Intrauterine Contraception –
Use in Nulligravid Women and Safety Aspects

Janina Kaislasuo

Academic Dissertation

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Supervised by: Professor Oskari Heikinheimo, MD, PhD, Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, Finland

and

Adjunct Professor Satu Suhonen, MD, PhD, Department of Social Services and Health Care, the Centralized Family Planning, Helsinki, Finland

Consultant supervisor: Adjunct Professor Pekka Lähteenmäki, MD, PhD, Department of Obstetrics and Gynaecology, University of Helsinki, Finland

Reviewed by: Adjunct Professor Dan Apter, MD, PhD, Family Federation’s Sexual Health Clinic, Helsinki, Finland

and

Adjunct Professor Ilkka Järvelä, MD, PhD, Department of Obstetrics and Gynaecology, University of Oulu and Oulu University Hospital, Finland

Official Opponent: Adjunct Professor Lena Marions, MD, PhD, Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden

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To my family
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IUD use in nulligravid women
Uterine size and intrauterine contraception
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1. ABBREVIATIONS

BMI = body mass index
CI = confidence interval
COC = combined oral contraceptive
DMPA = depot medroxyprogesterone acetate
HCP = health care provider
ICD-10 = International Classification of Diseases 2010
IUC = intrauterine contraception
IUD = intrauterine device
LAM = lactational amenorrhoea method
LARC = long-acting reversible contraception
LNG = levonorgestrel
LNG-IUS = levonorgestrel-releasing intrauterine system
   (52 mg, 20 µg/24 h)
LNG-IUS 13.5 mg = levonorgestrel-releasing intrauterine system
   (13.5 mg, 12 µg/24 h)
NOMESCO = Nordic Medico-Statistical Committee
NSAID = non-steroidal anti-inflammatory drug
OR = odds ratio
PCB = paracervical block
PID = pelvic inflammatory disease
ROC = Receiver Operating Characteristic
STD = sexually transmitted disease
STM = Ministry of Social Affairs and Health
THL = National Institute for Health and Welfare
UN = United Nations
WHO = World Health Organization
2. LIST OF ORIGINAL PUBLICATIONS

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3. ABSTRACT

The proportion of nulligravid and nulliparous women is increasing as women delay childbirth in developed countries. Simultaneously, contraceptive failure, unintended pregnancies and abortions, especially in women below the common childbearing age, are a global problem. By promoting intrauterine devices (IUDs) and subdermal implants, referred to as long-acting reversible contraceptives (LARC), among these women, contraceptive failure caused by non-compliance of the user can be minimized, in addition to providing easy and efficient long-term contraception. However, the risk of difficulties at IUD insertion in nulligravid/nulliparous women, as well as small uterine size, have both been considered as barriers limiting the use of intrauterine contraception (IUC) in these women.

The present studies were designed to study the barriers to IUC in nulligravid and nulliparous women. To compare both types of IUC available, we used the levonorgestrel-releasing intrauterine system (LNG-IUS) and the copper-releasing NovaT (TCu380Ag), with identical frames measuring 32 x 32 mm. To exclude any effect of prior pregnancy on the uterine cavity or the cervix, only nulligravid women were included. Difficulties at insertion, menstrual diaries kept after insertion (months 1–3) and at the end of the study (months 10–12) as well as adverse events were compared against uterine cavity measurements and pre-insertion menstrual characteristics reported by the women. In addition, as uterine perforation is mainly seen as a complication related to insertion, we retrospectively analysed women treated for this rare complication between 1996 and 2009 in our hospital district area.

We gave 165 nulligravid women requesting their first IUD a free choice between the two IUDs after contraceptive counselling. The majority, 113 women (68.5%), chose the LNG-IUS and 52 women (31.5%) chose the copper IUD. Insertion was easy in 89% of the women. The women were satisfied, with only 17/135 women (12.6%) available for follow-up discontinuing because of adverse events. The reported numbers of days of bleeding and pain were similar to that in earlier reports on parous women. Severe pain at insertion was reported.
by 56.5% of the women and severe dysmenorrhoea the only factor predicting severe pain (OR 7.9, 95% CI 2.5–24.9, p<0.001). Dysmenorrhoea was also related to more pain during the first months with both devices. Baseline spontaneous bleeding predicted bleeding with the LNG-IUS, but not with the copper IUD. Among women using the LNG-IUS, scanty menstrual bleeding (OR 8.2, 95% CI 1.4–48.2, p=0.02) and smoking (OR 8.2, 95% CI 1.8–38.6, p=0.007) predicted amenorrhoea at one year. Uterine measurements, particularly fundal cavity width, were small in comparison to the devices in a majority of the women. The odds of a difficult or failed insertion increased with shorter uterine length and a steeper flexion angle, but the great majority of insertions, even in small and more flexed uteri, were uneventful. Cervical tightness was the main reason for problems in cases of difficult insertion. No uterine threshold measurements predicting difficulties were found. Small uterine measurements were associated with both less bleeding and less pain among LNG-IUS users. Women with the widest fundal widths reported significantly more pain at the end of the one-year follow-up period compared with those with smaller widths. Uterine size did not affect bleeding in connection with the copper IUD, but there was a slight tendency towards more pain during long-term use among women with smaller uterine cavity measurements, although size groups were small with this device. Uterine size did not predict adverse events.

We found 75 cases of surgically treated uterine perforation during the 15–year long study period. The incidence of perforation was low, 0.4/1000 insertions, and similar with both types of IUC. Postpartum insertion, earlier presented as the main risk factor of uterine perforation, was also common in this population (64%). The majority of cases, 71%, presented with complaints of abnormal bleeding or pain, but 29% were asymptomatic and diagnosed in connection with missing threads or pregnancy. Pregnancy was more common with a misplaced copper IUD, 33% vs. 7% with a misplaced LNG-IUS (p=0.009). We found no severe complications or intra-abdominal adhesions caused by the misplaced devices. Adhesions were local and more common in copper IUD users (58% vs. 20%, p=0.002).
In conclusion, nulligravid women are satisfied users of modern IUC, with continuation rates and bleeding and pain profiles similar to those in parous women. Small uterine cavity measurements are not a barrier to IUC and pre-insertion ultrasonographic evaluation of uterine cavity size is unnecessary. As dysmenorrhea predicts both severe insertion pain and pain during the first months of IUD use, analgesia and counselling for these women should be highlighted. Although rare, the risk of uterine perforation is increased during the postpartum period, probably reflecting uterine involution as the main reason for this complication. Neither symptoms nor surgical findings are severe in connection with current devices.
4. INTRODUCTION

Fertile-aged women are divided by parity in gynaecological literature. A parous woman has delivered a child, either vaginally or by Caesarean section. A nulliparous woman has not delivered a child, but may have had a prior spontaneous abortion or termination of pregnancy. Nulligravid women are a subgroup of nulliparous women with no prior history of pregnancy.

The history of intrauterine contraception (IUC) has seen intrauterine devices (IUDs) of different sizes and shapes. Results with these devices have not always been beneficial for nulliparous women. The increased rate of pelvic inflammatory disease (PID) and subsequent infertility linked to IUC in nulliparous women during the 1970s harmed the reputation of IUC for decades. In addition, small uterine size in these women, causing problems during IUD insertion and use, has been a constant concern among physicians. Thus, IUDs were recommended only for parous women for decades (Toivonen and Luukkainen 1987). With the introduction of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the 1990s, the additional therapeutic benefits of the device have resulted in widespread promotion of the use of IUC.

The proportion of nulligravid/nulliparous women of reproductive age is increasing, as all developed countries have seen a constant increase in the age at first delivery as well as an increase in women choosing to remain childless (Oliveira da Silva et al. 2011, OECD 2011-2014, THL 2014a,). Women of all ages and parities have higher satisfaction and continuation rates with long-acting reversible contraception (LARC), including IUDs and subdermal implants, than with other methods (O’Neil-Callahan et al. 2013). With high rates of contraceptive failure and consequently unintended pregnancies and abortions globally, especially in young women, the importance of LARC has been highlighted during the last decade (ACOG 2012, Winner et al. 2012, CDC 2013, NICE 2014). Increased concerns regarding cardiovascular and thromboembolic health risks caused by combined hormonal contraception (Lidegaard et al. 2009, Bitzer et al. 2013) have additionally promoted the use of oestrogen-free contraceptives.
When the present studies were planned, only a handful of studies on nulligravid/nulliparous women using the LNG-IUS had been published. Conclusions from studies on copper IUDs in these women were skeptical, as the history of copper IUDs has seen higher rates of discontinuation in these women. Smaller uterine size in these women was linked to reports of adverse events and was considered as a barrier limiting the use of IUDs, in addition to historical safety concerns and higher rates of problematic insertions.

Studying uterine size in relation to successful IUD insertion and long-term use was the initial objective for the present studies. As pregnancy increases uterine size (Kurz et al. 1984), only nulligravid women were included in order to exclude any effect pregnancy may have on the uterine cavity or the cervix. To evaluate other potential factors related to problems at insertion or during long-term use, background characteristics were analysed. In addition, as uterine perforation is mainly seen as a complication related to insertion, and problematic insertions are more common in nulligravid/nulliparous women, we analysed patient characteristics and the clinical course of women treated for this rare complication in our hospital district area.
5. REVIEW OF THE LITERATURE

*Intrauterine contraception*

**Development**

*Inert and copper-releasing devices*  
The history of modern intrauterine contraception started in the 1920s, when a German, Dr. Gräfenberg, described an intrauterine ring made of silkworm gut and silver filaments and later found to contain copper. Endemic gonorrhoea, commonly causing infections, together with the political atmosphere in Germany condemning contraception, prevented the intrauterine ring from gaining popularity (*Thiery 2000*). Intrauterine contraception gained popularity in the 1960s. The first IUDs, including the popular s-shaped Lippes loop, were inert plastic devices, depending on a large size and surface area for an adequate contraceptive effect. Problems with bleeding and expulsion were common (*Kurz et al. 1984*). The first T-shaped IUD was developed by Dr. Tatum in the 1960s to fit the uterine cavity better and reduce problems associated with the devices (*Thiery 2000*). Side-effects were reduced, but pregnancy rates were high. By adding copper to the device, pregnancy rates could be reduced (*Zipper et al. 1971*) and thus the first copper-T IUD was introduced in 1974. Since then, a variety of devices of different shapes and sizes have been available. As T-shaped devices containing 380 mm$^2$ of copper (TCu380) have proven to be most effective and user-friendly (*O’Brien et al. 2008*), IUDs of other shapes have gradually been withdrawn, although T-models containing less copper are still available. In addition to the T-models, a frameless device, designed to better fit the uterine cavity and thus further reduce side-effects is available, but trials comparing this device with the TCu380 models have not verified its superiority (*O’Brien and Maarfleet 2005, Meirik et al. 2009*).

The inert plastic U-shaped Dalkon shield, introduced in 1970, greatly damaged the reputation of intrauterine contraception,
especially in young and nulligravid/nulliparous women, as unintended pregnancies resulting in septic abortions and deaths, and increased rates of infertility were described. Infections were later found to be the result of vaginal bacteria reaching the uterine cavity through the multifilament nylon thread used only in this device and infertility was a result of the infections (Tatum 1975). The device was withdrawn in 1974 after multiple lawsuits.

**Hormonal intrauterine contraception**

The first hormonal IUD was developed in the 1960s. By adding progesterone to an inert T-shaped plastic frame, the hope was to reduce uterine contractility and thus reduce expulsion rates. Instead, contraceptive efficacy was increased (Pharris et al. 1974) and menstrual blood loss reduced (Bergkvist and Rybo 1983). To lengthen the lifespan of the device, progesterone was replaced by levonorgestrel (LNG). The result was the LNG-IUS, made by adding a steroid reservoir covered with a silastic membrane onto the vertical arm of the frame of the copper device NovaT. The device was developed in Finland and introduced to the Finnish market in 1990 as the first country in the world.

The LNG-IUS has since gained increasing popularity owing to its additional therapeutic health benefits. The contraceptive effect is comparable to sterilization (Andersson et al. 1994). The reduction in menstrual blood loss and lower abdominal pain has widened indications to menorrhagia, dysmenorrhoea, adenomyosis and endometriosis and thus reduced the need for hysterectomy. The therapeutic effect on the endometrium has proven beneficial in treating hyperplasia and protecting the endometrium during hormone replacement therapy (Andersson and Rybo 1990, Heikinheimo and Gemzell-Danielsson 2012).

