULTS**

Serum inhibin B concentrations decreased from 48.62 ng/mL (SD 46.34) at randomisation to 25.78 ng/mL (SD 36.16) at 6 months, and to 18.86 ng/mL (SD 29.21) at 12 months (P = 0.02 for the first 6 months vs. baseline) (Figure 6). Women whose serum inhibin B concentrations were above 7 ng/mL at baseline (n=26) had significantly higher serum FSH level (P = 0.01) and tended to smoke (P = 0.06) more often than those whose serum inhibin B concentrations were below 7 ng/mL. In the regression analysis, a decrease in inhibin B concentration associated with hysterectomy (P = 0.05) and serum FSH concentration (P = 0.01) (Table 6).

Ovarian artery PI did not change during the follow-up (Figure 7). However, PI of the intraovarian arteries decreased significantly (Figure 8). Women whose PI measurements were successful at randomisation were younger (P = 0.04) and had higher serum inhibin B concentrations (P = 0.03) than those for whom PI measurements were unsuccessful. The PI of the intraovarian arteries decreased from 0.99 (SD 0.37) at baseline to 0.67 (SD 0.16) at 6 months and 0.66 (SD 0.18) at 12 months (P = 0.01) (Figure 8). Multiple regression analysis revealed a significant association between change in PI of intraovarian artery and hysterectomy (P = 0.05) (Table 6).

**LNG-IUS GROUP**

The Kupperman index did not change during the follow-up. However, after a year of LNG-IUS use, many of the general symptoms improved, but pain and headache increased (Table 4). The regression analysis showed associations between pain and LNG-IUS use (OR 1.7, CI 1.06-2.88). Serum FSH concentration associated positively with both serum inhibin B concentrations and intraovarian artery Blood flow (Table 6).

**FIGURE 7. OVARIAN ARTERY PI.**

Serum inhibin B concentrations decreased from 48.62 ng/mL (SD 46.34) at randomisation to 25.78 ng/mL (SD 36.16) at 6 months, and to 18.86 ng/mL (SD 29.21) at 12 months (P = 0.02 for the first 6 months vs. baseline) (Figure 6). Women whose serum inhibin B concentrations were above 7 ng/mL at baseline (n=26) had significantly higher serum FSH level (P = 0.01) and tended to smoke (P = 0.06) more often than those whose serum inhibin B concentrations were below 7 ng/mL. In the regression analysis, a decrease in inhibin B concentration associated with hysterectomy (P = 0.05) and serum FSH concentration (P = 0.01) (Table 6).

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**FIGURE 8. INTRAOVARIAN ARTERY PI.**

The groups had no statistically significant difference in BMD either at lumbar spine or femoral neck. The treatment modality did not have a significant effect on the outcome.
not explain the change in BMD in the lumbar spine or femoral neck. Smoking was associated with BMD change among the LNG-IUS users (P = 0.004 for the lumbar spine; P = 0.07 for the femoral neck). Also ET use correlated with BMD change in the lumbar spine (P = 0.004 for the lumbar spine; P = 0.07 for the femoral neck). Moreover, none of the potential explaining factors (treatment, smoking, ET use, BMI, oophorectomy, calcium use, physical activity) explained the change in BMD at either site.

Hysterectomy Group

Of the 54 women, 24 (44%) were menopausal. BMD was measured in all women at randomisation and in 49 women at the five-year follow-up (P = 0.82).

**HysterecToMy GroUp**

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**LNG-IUS Group**

After five years, the LNG-IUS was in situ in 25 women (47%). Twenty-seven women (51%) had undergone a hysterectomy. Of the 53 women, 21 (40%) were menopausal. BMD was measured in 50 women at randomisation and in 48 women after five years. No women reported bone fractures during the follow-up period.

BMD decreased at femoral neck, but not at lumbar spine (Table 8). Among the women using LNG-IUS throughout the study (n=25), results were similar to intention-to-treat analyses.

5.3 Sexual Functioning (Study IV)

Six months after the treatment women in the hysterectomy group experienced less sexual problems and higher intercourse frequency than LNG-IUS users. Sexual satisfaction and partner satisfaction did not differ between the groups.

**Hysterectomy Group**

Sexual satisfaction increased (Figure 9) and sexual problems decreased (Figure 10) six months after the operation. Furthermore, at the five-year follow-up, satisfaction with the partner increased (Figure 11).