To further reduce systemic exposure and progestin-related side-effects and to improve user satisfaction, a smaller LNG-IUS, the LNG-IUS 13.5 mg, designed for women with a small uterine cavity and to facilitate insertion in women with a tighter cervical canal, namely nulliparous women, has recently been introduced (Gemzell-Danielsson et al. 2012).
Mechanisms of action

**Copper-releasing devices**
When using a copper-releasing IUD, copper accumulates throughout the epithelium of the uterine cavity and fallopian tubes (Gemzell-Danielsson et al. 2013a) and concentrations are high enough to be toxic to both gametes and fertilized embryos (Ortiz and Croxatto 2007). Copper ions released from the device cause a local inflammatory response, disturbing the endometrial lining of the implantation site (Savaris et al. 2000). Copper also increases contractility of both the fallopian tubes and the myometrium (Gemzell-Danielsson et al. 2013a).

The main contraceptive effect of a copper IUD is attributed to prevention of fertilization, but in the event of fertilization also to the prevention of formation of viable embryos, and inhibition of implantation (Gemzell-Danielsson et al. 2013a). Markedly reduced incidences of implantation signs in women using copper IUDs in comparison with controls support this (Videla-Rivero et al. 1987). These mechanisms also make a copper device the most effective form of emergency contraception up to five days after unprotected sexual intercourse (Gemzell-Danielsson et al. 2013a).

**The levonorgestrel-releasing intrauterine system**
The constant local release of LNG results in endometrial concentrations significantly higher than with systemic methods and a subsequent endometrial suppression (Nilsson et al. 1982). Decidualization of the endometrium results in unresponsiveness to oestrogen (Jones et al. 2000, Luukkainen et al. 2001). Although histological changes are rapid and seen within one month after insertion of the device, some secretory activity can be seen during the first few months of use. The inflammatory response to the device also decreases within six months post-insertion (Jones et al. 2000). These gradual changes are often seen as irregular bleeding or spotting during the first three to four months of use and thereafter a gradual reduction of menstrual blood loss during the first year in seen (Luukkainen et al. 2001).
Concentrations of LNG in the myometrium and plasma are low, but not absent (Nilsson et al. 1982). Thus, hormonal side-effects, such as acne, weight change, breast tenderness and mood changes are seen in 1–2% of women (Luukkainen et al. 2001). Effects on ovulation are minimal during long-term use, with the majority of cycles being ovulatory (Nilsson et al. 1984). However, shortly after insertion, when LNG plasma concentrations are at their highest, many women have anovulatory cycles (Nilsson et al. 1980, Järvelä et al. 1998).

The cervical mucus becomes thick and impermeable, preventing sperm penetration into the uterus (Luukkainen et al. 2001). Current understanding also indicates prevention of fertilization, but the mechanism is still unclear (Ortiz and Croxatto 2007).
Global use of intrauterine contraception

According to the United Nations (UN) World Contraceptive Report in 2013, 14% of women who are married or cohabiting worldwide use intrauterine contraception. In parts of Asia the prevalence exceeds 40%, in Europe the prevalence is 12%, in Northern America 5%, in Latin America 7%, in Northern Africa 20% and in Sub-Saharan Africa only 0.5%. However, large regional differences exist and the prevalence in Africa and Asia is strongly dependent of the socio-economic status of the region (UN World Contraceptive report 2013). Prevalence increases with age and women under the age of 20 rarely use intrauterine contraception – national reports show rates of 0–3% (CDC 2010, Oliveira da Silva et al. 2011, NHS 2013/14, Läkemedelsverket i Sverige 2014). Figure 1 summarizes the prevalence of intrauterine contraception in European and other major countries.

IUDs are the most commonly used reversible contraceptives globally, while female sterilization has the largest prevalence overall (D’Arcangues 2007). In most developed countries the oral contraceptive pill, combined (COC) or progestin-only, and condoms are the most popular forms of contraception. This is also true in Finland, with 31% of fertile-aged women reporting using COCs or progestin pills. Intrauterine contraception and condoms are equally popular in second place, with a prevalence of 23% (Oliveira da Silva et al. 2011). The popularity of the LNG-IUS has steadily increased since its introduction and it currently represents approximately 85% of IUDs inserted in Finland annually (Oliveira da Silva et al. 2011).
Figure 1. Percentage of women aged 15–49 years using any IUD as contraception. Numbers are based on statistics from 2007–2011 according to availability by each country. Data from the Oliveira da Silva et al. 2011 and UN World Contraceptive report 2013.
Benefits of intrauterine contraception

Long-acting reversible contraception

Contraceptive methods can be divided into long-acting (LARC) and short-acting reversible methods (Table 1). Short-acting contraceptives are taken daily, weekly or monthly and require the user to be compliant. Long-acting contraceptives are not user-dependent and can be used continuously from 3–10 years without the need of continuous compliance. Additional methods commonly not included in the categories above include the lactational amenorrhoea method (LAM), sterilization, withdrawal and fertility-based awareness methods, where unprotected sexual intercourse is avoided on fertile days of the cycle. LAM is effective when the woman is amenorrhoeic, fully or nearly fully breastfeeding and less than six months post-partum and is widely used in developing countries. Withdrawal and fertility-based awareness methods are not recommended, as failure rates are high (WHO 2010, Trussell 2011).

Table 1. Modern contraceptive methods.

<table>
<thead>
<tr>
<th>Long-acting methods</th>
<th>Short-acting methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUDs</td>
<td><strong>Hormonal methods</strong></td>
</tr>
<tr>
<td>LNG-IUS (hormonal)</td>
<td>Combined*</td>
</tr>
<tr>
<td>Copper IUDs</td>
<td>Pill</td>
</tr>
<tr>
<td>Subdermal implant</td>
<td>Patch</td>
</tr>
<tr>
<td>Progestin releasing</td>
<td>Vaginal ring</td>
</tr>
<tr>
<td></td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td>Progestin only</td>
</tr>
<tr>
<td></td>
<td>Pill</td>
</tr>
<tr>
<td></td>
<td>Injection (DMPA**)</td>
</tr>
</tbody>
</table>

**Barrier methods**

- Diaphragm/sponge
- Condom
- Spermicide

IUD = intrauterine device, LNG-IUS = levonorgestrel-releasing intrauterine system, *Oestrogen + progestin, **DMPA = depot medroxyprogesterone acetate
User compliance and contraceptive efficacy

With high rates of unintended pregnancies and abortions globally, the importance of LARC has been highlighted during the last decade. In the U.S. 50% of all pregnancies are estimated to be unintended and half of these result from contraceptive failure (Winner et al. 2012). One in five of these unintended pregnancies occur in adolescents (ACOG 2012). The contraceptive efficacy of all available methods is high when used adequately, but problems with user compliance (forgetting pills, patches, rings or injections or inadequate use of non-hormonal methods) raise failure rates markedly (Table 2).

Problems with compliance, and thus risk for unintended pregnancy, is twice as high in women ≤ 20 years of age (Kost et al. 2008, Winner et al. 2012). Among these highly fertile and sexually active women, contraceptive counselling and provision of efficient and effective methods is crucial. In Finland adolescent pregnancy rates are low as a result of increased education, contraceptive counselling and provision of contraceptives. As LARC methods are non user-dependent, failure rates are low (Winner et al. 2012) and continuation at one and two years significantly higher than with other methods in all age groups (Peipert et al. 2011, O’Neil-Callahan et al. 2013). The Contraceptive CHOICE project, providing contraceptive counselling and any preferred contraceptives cost-free in the U.S., includes extensive studies confirming the benefits of LARC in reducing the costs and subjective burden of unintended pregnancy and as well as acceptance of IUDs in women of all ages, including adolescents (McNicholas et al. 2014, Contraceptive CHOICE project).
Table 2. Pregnancy rates (n/100) with different family planning methods during the first year of use and continuation rates after one year.

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical use</th>
<th>Perfect use</th>
<th>Continuation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No contraception</td>
<td>85</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Spermicides</td>
<td>29</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>27</td>
<td>4</td>
<td>43</td>
</tr>
<tr>
<td>Fertility awareness-based</td>
<td>25</td>
<td>3-5</td>
<td>51</td>
</tr>
<tr>
<td>methods (several)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parous women</td>
<td>32</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td>Nulliparous women</td>
<td>16</td>
<td>9</td>
<td>57</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>16</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>Condom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>5</td>
<td>49</td>
</tr>
<tr>
<td>Pill (combined and progestin-only)</td>
<td>8</td>
<td>0.3</td>
<td>68</td>
</tr>
<tr>
<td>Patch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>8</td>
<td>0.3</td>
<td>68</td>
</tr>
<tr>
<td>Injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestin (DMPA)</td>
<td>3</td>
<td>0.3</td>
<td>56</td>
</tr>
<tr>
<td>Combined</td>
<td>3</td>
<td>0.05</td>
<td>56</td>
</tr>
<tr>
<td>IUD LNG-IUS</td>
<td>0.2</td>
<td>0.2</td>
<td>80</td>
</tr>
<tr>
<td>Copper T</td>
<td>0.8</td>
<td>0.6</td>
<td>78</td>
</tr>
<tr>
<td>Subdermal implant</td>
<td>0.05</td>
<td>0.05</td>
<td>84</td>
</tr>
<tr>
<td>Sterilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.15</td>
<td>0.10</td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>0.5</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>Lactational amenorrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>method*</td>
<td></td>
<td>0.5-1.5</td>
<td></td>
</tr>
</tbody>
</table>

Safety of intrauterine contraception

Insertion

Modern IUDs are not only a result of development to increase user satisfaction and contraceptive efficacy, but also to facilitate insertion. Recent reviews on IUD insertion emphasize that insertions in nulligravid/nulliparous women should be considered clinical routine. Although cervical tightness is more likely in nulligravid/nulliparous women, difficulties may be encountered at IUD insertion in any woman (Bahamondes et al. 2014, Kaunitz and Nelson 2014). The proportion of difficult insertions in studies among women of different parities is 10–20%, with numbers somewhat smaller in parous women than in nulligravid/nulliparous women and few women requiring cervical dilatation, regardless of parity (Brockmeyer et al. 2008, Jensen et al. 2008, Bahamondes et al. 2011b, Marions et al. 2011, Bahamondes et al. 2014, Kaunitz and Nelson 2014). Adolescence does not increase the risk of difficulties (Bayer et al. 2012). The mode of delivery in parous women may influence insertion, as women with Caesarean section deliveries generally have a tighter cervical canal, comparable to that in nulligravid/nulliparous women, and the Caesarean section scar may cause uterine distortion (Bahamondes et al. 2011b).

Difficulties at insertion are mainly related to cervical tightness, but also to the experience of the health care provider (HCP). To ensure optimal results at IUD insertion, adequate training of HCPs and a good technique are is emphasized, as an inexperienced HCP (≤10 insertions annually) is a risk factor as regards both difficulties at insertion and uterine perforation (Harrison-Woolrych et al. 2003, Zhou et al. 2003). Recommended technical aspects to ensure optimal results at insertion are summarized in Table 3.
Table 3. Summary of technical recommendations for IUD insertion.

**Counselling and verbal anaesthesia**
Most effective in reducing both pain and anxiety.
No current evidence supporting prophylactic pharmacological pain management.

**Bimanual pelvic examination**
Anatomy, uterine position and size, rule out infection.

**Bivalve speculum examination**
Proper visualization of the cervix, rule out visible cervicitis, providing space for insertion.

**Use of metallic tenaculum**
Stabilizing the uterus and straightening uterine flexion.

**Uterine sounding prior to insertion**
Exploration of the cervical canal, determining uterine depth.

**Cervical dilatation**
Not recommended routinely as mechanical dilatation causes pain and vasovagal reactions. When needed, para- or intracervical block is recommended.

**Knowledge of insertion guidelines for each device**
The insertion technique for each device differs somewhat.

*Bahamondes et al. 2014, Kaunitz and Nelson 2014*

Severe pain at insertion is more common in nulligravid/nulliparous women, 14–21%, compared with 5–11% in parous women (*Suhonen et al. 2004, Hubacher et al. 2006, Jensen et al. 2008, Heikinheimo et al. 2010, Marions et al. 2011*). Parous women with only Caesarean section deliveries also experience more pain (*Allen et al. 2014*). Studies on prophylactic pharmacological pain management, including the use of non-steroidal anti-inflammatory drugs (NSAIDs), opioids, nitroprusside, lidocaine gel and misoprostol have revealed no evidence supporting their routine use, although NSAIDs are considered beneficial in reducing post-insertion pain by reducing uterine contractility (*Allen et al. 2009, Bahamondes et al. 2014, Kaunitz and Nelson 2014*). These studies, however, have mainly concerned parous women. In the absence of
efficient pharmacological pain reduction methods, the importance of counselling and verbal anaesthesia is increasingly being emphasized (Bahamondes et al. 2014, Kaunitz and Nelson 2014).