Since 50 of the 119 women randomised to the LNG-IUS group were hysterectomised during the study, the data were also analysed by actual treatment. There were only minor differences in outcomes compared to the intention-to-treat analyses. After six months, the increase in intercourse frequency did not reach statistical significance. In addition, at the five-year follow-up, the hysterectomised women’s (n = 159) partner satisfaction decreased (P = 0.02).

In univariate analyses, change in sexual satisfaction was not explained by individual factors tested (age, BMI, ET use, hot flashes, night sweats, vaginal dryness, lower abdominal pain, significant negative changes in life, smoking, lack of having someone with whom to ask for advice in difficult situations). However, the decrease in sexual problems was explained by ET use, and a decrease in both night sweats and vaginal dryness. According to multivariate model hysterectomy explained the increase in sexual satisfaction and the decrease in sexual problems (Table 9).

**LNG-IUS Group**

In the LNG-IUS group, there was no change in sexual satisfaction (Figure 9) or in sexual problems (Figure 10). Intercourse frequency did not change. From the 12-month follow-up onwards partner satisfaction had decreased (Figure 11). Since 50 of

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**Table 8. Bone Mineral Density (BMD, g/cm²) at 5-Year Follow-up.**

<table>
<thead>
<tr>
<th>Site</th>
<th>Hysterectomy (n=77)</th>
<th>LNG-IUS (n=49)</th>
<th>P-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.059 ± 0.104</td>
<td>1.037 ± 0.111</td>
<td>0.092</td>
</tr>
<tr>
<td>At 5-years</td>
<td>1.052 ± 0.106</td>
<td>1.039 ± 0.124</td>
<td>0.080</td>
</tr>
<tr>
<td>Change (%)</td>
<td>0.24 ± 0.740</td>
<td>0.07 ± 0.845</td>
<td>NS</td>
</tr>
<tr>
<td>P-value</td>
<td>0.02 NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 9. Multivariate Model to Explain Changes in Sexual Functioning After Treatment.**

<table>
<thead>
<tr>
<th>Change in sexual satisfaction</th>
<th>Treatment modality 0.14</th>
<th>Body mass index -0.11</th>
<th>Oestrogen therapy 0.01</th>
<th>Smoking -0.04</th>
<th>Living with partner 0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in sexual problems</td>
<td>Treatment modality -0.15</td>
<td>Body mass index 0.05</td>
<td>Oestrogen therapy -0.05</td>
<td>Smoking 0.00</td>
<td>Living with partner 0.05</td>
</tr>
</tbody>
</table>

**Figure 9. Change in Sexual Satisfaction.**

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the 119 women randomised to the LNG-IUS group were hysterectomised during the study, the data were also analysed by actual treatment (n=57). There were only minor differences in outcomes compared with the intention-to-treat analyses. Among LNG-IUS users (n = 59), the decrease in partner satisfaction at the 12-month follow-up did not quite reach statistical significance (P = 0.06).

According to the univariate analyses, the decrease in partner satisfaction associated with night sweats, hot flashes, lack of having someone with whom to ask for advice in difficult situations and having someone to share worries with. Significant negative changes in life did not influence sexual functioning. According to multivariate model smoking explained the decrease in partner satisfaction (Table 9).

### 6. Discussion

Karoliina Halmesmäki

Impact of hysterectomy and levonorgestrel-releasing intrauterine system on ovarian function, bone and sexual health in menorrhagic patients
6.1 METHODOLOGICAL ASPECTS
The randomised controlled ‘Vuokko’ trial started in 1994 with the primary objective of determining Health-Related Quality of Life and respective costs of hysterectomy or LNG-IUS when treating menorrhagia (Hurskainen et al. 2001, Hurskainen et al. 2004). In addition, it was also conducted to study many other effects of these treatment options. For this thesis the end-point parameters were ovarian function, BMD and sexual functioning. They were included in the original study design, and power calculations were performed to ensure that there was sufficient number of patients in these studies. Unfortunately, 42 % of the women assigned to the LNG-IUS group subsequently underwent a hysterectomy (Hurskainen et al. 2004). This may influence the LNG-IUS results. However, the results of these studies still show reliably the effect of the treatment decision. Actual treatment analyses were also performed, although it lowered the strength of randomisation.

Comparing surgical and medical treatment of menorrhagia is demanding. The patients could not be blinded to the treatment modalities. However, the gynaecologist performing the hysterectomy did not examine the patients at the follow-up visits. Also most of the women were referred to the hospital for operation and as a result they may have had the treatment preference. This may explain the relatively high discontinuation rate with LNG-IUS.

All five university hospitals in Finland were included in the study and the drop-out rate among the women participating in the study was low. This shows high commitment of both the participating women and the doctors. In addition the compliance bias is absent in this study. Selection bias is unlikely as well, because the inclusion criteria followed general clinical guidelines and exclusion criteria were not overly strict. Not all women referred for menorrhagia complaints were included, because some did not provide consent and some were unable to meet the inclusion criteria. Thus, it is obvious that the study represents women eligible for both treatment options and results are therefore generalisable to all menorrhagia patients. Moreover, randomisation performed separately for each centre in randomly varying clusters, ensured similarity also between the sub-study groups. Statistical analyses confirmed that the groups were comparable and the randomisation was successful.

Since waiting time for the operation was several months and varied between the centres, the follow-up visits took place at 6 and 12 months counted from treatment and not from randomisation. However, the five-year visit was appointed according to a randomisation time. Questionnaires were sent home by post, allowing the patients sufficient time to respond. ET use and smoking were also self-reported. This may have introduced a systematic recall bias but was avoided by randomisation. In addition, at the follow-up visits, the physical examination or the presence of a doctor did not influence the responses.

6.2 OVARIAN FUNCTION WHEN TREATING MENORRHAGIA
Hot flashes and serum FSH concentrations increased more among hysterectomised women than among LNG-IUS users. During the first six months serum inhibin B concentrations decreased in both groups. In the hysterectomy group only, the PI of intraovarian arteries decreased. In the multiple regression model, hysterectomy associated with these changes. However, serum oestradiol levels remained constant indicating that the ovaries still responded to the FSH stimulus. The present results suggest that hysterectomy influences intraovarian blood flow, which may, in turn, impair ovarian function. Moreover, the Kupperman score did not change.

Results are consistent with non-randomised studies in which climacteric hormonal profile and menopausal symptoms developed earlier among hysterectomised women than among women with an intact uterus (Cooper and Thorp, 1999, Farquhar et al. 2005, Hartmann et al. 1995, Oldenhave et al. 1993). However, in a small case-control study, serum FSH concentrations did not differ between hysterectomised women and controls during two-year follow-up (Chalmers et al. 2002). In contrast to study by Oldenhave (1993), among hysterectomised women in our study, serum FSH concentrations increased regardless of the women's age. This may be explained by a larger sample size and a randomised study setting.

An explanation for the mechanism of impaired ovarian function after hysterectomy is probably vascular. Diminished arterial blood flow increases ovarian congestion and oedema, resulting in stromal cell hyperplasia, thickening of the tunica albuginea and a significant decrease in follicular reserve (Souza et al.
This in turn decreases inhibin B production and is seen as a rise in serum FSH concentration (Muttukrishna et al. 2002). Reports on increased serum FSH concentration after both uterine artery embolisation and sterilisation support this vascular theory (Kelekci et al. 2005, Talândi et al. 2002). The Kupperman index was chosen to measure menopausal symptoms because it has been widely used to characterise and quantify menopausal symptoms since its publication (Kupperman et al. 1959). This also facilitates the comparison of results from different studies. Originally, the Kupperman test of menopausal distress was developed to measure symptoms in menopausal women. As women participating in the study were premenopausal, the Kupperman index may have been too robust to adequately detect minor differences between the groups. A new method to rate menopausal symptoms has subsequently been published (Schneider et al. 2006). The Menopause Rating Scale was only published in German (Hauser et al. 1994) when this study began. The English version was published in 2000 (Schneider et al. 2000). We considered it inappropriate to change the method during the study. Causes other than menopause can explain symptoms like vertigo, headache, and menopausal symptoms, increased serum FSH concentrations (Kelekci et al. 2005). It has been shown that serum inhibin B concentration declines 12 months after total abdominal hysterectomy, but serum FSH concentrations do not change (Nahas et al. 2005). In our study, serum inhibin B concentration declined rapidly in both groups. Due to the fact that during menopausal transition the decline in serum inhibin B concentration accelerates, and the difference between the study groups was not detected. Perhaps a more frequent sampling during the first six months of the study would have helped to see whether the decrease was faster in the hysterectomy group. Recently, a decrease in ovarian artery PI a year after hysterectomy was found (Petri Nahas et al. 2005). In our study, PI of ovarian arteries did not change, whereas the PI of intraovarian arteries decreased only among hysterectomised women. As PI correlates negatively with blood flow, ovaries may try to compensate posthysterectomy ischaemia by vasodilatation. The effect of LNG-IUS on ovarian function has not been reported, but the device may increase uterine artery PI in some LNG-IUS users (Javell et al. 1998). Slightly more ovarian cysts were present among LNG-IUS users than among hysterectomised women (Cheng et al. 2003). BMD was measured by DXA from the lumbar spine and femoral neck. Even if quantitative computed tomography would be able to distinguish cortical bone from trabecular bone, and is more sensitive to changes in BMD (Lane 2006), DXA is clinically the most often used. This method of measurement already exists and access to it was convenient. The results are also reproducible (Briot and Roux. 2005). Although a significant difference in BMD between the study groups was not seen, extending the follow-up might
have revealed the differences in postmenopausal bone loss.