**Uterine perforation**

Mechanical complications with intrauterine contraception are rare. An IUD may be fully outside the uterus or adherent, where removal by pulling visible threads is unsuccessful. An adherent IUD may be either partially perforating with the tail still in utero or embedded in the myometrium. In the case of an absent IUD, perforation and an intra-abdominal location must always be suspected, unless the woman is aware of expulsion. Perforation is the least likely option with missing strings, after unnoticed expulsion. In most cases the strings have retracted and the device is in place (Millen et al. 1978, Marchi et al. 2012)

**Mechanism of perforation**

Two different types of perforation have been proposed, immediate and late. In immediate perforation the uterine sound, the inserting tube or the IUD pierces the uterine wall at insertion and the IUD is either inserted directly into the abdominal cavity or later passes there through the iatrogenic opening of the uterine wall (Zakin et al. 1981a&b, Heartwell and Schlesselman 1983, Andersson et al. 1998). Proposed reasons for late perforation are discrepancy between the size of the IUD and that of the uterus, as well as uterine myometrial contractility gradually pushing the devices through the myometrium (Goldstuck and Wildemeersch 2014). Late perforation is supported by cases where the IUD has been seen normally positioned in utero prior to diagnosis of perforation (van Haudenhoven et al. 2006).
**Incidence and risk factors**
Both incidence and risk factors have been similar in prospective and retrospective studies. Table 4 summarizes results from prospective studies. Reported incidences are 0–2.2/1000 insertions with copper IUDs and 0.4–2.6/1000 insertions with the LNG-IUS (Andersson et al. 1998, Caliskan et al. 2003, van Haudenhoven et al. 2006). The post-partum period and breastfeeding are considered to be major risk factors as a result of uterine involution and increased contractility (Andersson et al. 1998, Caliskan et al. 2003, van Haudenhoven et al. 2006, van Grootheest et al. 2011). In addition to patient characteristics, HCP experience in the procedure, as well as an adequate insertion technique are crucial, as mentioned above. Perforations have occurred more often with inexperienced HCPs inserting fewer than 10 devices annually (Zakin et al. 1981a&b, Caliskan et al. 2003, Zhou et al. 2003, Harrison-Woolrych et al. 2003).

**Symptoms, severity, diagnosis and treatment**
The most common findings are abnormal bleeding and lower abdominal pain (van Grootheest et al. 2011). Missing threads in asymptomatic women (30%) are also a common finding (Gill et al. 2012). Reports of severe complications involving intestinal or bladder complications caused by a perforating IUD are rare, especially with modern T-shaped devices (Zakin et al. 1981a, Gill et al. 2012). Pregnancy may be the only reason to suspect misplacement of the device, especially with a copper IUD (Sivin and Stern 1979, Zakin et al. 1981a, Andersson et al. 1998).

If the IUD cannot be seen in vaginal ultrasonography, intra-abdominal misplacement can be confirmed with an abdominal X-ray. If the IUD is not detected in an X-ray, the device has been expelled (Boortz et al. 2012). Investigators in large case studies have recommended immediate removal in symptomatic cases and in relation to IUDs with a closed shape enabling intestinal herniation via the device, as these have been related to severe intestinal complications and morbidity (Zakin et al. 1981a, Gill et al. 2012). In contrast, the need to remove perforating T-shaped devices in asymptomatic cases has been questioned in many reports (Zakin et al. 1981b, Adoni and Chetrit 1991,
Markovitch et al. 2002, Haimov-Kochman et al 2003a). When treated, the procedure of choice is laparoscopy in cases of intra-abdominal location or partial perforation (Adoni and Chetrit 1991, Gill et al. 2012). Laparotomy can and should be avoided primarily, as the morbidity associated with the operation is greater than that in connection with the perforation itself in most cases (Adoni and Chetrit 1991, Gill et al. 2012, Mosley et al. 2012).
### Table 4. Studies on the incidence and risk factors of uterine perforation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study and devices included</th>
<th>Perforations/subjects</th>
<th>Incidence/1000 insertions</th>
<th>Identified risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartwell &amp; Schleselmann 1983</td>
<td>Case-control Cu-IUDs</td>
<td>32 / 529</td>
<td>-</td>
<td>Lactating vs. not lactating*** RR 10.1 (4.9–20.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Delivery &gt;2months (non-lactating) vs. nulliparous RR 9.0 (1.6–49.3)</td>
</tr>
<tr>
<td>Sivin and Stern 1994</td>
<td>Prospective LNG-IUS, NovaT</td>
<td>? / 2226</td>
<td>0–0.01 (1/100 years)</td>
<td>Not analysed</td>
</tr>
<tr>
<td>Caliskan et al. 2003*</td>
<td>Prospective Cu-IUDS</td>
<td>18 / 8343</td>
<td>2.2</td>
<td>Post-partum period vs. &gt; 12months post-partum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0-3 months OR 11.7 (2.8–49.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-6 months OR 13.2 (2.8–6.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prior abortion RR 2.1 (1.2–3.6)**</td>
</tr>
<tr>
<td>Harrison-Woolrych et al. 2003</td>
<td>Prospective Multiload 375</td>
<td>28 / 17469</td>
<td>1.6</td>
<td>Inexperienced inserter RR 2.3-7.3 (0.94–56.3)</td>
</tr>
<tr>
<td>Zhou et al. 2003</td>
<td>Prospective LNG-IUS</td>
<td>3 / 3519</td>
<td>0.9</td>
<td>To few cases to analyse.</td>
</tr>
<tr>
<td>Heinemann et al. 2014</td>
<td>Prospective LNG-IUS, Cu -IUDs</td>
<td>66 / 61380</td>
<td>1.2***</td>
<td>Lactating vs. not lactating**** RR 6.1 (3.6–10.1)</td>
</tr>
</tbody>
</table>

OR, Odds ratio; RR, risk ratio; CI, confidence interval. * nulliparity seen as a risk, only 2 nulliparous cases included in the study
**method unspecified **** LNG-IUS, 1.1; Copper IUDs, 0.9. **** time since last delivery NS.
Pelvic inflammatory disease and risk of infertility

With increasing popularity of intrauterine contraception in the 1970s, an increase in PID and subsequent tubal infertility was observed, especially in nulliparous women (Ory 1978, Cramer et al. 1985). Infertility was also seen in nulliparous former IUD users with no apparent history of PID, a factor later linked to asymptomatic PID (Gareen et al. 2000). Conclusions in many studies were to limit the use of IUC in nulliparous women. Further studies, however, identified multiple partners and the subsequent increased risk of sexually transmitted diseases (STDs) and PID in these women as the key risk factor, regardless of parity or age (Scott 1978, Osser et al. 1978, Luukkainen et al. 1979, Cramer et al. 1985, Lee et al. 1988, Struthers 1991). The risk of PID was extensively analysed in large studies performed by the WHO and the results supported findings in earlier smaller studies. An overall 1.5- to 2-fold risk of PID in women using any type of IUD was found compared with women using no contraception (Lee et al. 1983, Farley et al. 1992). The Dalkon shield differed from other studied devices, with an overall risk ratio of 8.4, equally elevated in both nulliparous and parous women. However, the elevated risk associated with all other types of devices was only present shortly after insertion, except for the Dalkon shield, with a 15-fold risk during long-term use (Lee et al. 1983). Although some increase in risk was seen in nulliparous women, further grouping revealed that this was accounted for by young age and greater risk of STDs, and not parity (Farley et al. 1992). In a different cohort a twofold risk of PID was also seen in older and parous women in monogamous relationships during the first months of use (Lee et al. 1988). Further studies by the WHO identified the risk of PID to be increased for only 20 days post-insertion.

Conclusions have been that the risk of PID is increased shortly after insertion, but lifestyle factors, i.e. multiple partners and the related increased risk of STDs affect this risk (Lee et al. 1983, Lee et al. 1988, Farley et al. 1992). Data on the risk of PID after IUD insertion in STD-infected women compared with infected women not having an IUD inserted is still inconclusive (Grimes 2000). Pre-insertion counselling and
assessing the risk of STDs in all women is therefore recommended at insertion. In the event of an STD, this should be treated, but the device need not be removed (Caddy et al. 2014). Prophylactic pre-insertion antibiotics have not been found useful and are thus not recommended (Grimes and Schulz 2001, Caddy et al. 2014).

Infertility has been linked to the presence of Chlamydia trachomatis antibodies, and not to past copper IUD use (Hubacher et al. 2001). This link was not known in the early 1970s, when the increased infertility rates caused concerns (Paavonen 2012). The copper IUD does not reduce the risk of PID, as has been the finding with systemic hormonal contraception (Senanayake and Kramer 1980) and the LNG-IUS (Toivonen et al. 1991, Berenson et al. 2013), a factor linked to thickening of the cervical mucus forming a barrier between the vagina and the uterus. Return to fertility and pregnancy rates after removal of copper IUDs (Skjeldestad and Bratt 1987, Bastianelli et al. 1998, Mansour et al. 2011) and the LNG-IUS (Bednarek and Jensen 2010, Mansour et al. 2011) have been found normal and similar to those in women not using contraceptives or using barrier methods only.
Continuation of intrauterine contraception

Uterine size

Along with earlier concerns of infertility related to copper and inert devices, smaller uterine size in nulligravid/nulliparous women and concerns about increased rates of expulsion, bleeding and pain related to this still limit the use of IUC in these women. Sound measures in IUD studies among nulligravid and nulliparous women have varied between 5 and 11 cm, with a mean of 7 cm (Suhonen et al. 2004, Brockmeyer et al. 2008, Marions et al. 2011) and a similar result, mean 7 cm (6–9 cm) was reported in nulligravid adolescents (Bayer et al. 2012). Results in parous women are similar, mean 7–7.5 cm (Andersson et al. 1994).

Uterine size increases with parity and also some extent age. Table 5 summarizes results from studies using either mechanical or imaging techniques to evaluate uterine cavity size. Three of the studies summarized in the review compared different measuring techniques in the same subjects (mechanical vs. hysteroscopy vs. post-hysterectomy measurement, mechanical vs. ultrasonography, and hysteroscopy vs. transvaginal vs. transabdominal ultrasonography). The different methods showed very similar results (Goldstuck 2012).

Table 5. Results from a review summarizing published studies on uterine size. Measurements are presented as mm±SD. Goldstuck 2012.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Parity</th>
<th>Mechanical measurements*</th>
<th>Imaging measurements*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cavity width</strong></td>
<td>Nulliparous</td>
<td>25.1 (17.8–32.2)</td>
<td>28.2 (21.0–33.0)</td>
</tr>
<tr>
<td></td>
<td>Multiparous</td>
<td>34.9 (23.4–53.0)</td>
<td>32.1 (26.0–38.0)</td>
</tr>
<tr>
<td><strong>Cavity length</strong></td>
<td>Nulliparous</td>
<td>33.7 (18.0–42.1)</td>
<td>37 (-)</td>
</tr>
<tr>
<td></td>
<td>Multiparous</td>
<td>38.6 (20.6–40.3)</td>
<td>44.3 (29.0–64.0)</td>
</tr>
</tbody>
</table>

* Wing Sound I-II, Cavimeter, Wang device, Batelle caliper, Novasure probe

** Hysteroscopy, ultrasonography
In the few studies on uterine size in women using intrauterine contraception, a large proportion of the studied women have had measurements smaller than modern devices, regardless of parity (Kurz 1984, Benacerraf et al. 2010, Canterio et al. 2010). Studies comparing uterine size women of different parity are summarized in Table 6.

Table 6. Results from studies evaluating uterine size by parity.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Parity</th>
<th>Fundal width (mm, mean±SD)</th>
<th>Cavity length (mm, mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nulligravid</td>
<td>Nulliparous</td>
</tr>
<tr>
<td>Kurz et al. 1984</td>
<td>n = 795</td>
<td>23.1±3.1</td>
<td>23.8±3.3</td>
</tr>
<tr>
<td>Cavimeter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benacerraf et al. 2010,</td>
<td>n = 184</td>
<td>27.1±6.7</td>
<td>28.3±7.5</td>
</tr>
<tr>
<td>3-D ultrasonography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasson 1974</td>
<td>n = 336</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wing Sound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurz et al. 1984</td>
<td>n = 795</td>
<td>31.8±4.8</td>
<td>32.2±5.1</td>
</tr>
<tr>
<td>Cavimeter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canteiro et al. 2010</td>
<td>n = 570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-D ultrasonography</td>
<td>-</td>
<td>37.0</td>
<td>38.4 (≥1 deliveries)</td>
</tr>
<tr>
<td>Sound measure</td>
<td>-</td>
<td>38.4</td>
<td>42.5 (≥1 deliveries)</td>
</tr>
</tbody>
</table>

The study by Kurz et al., who evaluated uterine size with a mechanical device, revealed that the overall cavity length was 33.3±2.0 mm (mean ±SD) and width 24.6 ± 2.9 mm. The study included women aged 15–44 years and of differing parity. Both fundal width and cavity length was more dependent on parity than age, but no significant correlation between either age or parity and size could be demonstrated. The study by Hasson revealed an average cavity length of 36 mm, with a clearer difference between nulliparous and parous women, but no significant
difference between women of different age groups (<20 to >40 years old). In the study by Canterio et al. the average cavity length was 36.8mm ± 6.1, with small differences in ultrasound measurements between women of different parity. However, 36% of all participants had a cavity length shorter than the studied devices (32 mm and 36 mm), regardless of parity. Another study, involving abdominal ultrasonography, demonstrated a clear correlation between increasing size versus the presence of menarche, adolescence and parity (Gadelha Da Costa et al. 2004). When comparing uterine size in adolescents aged 10–19 (n = 477) with adult women aged 20–40 (n = 351) the authors found that nulliparous and primiparous adolescents a had significantly smaller uterine volume than older women of similar parity. After two pregnancies, age no longer correlated with uterine size.

Uterine size also varies with the menstrual cycle, with the cavity being smallest at the beginning of the cycle (Hasson 1974, Wang 1982).

**Uterine size and intrauterine contraception**

Earlier inert devices relied on large size in relation to the uterine cavity for contraceptive efficacy. With the development of smaller devices better shaped to fit the uterine cavity, problems with excessive bleeding, pain and expulsion have been reduced. High complication rates seen with inert devices and prior copper-releasing models are considered a consequence of incompatibility between the device and the size of the uterine cavity, causing trauma to the endometrium and cramping of the uterus (Tejuja 1969, Kamal et al. 1971, Hasson et al. 1976, Goldstuck 1982, Hubacher 2007, Wildemeersch et al. 2013).

A normal cavity is considered to be the shape of a triangle. However, early studies using hysterography or silicon or rubber molds to depict the uterine cavity have demonstrated great variations in the shape of the uterine cavity (Hasson 1974, Wang 1982, Goldstuck 2012). Expulsions and complications with the Chinese stainless steel ring in one large study were related to abnormally shaped uteri, including both short, and wide as well as long and narrow cavities and bicornic uteri.
(Wang 1982). In earlier studies on copper-T IUDs, optimizing both the width of the horizontal arm (Hasson 1984, Kurz et al. 1984) and the length of the vertical stem (Kaivola 1986) in accordance with mechanically taken measurements improved user satisfaction and continuation rates. Clinical comparison between the smaller LNG-IUS 13.5 mg (28 x 30 mm) and the LNG-IUS (32 x 32 mm) across parity groups has not demonstrated differences in clinical outcome (Gemzell-Danielsson et al. 2012), but uterine size was not evaluated.

Recently, physicians found a significant difference in uterine cavity width between women with an embedded or abnormally positioned IUD (25 ± 8 mm) and women with normally positioned devices (32 ± 10 mm, Shipp et al. 2010). The same group found that women with an abnormally positioned IUD were twice as likely to complain of bleeding or pain in comparison with those with a normally placed IUD, 75% vs. 35% (Benacerraf et al. 2009). Similar studies on current models assessing the relationship between uterine length and adverse events are not available. However, expulsion does not seem to be related to short uterine length (Bahamondes et al. 2011a).

Opinions on whether or not smaller devices are needed differ. Concerns have also led to the development of the frameless copper device, but results in studies have not proven its superiority over the framed TCu380 models currently most used (O’Brien and Maarfleet 2006). In earlier studies on different models of copper devices the majority have revealed better performance with smaller devices in nulliparous women (Hubacher 2007). During the last decade the TCu380 has been recommended as the copper device of choice, as it has been found to have the best clinical and contraceptive performance (O’Brien et al. 2008). Recent studies mainly concern this device and the LNG-IUS, all with good outcome in both nulliparous and parous women (Lete et al. 1998, Brockmeyer et al. 2008, Bahamondes et al. 2011b, McNicholas et al. 2012, Berenson et al. 2013, Aoun et al. 2014).
Expulsion

When comparing different copper devices, many trials have revealed smaller expulsion rates with smaller devices, but the data is inconsistent. Expulsion rates range from 1.8–12.7% at 12 months and 2.5–13% at 24 months with models of different sizes and shapes (Hubacher 2007). Similarly, when comparing the same differently sized and shaped devices between women of different parity, most trials have revealed more expulsions in nulliparous women compared with parous women. Only with the currently used TCu380 models have rates been similar or lower in nulliparous women, 3.3% to 6.2% (Hubacher 2007).

With the LNG-IUS, expulsion rates have been similar or lower in nulligravid/nulliparous women in comparison with parous women. One year rates are 1–6% (Suhonen et al. 2004, Bahamondes et al. 2011b, Marions et al. 2011, Madden et al. 2014) in comparison with 2–8% in parous women (Jensen et al. 2008, Bahamondes et al. 2011b, Aoun et al. 2014). At three years the cumulative rates of expulsion have also been similar or lower in nulligravid/nulliparous women, 6.7%–6.9% vs. 5.8%–12.2% in parous women (Behringer et al. 2011, Madden et al. 2014). Recent studies have compared the LNG-IUS against the 4-mm-longer TCu380A used in the U.S. Expulsion rates with the copper device have been twofold in comparison with the LNG-IUS, not differing with parity (Bahamondes et al. 2011a, Aoun et al. 2014, Madden et al. 2014).

When comparing adolescents (aged ≤ 20 years) with adult women (aged > 20 years) of similar parity, results differ between studies. With both the TCu380A and the LNG-IUS, both similar rates (Aoun et al. 2014) and doubled rates of expulsion (Behringer et al. 2011, Madden et al. 2014) have been reported in adolescents.
Continuation rates and reasons for discontinuation in nulligravid/nulliparous and young women

Continuation rates at one and two years with current copper devices and the LNG-IUS are superior to those connected with all short acting contraceptive methods, regardless of parity and age (WHO 2010, O’Neil-Callahan 2013; Table 2). Age affects continuation rates with all contraceptives, as younger women tend to discontinue more often as a result of a desire for pregnancy, but also because of adverse events and, especially in the youngest group, financial problems. Adolescents are twice as likely as adult women to discontinue any form of contraception (O’Neil-Callahan 2013). Although this age group also discontinues LARC methods more often than adult women, the difference seen between the discontinuation rates with LARC methods is small between age groups (McNicholas et al. 2014).

Studies carried out to evaluate continuation rates in nulliparous women using the LNG-IUS include a large proportion of nulligravid women. Continuation rates at one year in these women are similar or superior to those in parous women, 80–93% (Suhonen et al. 2004, Jensen et al. 2008, Bahamondes et al. 2011b, Behringer et al. 2011). When dividing nulligravid/nulliparous adult women by age and comparing women of < 25 years of age with older women, the findings remain the same (Marions et al. 2011). In a long-term study on parous women using the NovaT IUD (32 x 32 mm) or the LNG-IUS (32 x 32 mm), the only difference between age groups was higher removal rates because of a desire for pregnancy in women younger than 30 years of age (Andersson et al. 1994), but continuation rates were similar with both devices (Andersson et al. 1994, Sivin and Stern 1994). Comparative studies with the TCu380A (32 x 36 mm) used in the U.S. and the LNG-IUS, including nulligravid/nulliparous and parous women, indicate continuation rates overall are somewhat lower with the copper device, but similar across parity groups (Berenson et al. 2013, Aoun et al. 2014). In the study by Aoun et al. (2014), nulliparous women reported more dysmenorrhoea, but continuation rates were not affected. Other copper devices have not been compared with the LNG-IUS in large
studies. Continuation rates in adolescents (aged ≤ 20 years) using the LNG-IUS do not differ from those in adult women (Behringer et al. 2011, Marions et al. 2011, Berenson et al. 2013). However, comparative studies with TCu380 models and the LNG-IUS have revealed higher rates of discontinuation with the copper device in adolescents, mainly because of pain (Rosenstock et al. 2012, Berenson et al. 2013, Aoun et al. 2014). Discontinuation as a result of bleeding disturbances does not differ between parity or age groups with either type of device (Andersson et al. 1994, Bahamondes et al. 2011b, Behringer et al. 2011, Berenson et al. 2013, Aoun et al. 2014), with 1–5% requesting removal for this reason (Bahamondes et al. 2011b, Behringer et al. 2011), although the proportion reporting changes or disturbances in menstruation is significantly greater in all women using IUC.

The contraceptive efficacy of the NovaT has been compared with that of the LNG-IUS only in parous women, the results being similar with both devices (Sivin and Stern 1994). In contrast, the efficacy of the TCu380A used in the U.S. has been somewhat lower than that of the LNG-IUS across all age groups and parities in adult women, although pregnancy rates with both devices are low (Berenson et al. 2013, Aoun et al. 2014, McNicholas et al. 2014, Heinemann et al. 2015). Most studies indicate comparable contraceptive efficacy of both types of IUC in adolescents and adult women, but the study by Berenson et al. (2013), including 90 000 women, revealed a significantly higher risk for pregnancy with both devices in adolescents compared with women aged ≥ 25 years (OR 1.42 1.13–1.79), but not compared with women aged 20–24 years.
**Current guidelines**

With positive results on safety and user satisfaction associated with modern IUC, as well as excellent contraceptive efficacy, current guidelines strive to promote its use globally, and especially in young and nulligravid/nulliparous women. The medical eligibility criteria for contraceptive use, published in 2010 by the WHO, cautiously recommend IUC for both women under the age of 20 and adult nulligravid/nulliparous women (category 2/4 = generally use the method), stating that data on the risk of infertility remains conflicting, but evidence supporting the safety of IUD use in these women is increasing (WHO 2010). Newer national guidelines recommend LARC, including intrauterine contraception, as first-line contraception in both adolescents and nulligravid/nulliparous women (ACOG 2012, CDC 2013, NICE 2014). Finland currently has no national guideline on contraceptive use, but the Finnish National Institute for Health and Welfare (THL) recommends IUC to be promoted among nulligravid/nulliparous women (THL2014c).
6. AIMS OF THE STUDY

The aims of the prospective study on nulligravid women were:

• To assess IUD insertion in nulligravid women and to identify factors related to difficulties at IUD insertion.

• To assess bleeding, pain and user satisfaction among nulligravid women during the first year of use with the LNG-IUS or a copper-releasing IUD (NovaT®, TCu380Ag).

• To assess the potential effects of uterine size, evaluated by ultrasonography, on IUD insertion and long-term use.

The aims of the registry-based study were:

• To examine the incidence of and factors associated with uterine perforation in connection with IUD use in Finland.

• To evaluate the clinical course and findings at surgery among women treated for IUD perforation.
7. SUBJECTS AND METHODS

Prospective study on nulligravid women and uterine size

The study was carried out at the Centralized Family Planning of the City of Helsinki. Women who contact the clinic with a request for contraception are counselled by trained midwives. Nulligravid women aged 18 or above requesting their first IUD after contraceptive counselling, either the LNG-IUS or a copper-releasing device, were invited to join the study. Inclusion and exclusion criteria are shown below (Table 7).

Between January 1st, 2011 and July 31st, 2012 we enrolled 165 women. The women were given a free choice between the devices used in the study, the LNG-IUS (Mirena®) and the copper-releasing device NovaT® (TCu380Ag). Both devices are T-shaped, have frames of equal size and measure 32 x 32mm. The inserting tubes of the devices, however, differ in size as the hormonal cylinder of the LNG-IUS makes its vertical arm slightly wider. The traditional LNG-IUS inserter has an outer diameter of 4.75 mm and the newer inserter a diameter of 4.40 mm. As the new inserter was introduced during the study period, both were used

### Table 7. Inclusion and exclusion criteria in the study on nulligravid women.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 years</td>
<td>Known structural uterine abnormality</td>
</tr>
<tr>
<td>Resident of Helsinki</td>
<td>Submucous or intramural fibroid</td>
</tr>
<tr>
<td>No prior pregnancies</td>
<td>Acute gynaecological infection</td>
</tr>
<tr>
<td>No contraindication to IUD use</td>
<td>Suspicion of gynaecological malignancy</td>
</tr>
<tr>
<td>Understands Finnish or Swedish (language in diaries)</td>
<td>In addition, with the copper-releasing IUD:</td>
</tr>
<tr>
<td></td>
<td>Bleeding disorder</td>
</tr>
<tr>
<td></td>
<td>Heavy bleeding causing anaemia</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td></td>
<td>Allergy to copper or nickel</td>
</tr>
</tbody>
</table>
according to availability. Any possible effect on insertion of the differing size of the inserters was tested before proceeding with analyses. The insertion tube of the copper IUD has an outer diameter of 3.65 mm.

One experienced gynaecologist (SS) treated all the women, and interviewed them as regards demographic and menstrual characteristics prior to insertion. Women using hormonal contraception at the time were asked to report details of their spontaneous menstruation. They reported the amount of bleeding on a Likert scale of none, spotting, scanty, normal and heavy. In analyses, the first three categories were combined into one group, as women reporting no bleeding or spotting in spontaneous cycles were few. Similarly, the women reported menstrual pain as none, minimal, disturbing and severe. In analyses, the categories none and minimal were combined into one group, as only a few women reported no pain. Disturbing and severe menstrual pain was analysed both separately and as one group of dysmenorrhoea against the group of none to minimal pain. Table 8 summarizes subject characteristics.