Results from studies focusing on BMD and hysterectomy have been controversial. Improved (Cheng et al. 2003, Grainge et al. 2001, Tappurainen et al. 1995), stable (Shibayeh, 2003) and decreased (Duraes Simoes et al. 1995, Watson et al. 1995) BMD after hysterectomy have been reported. Only one study reported the effect of LNG-IUS on BMD. The effect of LNG-IUS on BMD at mid-shaft of the ulna and distal radius BMD was similar to the copper-IUS (Bahamondes et al. 2005).

All these previous studies on hysterectomy or LNG-IUS have been non-randomised and prone for bias. The effect of confounding factors has been difficult to rule out. Our randomised study setting diminishes the probability of bias, and including of possible confounding factors to the study protocol made possible comprehensive regression analyses.

The positive influence of oestrogen on BMD has been well-demonstrated (Sirola et al. 2003). Also BMI is linked with BMD. BMI < 25kg/m² is associated with low BMD and increased vertebral fracture risk (Nevitt et al. 2005). High body weight may affect BMD by increasing mechanical stress on bone and enhancing peripheral conversion of androstenedi-one to estrene (Murillo-Urbi et al. 2000). Smoking has several anti-oestrogenic effects and may decrease BMD by impairing ovarian function and increasing oestrogen turnover in the liver (Lambert-Messerlian and Harlow, 2006, Mueck and Seeger, 2005). In the LNG-IUS group, but not in the hysterectomy group, the BMD decrease was associated with smoking. This difference between the groups may be explained by the small number of women. Moreover, the effect of hysterectomy on BMD may mask the effect of smoking.

Being the first randomised study in this field, there are some limitations in interpreting the results. The present study had a relatively small number of patients, and the high number of hysterectomies in the LNG-IUS group confounds the setting. However, according to power calculations, it was possible to detect a 10% decrease in BMD, if such existed. Moreover, the short follow-up and use of ET remained a problem. ET use was, however, equally common in the study groups. Since half of the women were hysterectomised during the study period, the results were also analysed according to actual treatment. This did not influence the outcome. Certainly, bone turnover markers would have been important to analyse as well, for change in osteocalcin predicts vertebral fracture better than changes in BMD (Sarkar et al. 2004).

6.4 SEXUAL FUNCTIONING WHEN TREATING MENORRHAGIA

Women in the hysterectomy group experienced less sexual problems and higher intercourse frequency than LNG-IUS users. After one year, hysterectomised women were also more satisfied with their partners than women using LNG-IUS.

Our results are in line with previous randomised studies. According to these studies hysterectomy has no negative effect on sexual functioning (Ellerbrink et al. 2003, Rhoads et al. 1999, Thakar et al. 2002, Zobbe et al. 2004), but may in fact improve it (Kuppermann M. et al. 2005). This may be related to the indication of hysterectomy. If a hysterectomy is performed for a bothersome reason, and the hysterectomy relieves the symptoms, then there can be an improvement in sexual functioning. The effect of LNG-IUS on sexual functioning has not been previously studied in a randomised study setting. However, it has been suggested that LNG-IUS should not disturb sexual intercourse (Baldazzi et al. 2003). Moreover, vaginal dryness is not expected as serum concentration of LNG is extremely low (Barbosa et al. 1990) and the influence of the device on ovarian function is limited (Nass et al. 2003). Therefore LNG-IUS users are not expected to suffer from decreased intercourse.