The women were asked to take the equivalent of 800 mg of ibuprofen or 1000 mg of paracetamol one hour prior to the insertion, as is standard practice at the clinic, and to empty their bladders. Immediately before insertion, the gynaecologist measured the uterus using vaginal 2-D ultrasonography and carried out a clinical pelvic examination including measurement of uterine depth with a metallic sound. Uterine cavity length and cervical length were measured separately in a sagittal plane and summed to calculate total uterine length. Fundal width was measured at the widest possible point in a transverse plane. The uterine flexion angle was calculated as the angle between the cavity and the line of cervical length measurements (Figure 2). As uterine position (ante- vs. retroversion) was insignificant in analysis of insertion pain and difficulties, flexion angle was coded as ranging from 0 to 180 degrees, with 180 degrees being a straight uterus.
Table 8. Characteristics of the studied nulligravid women. Data are presented as median (range) unless otherwise specified.

<table>
<thead>
<tr>
<th></th>
<th>All women (n=165)</th>
<th>LNG-IUS (n=113, 68.5%)</th>
<th>Copper IUD (n=52, 31.5%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>24.0 (18-43)</td>
<td>23.0 (18-43)</td>
<td>25.0 (19-37)</td>
<td>0.03</td>
</tr>
<tr>
<td>Agegroups n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>11 (6.7)</td>
<td>9 (8.0)</td>
<td>2 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td>20-24</td>
<td>79 (47.9)</td>
<td>60 (53.1)</td>
<td>19 (36.5)</td>
<td>NS</td>
</tr>
<tr>
<td>25-35</td>
<td>68 (41.2)</td>
<td>39 (34.5)</td>
<td>29 (55.8)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;35</td>
<td>7 (4.2)</td>
<td>5 (4.4)</td>
<td>2 (3.8)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td>23.3 (16.9-55.2)</td>
<td>22.3 (16.9-42.6)</td>
<td>22.6 (17.7-55.2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Smoking n (%)</strong></td>
<td>40 (24.2)</td>
<td>30 (26.5)</td>
<td>10 (19.2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dyspareunia n (%)</strong></td>
<td>28 (17.0)</td>
<td>21 (18.5)</td>
<td>7 (13.5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dyschezia n (%)</strong></td>
<td>39 (18.2)</td>
<td>22 (19.4)</td>
<td>8 (15.4)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Abdominal pain other than menstrual n (%)</strong></td>
<td>70 (42.4)</td>
<td>52 (46.0)</td>
<td>18 (34.6)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Age at menarche</strong></td>
<td>12.0 (8-17)</td>
<td>12.0 (8-17)</td>
<td>13.0 (9-16)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Reported spontaneous bleeding n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>1 (0.6)</td>
<td>1 (0.9)</td>
<td>0 (-)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spotting or scanty</td>
<td>20 (12.1)</td>
<td>13 (11.5)</td>
<td>7 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>99 (59.3)</td>
<td>58 (51.3)</td>
<td>40 (76.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy</td>
<td>46 (27.9)</td>
<td>41 (36.3)</td>
<td>5 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days with bleeding</td>
<td>5 (0-39)</td>
<td>5 (0-39)</td>
<td>5 (3-8)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cycle length</strong></td>
<td>28 (21-135)</td>
<td>28 (21-135)</td>
<td>28 (21-80)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Reported menstrual pain n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or minimal</td>
<td>84 (50.9)</td>
<td>48 (42.8)</td>
<td>36 (69.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>50 (30.3)</td>
<td>36 (31.9)</td>
<td>14 (26.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe dysmenorrhoea</td>
<td>31 (18.8)</td>
<td>29 (25.7)</td>
<td>2 (3.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Days with menstrual pain</td>
<td>1.75 (0-7)</td>
<td>2 (0-7)</td>
<td>1 (0-4)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Need for analgesics at time of menses n (%)</strong></td>
<td>102 (61.8)</td>
<td>81 (71.7)</td>
<td>21 (40.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 2. Cavity length (A) and cervical length (B) were measured separately in a sagittal plane (left) and summed to calculate total uterine length (A+B). The flexion angle (C) was calculated by measuring the angle between the lines of the length measurements (A+B) in the sagittal plane. Fundal width (D), here demonstrated in an antero-posterior view, was measured at the widest point in a transverse plane.

Immediately after insertion the correct location of the IUD was checked ultrasonographically. Both the woman and the gynaecologist evaluated insertion pain on a Likert scale of none, mild, moderate, severe and intolerable. In addition, the gynaecologist evaluated the insertion by classifying the procedure as easy, difficult or failed and assessing the reason for a possible failed insertion. Cervical traction to straighten the uterus and the need of dilatation was recorded, as was the possible need of paracervical block (PCB) or use of misoprostol to soften the cervix. Only the use of metallic Hegar dilators was considered to be dilatation. PCB (lidocaine, 10 mg/mL) and sublingual misoprostol (0.4 mg) were used only in cases where pain or cervical tightness would have prevented the insertion.

After insertion women kept daily diaries on bleeding, pain and use of pain medication during two separate reference periods of 90 days. The 1st reference period started at the day of insertion (months 1–
3). The 2nd reference period comprised the last 90 days of the first year of IUD use (months 10–12). The women noted days with bleeding and days with spotting. In cases of lower abdominal pain, the women assessed the intensity as mild, equal to menstrual pain or exceeding menstrual pain.

All women were scheduled for two follow-up visits, the first one at three months and the second one at one year after insertion. They were asked to return their diaries at the visits. In addition, the women were asked to contact the clinic between scheduled visits if needed and in the case of a desire to discontinue IUD use. The first visit was primarily with a midwife, who interviewed the woman and checked the IUD threads. In cases of difficult insertion, difficulties during the first three months or missing threads, the gynaecologist examined the woman by means of vaginal ultrasonography. The one-year visit was to the gynaecologist performing insertions.

Diaries were analysed according to WHO recommendations (Belsey et al. 1986). Numbers of days of bleeding and spotting days in each reference period were counted separately as well as together. In addition, each month was studied separately. Numbers of episodes of bleeding and spotting and length of the episodes, cycles and bleeding/spotting-free intervals were noted and thus bleeding patterns could be assessed. One bleeding/spotting-free day was considered to belong to the episode surrounding it. Prolonged bleeding was defined as bleeding/spotting episodes lasting more than 14 days, frequent bleeding as more than five episodes per reference period and infrequent bleeding as 1–2 episodes per reference period. Results from diaries were also compared with the uterine measurements taken prior to insertion and with menstrual characteristics reported by the women.

**Ethics**
The Ethics Committee of the Hospital District of Helsinki and Uusimaa gave a positive statement (n:o 149/13/03/03/2010) as did the City of Helsinki Health Center (n:o 10-1137/054), and the study was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01685164).
**Statistical analysis**
Statistical analysis was carried out using SPSS Statistics Software 21.0 (IBM, New York, USA). Statistical significance was defined as $p < 0.05$. Chi-square and Fisher’s exact tests were used to compare categorial variables and the Mann–Whitney $U$ test was similarly used for continuous variables. Uterine measurements were initially analysed as continuous variables and tested against different parameters to find correlations. Measurements were then grouped by medians, quartiles and quintiles. In quartile and quintile analysis, groups were created by dividing uterine measurements into equally wide groups, not by making groups by number of women.

When seeking predictive size measurements, flexion angle and patient characteristics in relation to difficulties at IUD insertion, binominal and multiple regression were used. When searching for threshold measurements predicting insertion difficulties (easy vs. difficult-failed insertion) the Receiver Operating Characteristic (ROC) curves were used. For each measurement variable, different point estimates suggested on the curve were tested against difficulties at insertion to determine possible threshold measurements. Initial analyses were carried out separately by type of device and type of inserting tube used at insertion of the LNG-IUS, but as no significance was found in difficulty of insertion, the women were analysed as one group and type of IUD was used as a confounding variable.

Correlation between uterine measurements and bleeding, spotting and reported pain during follow-up was analysed by using Spearman’s correlation. When analysing diary data, linear regression was used to find predictive models for continuous variables and binominal logistic regression similarly for categorial variables. After grouping measurements by medians, quartiles or quintiles, the Mann–Whitney $U$ test was used to compare results between the IUD groups, as well as when analysing differences between bleeding and pain within each IUD group.
Registry-based study on uterine perforation

Women surgically treated for uterine perforation were identified from the nationwide Hospital Discharge Register by combining ICD-10 (International Classification of Diseases, 2010) and the operation codes of the Nordic Medico-Statistical Committee (NOMESCO 2010) Classification of Surgical Procedures (Table 9). There is currently no specific code for perforation caused by an IUD.

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Operative code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T83.3</td>
<td>JAL-10</td>
<td>Mechanical complication by an IUD</td>
</tr>
<tr>
<td>T19.3</td>
<td>JAL-11</td>
<td>Intrauterine foreign body</td>
</tr>
<tr>
<td>Z30.1</td>
<td>JAL-20</td>
<td>IUD insertion- and follow-up related codes</td>
</tr>
<tr>
<td>Z30.5</td>
<td>JAL-22</td>
<td>Removal of foreign body from the uterus</td>
</tr>
</tbody>
</table>

The study period was 15 years, starting on January 1\textsuperscript{st} 1996, when ICD-10 was introduced in Finland, and ending on December 31\textsuperscript{st} 2009. Hospital records were examined to assess patient characteristics, insertion-related data, pre-diagnostic symptoms and findings in surgery. As only records from the Hospital District of Helsinki and Uusimaa could be retrieved, the study was limited to women treated in this area. In the incidence calculations only cases with time of insertion falling inside the study period were included in order to exclude the possibility of some patients having been treated prior to the study and thus falsely lowering the incidence prior to 1996. When assessing the clinical course of the patients, only cases where the type of device could be defined were analysed. Figure 3 shows the study flowchart.
Figure 3. Flowchart of IUD-related uterine perforation studies.
The incidence of uterine perforation with an IUD was calculated by using sales figures provided by the pharmaceutical company marketing the LNG-IUS and the NovaT (Bayer AG, Berlin, Germany). The two devices account for more than 95% of all nationwide sold IUDs during the study period. Sales figures for a copper IUD marketed by another company could not be retrieved. As only patients treated within the Helsinki and Uusimaa area could be analysed, incidence was calculated using sales figures from this area. Devices sold in this area account for 29% of devices sold nationwide, as did the proportion of women identified from the nationwide register. Precise sales figures by geographical area are available for the LNG-IUS from 1997 and for copper-releasing devices from 2004. Numbers prior to this were estimated as 33% of devices sold nationwide annually for the LNG-IUS and 25% for the copper-releasing device according to recent precise geographical sales figures. The LNG-IUS has accounted for the great majority of sold devices in recent years (80–88%).

By analysing hospital records, data on patient characteristics, insertion, pre-diagnostic symptoms, clinical course and operative findings could be assessed. Patient characteristics are shown in Table 10.

**Ethics**
The Ethics Committee of the Hospital District of Helsinki gave the study a positive statement (n:o 51/13/03/03/2010) and the study was approved by the hospital. The Ministry of Social Affairs and Health (STM) and the National Institute for Health and Welfare (THL) gave their approval to use the registry data (n:o STM/1771/2010).

**Statistical analysis**
Statistical analysis was carried out using SPSS Statistics Software 18.0 (IBM, New York, USA). Statistical significance was defined as $p < 0.05$. The retrospective nature and lack of a control group limited analyses to a descriptive nature. The Mann–Whitney $U$ test, Chi-square tests and Fisher’s exact test were used to analyse and compare LNG-IUS users with women using copper IUDs.
Table 10. Selected demographic characteristics of women with surgically removed perforating or embedded IUDs. The data is presented as n (%) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>LNG-IUS n = 54</th>
<th>Copper IUD n = 21 *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 75</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (20-65)</td>
<td>35 (24-47)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23.2 (17.9-39.6)</td>
<td>22.8 (19.7-36.5)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Parous</td>
<td>53 (98)</td>
<td>21 (100)</td>
</tr>
<tr>
<td><strong>Prior vaginal delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 (89)</td>
<td>17 (81)</td>
</tr>
<tr>
<td><strong>Delivery within 12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing n = 2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 months</td>
<td>9 (17)</td>
<td>6 (28.5)</td>
</tr>
<tr>
<td>3-6 months</td>
<td>17 (31.5)</td>
<td>6 (28.5)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>7 (13)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>No recent delivery</td>
<td>20 (37)</td>
<td>5 (24)</td>
</tr>
<tr>
<td><strong>Breastfeeding at time of insertion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing n = 29 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (24)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>No</td>
<td>20 (37)</td>
<td>4 (19)</td>
</tr>
<tr>
<td><strong>Amenorrhea at time of insertion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing n = 43 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (24)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>No</td>
<td>8 (15)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Prior abdominal or gynaecological surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>3 (6)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Salpingectomy (ectopic pregnancy)</td>
<td>0</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Curettage</td>
<td>13 (24)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>- 1 procedure</td>
<td>5/13 (38)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>Leep treatment</td>
<td>5 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Intestinal surgery</td>
<td>4 (7)</td>
<td>3 (14)</td>
</tr>
</tbody>
</table>

*Fincoid 1, FlexiT 1, NovaT380Ag 13, unspecified type of Cu-IUD 6
8. RESULTS

STUDY ON NULLIGRAVID WOMEN

Type of IUD chosen
The majority, 113 women (68.5%), chose the LNG-IUS, while 52 women (31.5%) chose the copper IUD. Self-reported heavy menstrual bleeding (OR 7.02, 95% CI 2.32–21.18, p = 0.001) and dysmenorrhoea (OR 3.21, 95% CI 1.58–6.55, p = 0.001) affected choice towards the LNG-IUS. In particular, women with severe dysmenorrhoea chose the LNG-IUS (OR 14.00, 95% CI 2.37–82.72, p = 0.004).

Uterine measurements
Size measurements are shown in Figure 4 and flexion angles in Figure 5. As the quality of the ultrasonographic pictures was poor in four cases, 161 cases could be assessed. Measurements were small compared with the measurements of the IUDs. Cavity length was shorter than 32 mm in 53 women (32.9%) and fundal width smaller than 32 mm in 158 women (98.1%). The sound measure was 11.7 ± 7.9 mm (mean ± SD) longer than total uterine length measured by ultrasonography. Flexion angles ranged from 61 to 173 degrees, with a median of 121.5 degrees.
Figure 4. Uterine dimensions as measured by ultrasonography and sound measurement (median, 25th and 75th percentiles and min/max). Cavity area is presented as cm$^2$, other measurements as millimetres (mm).

Figure 5. Distribution of flexion angles. Median 121.5, range 61–173. The angle of a straight uterus is 180 degrees.
Insertion and effect of uterine size on insertion difficulties
Most insertions (n=147, 89.1%) were classified as easy, 86.7% (98/113) in the LNG-IUS group and 94.2% (49/52) in the copper IUD group (p=0.30). The type of inserting tube used in connection with the LNG-IUS was an insignificant factor. In addition to the standard metallic sound, a smaller silicone sound was needed to explore the cervical canal prior to insertion in 11 of these cases (6.8%)

Of the 15 (9.1%) difficult insertions, 13 (11.7%) occurred in the LNG-IUS group and two (3.9%) in the copper IUD group. Five difficult insertions required no additional cervical procedures. Metallic Hegar dilators were used in ten cases (6.2%), combined with PCB in six cases (3.7%) where pain would have prevented insertion otherwise. Misoprostol was used in combination with Hegar dilatation in three difficult cases (1.9%) with cervical stenosis.

Three insertions failed (1.8%); one because of pain (copper IUD), one because of a bicornic uterus preventing the IUD fitting properly (LNG-IUS), and one insertion was cancelled because of a hypoplastic uterus (LNG-IUS, total uterine length by ultrasonography 42 mm and sound measure 45 mm).

Analysis suggested a correlation between difficult insertion and small length measurements and flexion angles (Table 11). Uterine position (ante- vs. retroversion) and subject characteristics were insignificant.

<table>
<thead>
<tr>
<th>Table 11. Measurements by ease of insertion (median).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement</strong></td>
</tr>
<tr>
<td>Total uterine length (mm)</td>
</tr>
<tr>
<td>Cavity length (mm)</td>
</tr>
<tr>
<td>Cervical length (mm)</td>
</tr>
<tr>
<td>Fundal width (mm)</td>
</tr>
<tr>
<td>Uterine cavity area (cm²)</td>
</tr>
<tr>
<td>Flexion angle (degrees)</td>
</tr>
</tbody>
</table>
With every increasing millimetre in total length (OR 0.86, 95% CI 0.78–0.96, p = 0.006) and increasing degree of flexion angle (OR 0.96, 95% CI 0.93–0.99, p = 0.004) the odds of a difficult insertion decreased. Cavity and cervical length were not significant separately.

When grouping the women by uterine length smaller than the median (64.4 mm) was associated with a difficult insertion (OR 3.63, 95% CI 1.13–11.67, p = 0.03), both independently and when adjusting by type of IUD, absence of bleeding at insertion and patient characteristics shown in Table 10 (OR 5.59, 95% CI 1.01–28.89, p = 0.04). This was also seen as regards flexion angle (univariate analysis OR 5.36, 95% CI 1.48–19.47, p = 0.01 and multivariate analysis OR 5.82, 95% CI 1.54–21.98, p = 0.009). Grouping by quartiles of size did not reveal significant information. No predictive threshold measurements were found using the ROC curve, as the best point estimate predicted only 19–23% of difficult insertions for each measurement.

**Insertion pain**
Eighteen women (11.2%) reported mild pain, 49 women (30.4%) moderate pain, 91 women (56.5%) severe pain and three women (1.9%) intolerable pain. The physician commonly assessed pain as one step milder than did the woman undergoing insertion (p < 0.001). The absence of bleeding during insertion did not correlate with ease of insertion or pain experience. There was no difference in pain perception regards the two LNG-IUS insertion tubes. Women who had the copper IUD inserted experienced less severe pain and none experienced intolerable pain in comparison with women fitted with a LNG-IUS (OR 0.45, 95% CI 0.23–0.89, p = 0.02). However, when adjusted by level of menstrual pain this difference became insignificant (OR 0.6, 95% CI 0.29–1.22, p = 0.16). In univariate analysis only, every increasing millimetre in fundal width and cm² in cavity area decreased the odds of severe or intolerable pain, as did total length exceeding the median measurement. Other uterine size measurements were insignificant, as was multivariate analysis of all uterine measurements. Severe dysmenorrhoea was the only predictor of severe/intolerable
insertion pain and the odds ratio increased in multivariate analysis (Table 12).

Table 12. Odds of severe (n=91, 56.5%) and intolerable (n=3, 1.9%) insertion pain grouped by self-reported level of menstrual pain in spontaneous cycles.

<table>
<thead>
<tr>
<th>Menstrual pain</th>
<th>Univariate analysis*</th>
<th>Multivariate analysis**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>None/mild</td>
<td>83 (51.6)</td>
<td>reference</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>48 (29.8)</td>
<td>1.4 (0.7-2.9)</td>
</tr>
<tr>
<td>Severe dysmenorrhoea</td>
<td>30 (18.6)</td>
<td>5.1 (1.8-14.7)</td>
</tr>
</tbody>
</table>

*p = 0.009  
**p = 0.002  

Continuation rates and adverse events
The women were generally satisfied during follow-up. The study flowchart (Figure 6) shows continuation rates and Table 13 shows adverse events leading to IUD removal. The first diary was returned by 134 women (82.7% of the 162 women with a successful insertion), the second by 102 women (87.9% of the 116 women still using the IUD at one year) and both by 96 women (82.7% of the 116 women still using the IUD at one year).

Table 13. Adverse events causing discontinuation n (%).

<table>
<thead>
<tr>
<th></th>
<th>LNG-IUS n = 10/93 (10.8%)</th>
<th>Copper IUD n = 7/42 (16.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expulsion</td>
<td>3 (3.2)</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Bleeding / pain</td>
<td>4 (4.3)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Acne</td>
<td>2 (2.2)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Premenstrual symptoms</td>
<td>1 (1.0)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

p-values NS.

Women discontinuing because of expulsion or disturbing bleeding or pain had similar uterine measurements as those continuing IUD use. In univariate analyses, expulsion was associated with difficult insertion (OR
6.7, 95% CI 1.1–41.8, p = 0.04), obesity (BMI > 30 kg/m², OR 15.3, 95% CI 2.6–88.0, p = 0.002) and dyspareunia before IUD insertion (OR 6.22, 95% CI 1.6–33.3, p = 0.03). In multivariate analysis only obesity persisted as a factor predicting expulsion (OR 10.0, 95% CI 1.5–67.1, p = 0.02).

**Figure 6.** Flowchart of study participants. LNG-IUS = levonorgestrel-releasing intrauterine system, Copper IUD = copper-releasing intrauterine device, NovaT.
Results from diaries concerning bleeding and pain
With both devices a high number of bleeding/spotting days occurred during the first month, but thereafter a rapid decrease was seen. Bleeding/spotting stabilized after the first month among copper IUD users, while it continued to decrease month by month among LNG-IUS users (Figure 7). There was no statistically significant difference in the median number of bleeding/spotting days between the two groups in the 1st reference period (months 1–3, p = 0.21).

Figure 7. Median numbers of bleeding/spotting days per month with 25th and 75th percentiles.
By the 2\textsuperscript{nd} reference period both bleeding and spotting days had decreased significantly among LNG-IUS users in comparison with copper IUD users (median decrease 28 vs. 10 days respectively, p < 0.001). Amenorrhoea and spotting-only was common among LNG-IUS users, while all copper IUD users experienced bleeding days throughout the study period (Table 14).

\textbf{Table 14. Proportion of women (%) with bleeding patterns classified by WHO criteria.}

<table>
<thead>
<tr>
<th>Bleeding pattern</th>
<th>Reference period</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LNG-IUS months 1-3</td>
<td>LNG-IUS months 10-12</td>
<td>Copper IUD months 1-3</td>
<td>Copper IUD months 10-12</td>
<td></td>
</tr>
<tr>
<td>Regular bleeding</td>
<td>8.8</td>
<td>27.0</td>
<td>23.2</td>
<td>64.2</td>
<td></td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>0</td>
<td>25.7</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Spotting only</td>
<td>1.1</td>
<td>14.9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infrequent bleeding</td>
<td>14.3</td>
<td>23.0</td>
<td>2.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>57.1</td>
<td>1.4</td>
<td>27.9</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>14.3</td>
<td>4.1</td>
<td>27.9</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

During the first month after insertion the total number of days with pain was similar in both groups; median 12 among LNG-IUS users and 11.5 among copper IUD users. As seen with bleeding/spotting, pain stabilized after the first month in copper IUD users (to 4-6 days), while continuing to decrease to a monthly median of 0–1 before the 2\textsuperscript{nd} reference period among LNG-IUS users. In the 1\textsuperscript{st} reference period there was no difference in reported number of days with pain between groups. In the 2\textsuperscript{nd} reference period copper IUD users reported more pain than LNG-IUS users (p <0.001).
Impact of subject characteristics on bleeding and pain

Spontaneous bleeding affected bleeding with the LNG-IUS, but not with the copper IUD. LNG-IUS users reporting scanty spontaneous bleeding had fewer bleeding/spotting days throughout the study in comparison with those reporting normal or heavy bleeding; median 13 vs. 37 and 38.5 days, respectively in the 1st reference period \( (p = 0.02) \), and respectively, median 0 vs. 10.5 and 10.5 days in the 2nd reference period \( (p = 0.03) \). Scanty bleeding predicted amenorrhoea in the 2nd reference period both independently \( (\text{OR} \ 7.93, 95\% \text{ CI} \ 1.73–36.46, \ p=0.008) \) and when tested against uterine measurements \( (\text{OR} \ 8.17, 95\% \text{ CI} \ 1.38–48.21, \ p = 0.02) \). Similarly smoking predicted amenorrhoea both independently \( (\text{OR} \ 3.60, 95\% \text{ CI} \ 1.18–11.00, \ p = 0.03) \) and when tested against bleeding characteristics and uterine measurements \( (\text{OR} \ 8.23, 95\% \text{ CI} \ 1.76–38.56, \ p = 0.007) \).

Menstrual pain prior to IUD insertion correlated with reported pain during IUD use. During the 1st reference period LNG-IUS users with no or mild menstrual pain reported less pain \( (\text{median} \ 14 \text{ days}) \) in comparison to women with dysmenorrhoea \( (\text{median} \ 20.5 \text{ days}) \), and particularly severe dysmenorrhoea \( (\text{median} \ 34.5 \text{ days}, \ p < 0.001) \). This was also seen in the 2nd reference period \( (\text{median} \ 1 \text{ vs.} \ 6.5 \text{ and} \ 9.0 \text{ days}, \text{respectively}, \ p = 0.02) \).

Among women using the copper IUD, a similar difference between different categories of menstrual pain was seen in the 1st reference period \( (\text{median} \ 20 \text{ vs.} \ 35 \text{ and} \ 45 \text{ days}, \ p = 0.01) \). During the 2nd reference period there was no difference in reported number of total days with pain \( (\text{median} \ 17–18 \text{ days}) \). However, the only two women with severe dysmenorrhoea had discontinued the study \( (\text{pain, lost to follow-up}) \).