Measuring sexual functioning is difficult, because a woman’s sexuality is influenced by several psychosocial factors. The relative importance of one specific factor is difficult to qualify and thus the effect of treatment should be studied in randomised settings. Most of the studies concerning sexuality after treatments are related hysterectomy. The settings have been usually operation and not reason based. This study had an excellent follow-up with randomisation between operative and conservative treatment. Outcomes were based on validated instruments (McCoy and Davison, 1983, Wiklund et al. 1993a) used before and after the intervention. Subjects were stratified for significant confounding and demographic characteristics. Not only treatment modality, but also several other factors had an impact on sexual functioning. The sexual functioning was adjusted also by BMI, ET use, living with a partner and smoking. In the present study smoking was the only factor correlating with decreased partner satisfaction. Smoking associates with social skills (De Vogli and Santinello, 2005) and may also have an effect on sexual functioning. Moreover, smoking causes early menopause by directly diminishing ovarian reserve (Cooper et al. 1995, Lambert-Messerlian and Harlow, 2006). ET alleviates menopausal symptoms and lubrication problems. Also in our study, ET use relieved sexual problems. This may be explained by the assumption that there is a decrease in vaginal dryness and increase in libido with ET use (Vestergaard et al. 2003).

It is difficult to explain why partner satisfaction decreased among LNG-IUS users. The dynamics of the relationship were not analysed, as sexual partners were not interviewed. Sexual functioning may be influenced by lower abdominal pain experienced more often by LNG-IUS users than by hysterectomised women (Hurskainen et al. 2001). Moreover, while the study setting was randomised, women could not be blinded to treatment modality. Possibly women and their partners had expectations for receiving a hysterectomy and a more negative attitude towards LNG-IUS, as it was a novel treatment for menorrhagia in the late 1990s. Also, the intermitting bleeding and spotting that occurred during the first six months of LNG-IUS use may have disturbed sexual functioning. Age-related changes may also create discrepancies in sexual needs and decrease satisfaction with a partner. However, this does not explain the difference between the groups in a randomised setting. Moreover, the clinical meaning of this finding remains to be studied.
Impact of hysterectomy and levonorgestrel-releasing intrauterine system on ovarian function, bone and sexual health in menorrhagic patients

7. Future prospects
7. FUTURE PROSPECTS

The follow-up of these women continues. As the majority of the patients will reach menopause by the 10-year follow-up, it will be possible to evaluate cost-effectiveness and Health-Related Quality of Life at the end of reproductive life, when no additional costs from menorrhagia are expected. Moreover, since hysterectomy appears to impair ovarian function (Farquhar et al. 2005), and early menopause in turn has been linked to an increased risk for cardiovascular disease (Anonymous 2006, Howard et al. 2005, Punnonen et al. 1987), an important area of future research is whether the incidence of cardiovascular disease is increased in women treated with hysterectomy or with LNG-IUS for menorrhagia. It has been postulated that hysterectomy may increase incidence of stress incontinence (Neumann et al. 2007). Therefore, the incidence of urinary incontinence will also be evaluated in our study population. In all, the 10-year follow-up is anticipated to reveal significant information on long-term health of women treated for menorrhagia.

The effect of hysterectomy or LNG-IUS on serum AMH concentrations and AFC remain to be studied. Results concerning ovarian blood flow need to be confirmed by 3-dimensional ultrasound. Since hysterectomy seems to decrease BMD at lumbar spine, the effect of operation on fracture risk is important to know as population ages. Fracture risk assessment requires a larger study sample with longer follow-up period, however. Regarding sexual functioning, the effect of hysterectomy or LNG-IUS on partner satisfaction is an interesting area of future research. Moreover, randomised controlled studies comparing the effect of conservative and operative treatment on sexual functioning in symptomatic menorrhagia patients are still scarce.
8. Conclusions
HYSTERECTOMY seemed to affect ovarian function and BMD more than LNG-IUS. Sexual functioning however, improved more among hysterectomised women than among LNG-IUS users. The conclusions are based on the following findings:

1) Increase in serum FSH concentration and menopausal symptoms appeared earlier among hysterectomised women than among LNG-IUS users.
2) Decrease in serum inhibin B concentration did not differ between the groups, but ovarian blood flow changed only among hysterectomised women.
3) Decrease in lumbar spine BMD occurred among hysterectomised women, but not among LNG-IUS users. Femoral neck BMD decreased in both groups.
4) Sexual satisfaction increased and sexual problems decreased among hysterectomised women six months after the treatment. Intercourse frequency also increased. LNG-IUS did not have similar effects. Although the two groups did not differ at the one-year and five-year follow-ups in terms of sexual functioning, partner satisfaction among LNG-IUS users decreased.
9. Summary in Finnish

Karoliina Halmesmäki
Impact of hysterectomy and levonorgestrel-releasing intrauterine system on ovarian function, bone and sexual health in menorrhagic patients


10. Acknowledgements
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