A painful or difficult insertion was not associated with pain during IUD use.
**Uterine size and bleeding**

Among LNG-IUS users, increasing size measurements correlated with more bleeding/spotting and spotting-only days in both reference periods. As this association was not found for bleeding-only days, the significance can be assumed to concern spotting primarily. Increasing total uterine length (correlation coefficients $r = 0.27$ and $0.28$, $p = 0.01$), cavity length ($r = 0.29$ and $0.32$, $p = 0.01$) and cavity area ($r = 0.22$ and $0.33$, $p < 0.001$) correlated with more bleeding/spotting days in the $1^{\text{st}}$ reference period. This was confirmed when grouping women by uterine size (Figure 8). In both median and quartile analysis, fewer bleeding/spotting days were seen with smaller measurements. In addition, in quartile analysis, women with the smallest measurements consistently reported the fewest number of bleeding/spotting days. No significant correlations between uterine size and bleeding were found among copper IUD users (Figure 9).

Uterine size was also tested against reported spontaneous bleeding and no significant relationships were found. However, there was a trend towards women reporting scanty bleeding having measurements below the median, while the distribution among women with normal or heavy bleeding was more even. When dividing by quartiles, the measurements in women with scanty bleeding were equally distributed between the $1^{\text{st}}$ and $2^{\text{nd}}$ quartiles.
Figure 8. Median numbers of days of bleeding/spotting among the LNG-IUS users as grouped by uterine size. Quartiles represent results by dividing each measurement into four equally wide size groups, with the number of women in each group varying. Significant differences are shown.
Figure 9. Median numbers of days of bleeding/spotting among the copper IUD users as grouped by uterine size. Quartiles represent results by dividing each measurement into four equally wide size groups, with the number of women in each group varying. No significant differences were found.
Uterine size and pain
Among LNG-IUS users, no correlation between reported pain and uterine size measurements, when analysed as continuous variables, were found in either reference period. When grouping by median measurements, women with smaller measurements reported less pain (Figure 10). In the 2nd reference period, again women in the smallest size quartile reported the least pain. As with bleeding/spotting days, those with the widest fundal width reported markedly more pain in comparison with other women. In multivariate analysis including menstrual pain and uterine measurements, increasing fundal width was still associated with intense pain (exceeding menstrual pain) in the 2nd reference period (p = 0.01). Dysmenorrhoea and severe dysmenorrhoea remained the only significant predictors of total days with pain in both reference periods when tested against all other measurements.

Among copper IUD users neither uterine measurements (Figure 11) nor patient characteristics were significant predictors of pain.
**Figure 10.** Median numbers of days of pain among the LNG-IUS users as grouped by uterine size. Quartiles represent results by dividing each measurement into four equally wide size groups, with the number of women in each group varying. Significant differences are shown.
Figure 11. Median numbers of days of pain among the copper IUD users as grouped by uterine size. Quartiles represent results by dividing each measurement into four equally wide size groups, with the number of women in each group varying. No significant differences were found.
**STUDY ON UTERINE PERFORATION**

**Incidence of perforation**
The incidence study involved 51 women treated for perforation with an LNG-IUS and 17 women with copper IUDs. As annual sales numbers were markedly higher for the LNG-IUS, the incidence of perforation was similar with both types of device, 0.4/1000 insertions.

**Insertion and patient characteristics**
General practitioners had inserted 27 (40%) and gynaecologists 22 (29%) of the devices. Data on the inserting HCP was missing in 21 cases (31%). Five devices (7%) had been inserted under general anaesthesia because of previous problems at insertion, or following curettage or hysteroscopy. These women had not delivered within the previous year. In 11 cases (16%) the hospital physician examining the woman at diagnosis had commented on extensive flexion of the uterus.

Only one woman was nulliparous. In 45/68 cases (66.0%), the woman had delivered less than one year prior to IUD insertion (Table 10). One woman had delivered by Caesarean section more than three months prior to insertion; all other deliveries were vaginal. Thirty-eight devices (55.9%) had been inserted less than six months post-partum and 15 devices (22.1%) less than three months post-partum. Twenty-two women (32.3%) were known to have been breastfeeding at the time of IUD insertion and 17 breastfeeding women (25.0%) were amenorrhoeic. Breastfeeding women more often reported pain at insertion than women not breastfeeding (75% vs. 64%, p = 0.009).

**Clinical course of perforations**
The type of device could be specified in 75 cases, 54 women used the LNG-IUS (72%) and 21 women a copper IUD (28%). Complaints of abnormal bleeding, lower abdominal pain or both, in combination with missing threads or an adherent IUD led to diagnosis in all 53 symptomatic women (71%, Figure 12). Asymptomatic women (n = 22, 29%) were diagnosed at routine follow-up visits when threads were
missing or in relation to unintended pregnancy. Pregnancies (n = 11) occurred more often following perforation with a copper IUD (n = 7/21, 33% of women) than with the LNG-IUS (n = 4/54, 7%, p = 0.009). One tubal pregnancy (LNG-IUS group) was diagnosed, while ten pregnancies were intrauterine. One woman had a miscarriage, seven chose termination and two continued their pregnancies successfully. The only patient with symptoms of infection (PID) had had the LNG-IUS inserted 4 years prior to symptoms and presented with an unintended pregnancy. At surgery, however, the IUD was high up in the omentum and unrelated to any infection.

Figure 12. Clinical symptoms of the 75 women diagnosed with perforation by the LNG-IUS (n = 54) or by a copper IUD (n = 21). The p-values reflect differences between the two device types.

The median time from insertion to diagnosis was 5 months (0–69 months). The onset of symptoms could be defined in 28 (53%) of the symptomatic patients. In 26/28 cases the symptoms were immediate (<24 h in 21 women and 1–5 days in five women), with complaints of pain and in six cases combined with abnormal bleeding. Only 12 of these women (46%) sought treatment within a month.
Diagnosis, treatment and findings at surgery
The primary diagnostic examination was commonly vaginal ultrasonography (n = 70; 93%). To verify the diagnosis of a missing IUD, either abdominal X-ray (n = 57; 76%), hysteroscopy (n = 20; 27%), diagnostic curettage (n = 8, 11%) or a combination of these was carried out. Computerized tomography was used once, as ultrasonography and X-ray examination failed to reveal a clear location of the IUD. Laparoscopy was scheduled only after at least one of the diagnostic methods mentioned above had been performed to confirm the diagnosis. A total of 23 women (31%) underwent multiple procedures, hysteroscopy or curettage prior to abdominal surgery.

The location of the IUDs and operative findings are shown in Table 15. In addition to 67 intra-abdominal IUDs, two IUDs that partially perforated the uterus were removed by way of laparoscopy. One intra-abdominal device was removed during a Caesarean section. Five intra-mural or partially perforating devices could be removed by way of hysteroscopy.

Table 15. Findings at laparoscopic surgery.

<table>
<thead>
<tr>
<th>Location of IUD</th>
<th>n (%)</th>
<th>Adhesions at surgery n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All women</td>
<td>LNG-IUS (20)</td>
</tr>
<tr>
<td></td>
<td>21/70 (30)</td>
<td>10/51 (20)</td>
</tr>
<tr>
<td>Intra-abdominal:</td>
<td>68/75 (91)</td>
<td></td>
</tr>
<tr>
<td>-omentum</td>
<td>44/68 (65)</td>
<td></td>
</tr>
<tr>
<td>-pelvis:</td>
<td>24/68 (35)</td>
<td></td>
</tr>
<tr>
<td>-Pouch of Douglas</td>
<td>10/24 (42)</td>
<td></td>
</tr>
<tr>
<td>-near the ovaries</td>
<td>13/24 (54)</td>
<td></td>
</tr>
<tr>
<td>-bladderpouch</td>
<td>1/24 (4)</td>
<td></td>
</tr>
<tr>
<td>Embedded in utero</td>
<td>4/75 (5)</td>
<td></td>
</tr>
<tr>
<td>Partially perforating</td>
<td>3/75 (4)</td>
<td></td>
</tr>
</tbody>
</table>

* Women treated by way of hysteroscopy were excluded from adhesion calculations (two intramural LNG-IUSs, two intramural copper IUDs, one partially perforating LNG-IUS)
Surgical findings were mainly minimal. Adhesions were found in 7 (35%) of the asymptomatic women and in 14 (28%) of the symptomatic women. Women with a copper IUD had significantly more adhesions than women with an LNG-IUS ($p = 0.002$, Table 15). All adhesions in connection with copper IUDs were dense with the device embedded inside, but restricted to a small area around the device. In contrast, adhesions in connection with the LNG-IUS were filmy and in 4/10 cases (40%) unrelated to the location of the device. Adhesions were most common in women treated 1–6 months after insertion. No IUD-related infections were diagnosed, but four cases of sterile inflammation involving a copper IUD were found. In four women who experienced with acute pain at insertion, small haematomas and uterine erythema were seen in relation to the recent perforation. No intestinal or vascular complications were found.
9. DISCUSSION

Intrauterine contraception in nulligravid women

We found nulligravid women to be satisfied users of intrauterine contraception. Nine out of ten insertions were classified as easy, which is similar to (Suhtonen et al. 2004, Brockmeyer et al. 2008) or higher than findings in prior studies (Bahamondes et al. 2011b, Marions et al. 2011). In studies with higher rates of difficult insertions, a large proportion of HCPs have commonly been involved in performing the insertions. In this study, one experienced gynaecologist inserted all IUDs, eliminating inexperience and differing assessments as confounding factors.

Insertion difficulties were mainly related to a tight cervix. The difference between the rates of easy insertions, 86.4% in the LNG-IUS group vs. 94% in the copper IUD group, is equal to the difference seen when comparing the new smaller LNG-IUS 13.5 mg with the earlier device (Gemzell-Danielsson et al. 2012). The diameters of the NovaT and LNG-IUS 13.5mg insertion tubes are similar and approximately 1 mm smaller than that of the earlier LNG-IUS, giving a difference of 2 mm in tube circumference, thus suggesting that this is the main reason for the difference in difficulties.

Although the vast majority of insertions were easy, severe pain was common. The proportion of women reporting severe pain was significantly higher than in prior studies (Suhtonen et al. 2004, Hubacher et al. 2006, Jensen et al. 2008, Marions et al. 2011). This difference may be accounted for by the timing of pain assessment, which here was immediately after insertion. This has previously been shown to affect pain assessment, with pain reported after three minutes being significantly less than immediate pain (Goldstuck et al. 1985). Most women report the intensity of pain at insertion as being similar to menstrual pain and the duration of pain as very short (Brockmeyer et al. 2008, Marions et al. 2011). In addition, the majority of women would undergo IUD insertion again and also recommend it to their friends, regardless of pain (Rapkin et al. 2014).
Results from diaries and follow-up were comparable to those from earlier similar studies on parous women. Similarly to parous women, bleeding/spotting days were frequent during the first month with both devices. As also reported in parous women (Andersson et al. 1994, Suvisaari and Lähteenmäki 1996, Jensen et al. 2008), bleeding/spotting thereafter stabilized in connection with the copper IUD, while continuing to decrease to 0-2 days per month among LNG-IUS users at the end of the study. Reports on pain followed the same pattern. Although bleeding disturbances were common with both devices during the first months, none discontinued before the 3-month follow-up visit, reflecting successful counselling. In addition, we found no pregnancies and low expulsion rates, additionally supporting the suitability of IUC in nulligravid women.

The continuation rate at one year was similar to or somewhat lower than that in earlier studies (Brockmeyer et al. 2008, Bahamondes et al. 2011b, Behringer et al. 2011, Marions et al. 2011). However, only around 11% discontinued because of an adverse event. Despite attempts to contact all women not attending follow-up visits, some 18% were lost to follow-up with no verification of the status of the IUD one year after insertion. These women had moved to other parts of the country. In studies in which nulligravid or nulliparous women using the LNG-IUS have been compared with parous women, parity has not affected continuation rates (Bahamondes et al. 2011b, Berenson et al. 2013). In the few trials where T-shaped copper IUDs have been compared in women of different parities, similar results have been reported (Sivin and Stern 1979, Petersen et al. 1991). Although the difference was small, we found a somewhat higher continuation rate with the LNG-IUS than the copper IUD, similarly to recent U.S. studies in which the slightly longer copper IUD, the TCu380A, has been used (Berenson et al. 2013, Aoun et al. 2014). Differences in bleeding have not been reported among women of different parities or ages using either type of device. One recent study with the LNG-IUS and the TCu380A (Aoun et al. 2014) revealed that nulliparous women reported more pain, but the device was not specified. Studies involving only the LNG-IUS have revealed no such difference between women of different
parities. When assessing only age, no difference in reported pain can be found between adult women of different ages (commonly divided $\geq 25$ years of age), with either device type. However, adolescents report pain and discontinue more often as a result of pain connected with the TCu380A, but not the LNG-IUS (Peipert et al. 2011, Berenson et al. 2013). The findings may reflect either menstrual characteristics, inability to tolerate levels of bleeding or pain normally associated with IUDs, or the smaller uterine size in adolescents causing problems with the longer device, as adolescents have a smaller uterine size than adult nulliparous women (Gadelha da Costa et al. 2004).

The higher continuation rates with the LNG-IUS observed in all women most likely reflect the differing mechanisms of the devices, as women using the LNG-IUS generally report lighter bleeding and less or similar cramping versus before the IUD, in contrast to copper IUD users. This greatly affects user satisfaction, positively for the LNG-IUS and negatively for the copper IUD, as increased bleeding and cramping are the leading reasons for discontinuing (Grunloh et al. 2013, Diedrich et al. 2014).

**Dysmenorrhoea**

Severe dysmenorrhoea was the only factor predicting severe pain at insertion and also the only factor statistically significantly associated with reported days of pain during long-term use. Thus, interviewing women as regards menstrual characteristics provides a predictor of insertion pain and a means of counselling women on the expected pain profile at insertion and during the first few months. Counselling lowers anxiety at insertion, lowering expected pain (Allen et al. 2014), which again lowers actual pain (Goldstuck et al. 1985). Counselling about expected changes in menstruation also increases continuation and satisfaction rates during long-term use (Backman et al. 2002).

The finding that dysmenorrhoeic women reported more pain at the beginning of IUD use was expected. Dysmenorrhoea is associated with uterine hypercontractility (Dawood 1985) as well as an altered response of the central nervous system to pain (Vincent et al. 1985).
2011), explaining the increased response to the uterine irritation caused by the IUD. Although the number of days with pain increased with increasing intensity of menstrual pain during the first months, the effect was small during the second reference period. The median number of days with pain was still related to the level of menstrual pain, but days with pain had decreased significantly more in women with dysmenorrhea, especially in those with severe dysmenorrhea. Women using the copper IUD reported a clearly higher number of days with pain during the second reference period, with no difference in comparison with the intensity of menstrual pain before the IUD. The differing findings are again related to the mechanism of action of the devices, as the LNG-IUS gradually decreases contractility with the gradual suppression of the endometrium, while no such transformation is seen in connection with copper IUDs.

**Uterine size – effect on insertion and long-term use**

Menstrual diary and insertion data have not previously been compared with uterine measurements. The ultrasonographic measurements in the present study were smaller than the studied devices (32 x 32mm) in a majority of the women. Both cavity length and fundal width were smaller than in prior ultrasonographic studies (Benacerraf et al. 2010, Canterio et al. 2010). The measurements were drawn as straight lines on pictures of slightly curved uteri, giving at least length measurements smaller than the actual size of the uterus. This, however, is the measuring technique normally used in clinical settings. With the exception of one woman with the insertion cancelled due to a hypoplastic 4.5-cm-long uterus, the sound measure was ≥ 6.0 cm in all subjects. In contrast, the length evaluated by ultrasonography was 45–60 mm in numerous women. Thus, the sound measure, following the curvature of the uterus gives a more reliable evaluation. We observed surprisingly small fundal width measurements, the median being 9 mm smaller than the width of the studied devices, but saw no negative results of small width with either device. In contrast, the only significant finding was increased intense pain in long-term use among LNG-IUS users with fundal width
measurements in the highest quartile. The precise correct point of measuring width is challenging to determine and thus the observed narrow width measurements are unlikely to reflect the true functional width of the uterus. In addition, as the frames of the studied devices are highly flexible, the device is likely to flex and adapt to the uterine cavity.

We found a correlation between difficult insertion and small total uterine length and steep flexion angle; a novel finding. However, the majority of insertions in small and flexed uteri were uneventful, 82–83% in comparison with 95–96% in women with measurements above the medians of both parameters. Thus, this finding cannot be considered a significant predictor restricting IUD insertion. This conclusion is strengthened by the fact that no significant findings were revealed after dividing the measurements into quartiles and no good predictive threshold measurements were found in ROC analysis. In addition, the proportion of easy insertions observed with the NovaT measuring 32 x 32mm was equal to that with the new smaller LNG-IUS 13.5mg, measuring 28 x 30mm (Gemzell-Danielsson et al. 2012), further indicating that cervical tightness and not uterine size is responsible for the majority of difficulties at insertion. A steep flexion angle does propose a challenge at insertion in any woman, but with an adequate technique, anatomical knowledge and straightening of the uterus at insertion, the flexion angle can usually be overcome, as recommended in practical guidelines (Bahamondes et al. 2013, Kaunitz and Nelson 2014).

Summary and clinical implications

The findings in this study support the fact that small uterine measurements are not a contraindication to IUD use. Results do not support that smaller IUDs should be preferred among adult nulligravid or nulliparous women. Small uterine size observed in pre-insertion ultrasonography did not predict a worsened clinical outcome. Measuring the uterus with ultrasonography may give a false impression of a small uterus and thus prevent women from using IUC. Although uterine size has not been evaluated before, numerous recent studies have
repeatedly shown encouraging positive results in nulligravid/nulliparous women using both types of IUC, results similar to and strengthened by our own. Nulligravid and nulliparous women have not been compared against each other as regards IUC, but usually studied as one group. However, the results of studies defining all participants as nulligravid do not differ from those including both nulligravid and nulliparous women. The finding in our study that women with the smallest uteri reported less bleeding and pain with the LNG-IUS in comparison with other women is encouraging and also positive as regards adolescent users. Although we did not find any clear differences between women with differently sized uteri using the copper IUD, there was a slight trend towards more pain in long-term use among women with small measurements. As the study population was only half the size of the LNG-IUS population, and groups in quartile analysis were small, this may confound the results. Nevertheless, the finding may also explain the higher discontinuation rates related to pain among adolescents in other studies. The TCu380A in these studies is 4mm longer than the NovaT used in our study and adolescents have smaller measurements than adult women of similar parity (Gadelha Da Costa et al. 2004). However, discontinuation among adolescents may also reflect the fact that they more easily discontinue any form of contraception in comparison with adult women (Rostenstock et al. 2012).

Age at first delivery has steadily increased in all developed countries, and is currently nearing 30 years. The average fertility rate is 1.5 to 2.5 children/woman (OECD 2011-2014, THL 2014a, Oliveira da Silva et al. 2011). Thus the average woman needs contraception throughout the majority of her fertile years, half of them spent as nulligravid/nulliparous. Acceptance and satisfaction with current intrauterine devices is not a problem in any age or parity group, as shown in the Contraceptive CHOICE project. Providing contraceptive counselling and any form of contraception cost-free has shown the importance of these factors in increasing contraceptive efficacy, especially among adolescents and young women, thus reducing costs and the subjective burden of unplanned pregnancies (Winner et al. 2011, Peipert et al. 2011, Peipert
et al. 2012, Secura et al. 2014). However, there is still a need to counsel women on contraceptive options, as prior studies in addition to the CHOICE project, have shown an increased prevalence of IUC in women with the best knowledge of contraceptive methods (Gemzell-Danielsson et al. 2013a). This is best achieved by educating HCPs, as misconceptions and poor knowledge of current positive recommendations regarding IUC in young women remains a barrier (Stubbs and Schamp 2008, Fleming et al. 2010, Tyler et al. 2012).

**Uterine perforation**

Women with IUD-related perforation represented typical IUD users, parous women in their 30's. Thus a nulliparous woman is not a typical risk patient in this regard, despite a larger proportion of difficult insertions in this group. This is supported by the outcome of other studies with only a minimal proportion of nulliparous women represented. However, as nulliparity has been seen as a contraindication to IUD insertion in the past, this does create a bias.

We found the incidence of perforation to be low and similar with both types of IUC. Rates were similar to or somewhat smaller than those in prior reports. Although the nature of the study enabled only an observation viewpoint, findings on patient characteristics are in line with those of the majority of previous studies, both case-control (Heartwell and Sclesselman 1983, Caliskan et al. 2003,) and observation (Andersson et al. 1998, Haimov-Kochman et al 2003b, van Haudenhoven et al. 2006) in which the post-partum period and lactation (Heartwell and Schlesselman 1983, Heinemann et al. 2014) have been identified as independent risk factors. Insertion during the post-partum period is generally considered easy, as the cervix is usually soft and wide. Prior reports have also suggested the procedure to be painless in lactating women, with perforation occurring more easily and even unnoticed, without the woman complaining of pain (Chi et al. 1989). In our study this was not confirmed, as lactating women reported pain more often than non-lactating women. With involution of the uterus in the post-partum period, making it smaller, softer and thinner, as well as the
oxytocin-induced contractility related to lactation (Andersson et al. 1998), both early and late perforation are possible. Extensive forces markedly exceeding average insertion forces are needed to perforate the uterus (Goldstuck and Wildemeersch 2014). Thus, immediate perforation in connection with an adequate insertion technique is unlikely. Forces needed to perforate an involuted uterus are presumably smaller.

We did not identify severe adverse events caused by perforation, although a few women underwent laparoscopy soon after the diagnosis as a result of acute pain. The only acute adverse event identified was a bleeding ectopic pregnancy. In this study, the mild or absent symptoms and unexpected pregnancy leading to diagnosis are in line with other similar studies. Life-threatening intestinal or vascular complications have been linked to IUD models of closed shape (Zakin et al. 1981a), although non-threatening intestinal embedment has been described with all copper models as well as the LNG-IUS. The current models are flexible, blunt and non-irritating, thus minimizing the inflammatory and erosive effect of the perforating device. Similar rates of adhesions in connection with the NovaT have been described before (Caliskan et al. 2003). No studies describe severe adhesions in connection with the LNG-IUS. The difference in pregnancy rates related to the device types can be explained by the mechanisms of action of the devices. In a pharmacological case report study describing an omental LNG-IUS, a 10-fold increased plasma level of LNG compared with levels seen with the device in utero, was explained by the extensive vascularity of the omentum, enabling easy absorption. The LNG plasma level was similar to that seen with progestin pills, and thus anti-ovulatory (Haimov-Kochman et al. 2003b). Similarly, anti-inflammatory and immunosuppressive effects of progesterone may reduce adhesion formation with a perforating LNG-IUS (Haimov-Kochman et al. 2003a). In contrast, the local sterile inflammation initiated by copper-releasing devices is presumably predisposing to adhesion formation outside the uterus. When this local effect is absent from the uterine cavity and copper levels in the genital tract are low, the contraceptive effect is easily lost. Thus, an alternative contraceptive is needed immediately
after diagnosis of perforation. Conversely, as the removal of intra-abdominal IUDs in asymtomatic women has been questioned, at least women desiring pregnancy should have the device removed, as it may prevent pregnancy.

Strengths and limitations

Study on nulligravid women
All nulligravid women requesting IUC in public health care in Helsinki are referred to the Family Planning Clinic. As IUC in this group of women is still minimal and the great majority of Finnish women opt for the LNG-IUS, our enrolment period was markedly prolonged and finally stopped at 19 months. The aim of having two equally sized IUD groups could not be achieved, and thus comparison of the outcomes between the two IUD groups is weakened. Similarly, as the copper IUD group is small, analysis of diary data is significantly weakened in this group.

The fact that all women were treated at one clinic, and by one physician, strengthens the results. By using only one physician, inter-observer differences could be eliminated as a confounding factor. Thus, all subjects were evaluated equally, strengthening both collection of background and insertion data and leading to uniformity of the insertion technique and ultrasonographic evaluation of the uterus. The expertise of the gynaecologist, however, weakens generalization regarding the rate of uneventful insertions, as inserter experience is a factor repeatedly shown to influence the ease and success of IUD insertion.

Uterine measurements were taken using a standard 2-D ultrasonographic measuring technique. Measurements were taken only once and by one person. The pictures were, however, inspected and measurements read from them by another physician. Thus, measurements were validated by two physicians separately and any images of poor quality were excluded from size analyses. Repeatability of the same measurements, however, cannot be assessed, since the procedure was carried out only once.
As the age of the women ranged from 18 to 43, generalizing the results to apply to the youngest women can be questioned. However, no significant differences in uterine size or clinical outcome were found when dividing the women into age groups (<20, 20–24, 35–35 and >35 years, data not shown).

**Perforation study**

As uterine perforation with an IUD does not have its own ICD-10 code this limits proper identification of patients as physicians may use differing codes for the same procedure. Operative codes related to foreign objects are, however, precise and thus we can be reasonably confident to have included all surgically treated IUD-related perforations in the study. In addition, the registry used to identify patients was not limited to gynaecological patients. Thus, records of women treated by abdominal surgeons, coded with diagnoses related to removal of a foreign object could be checked to verify if the case involved an IUD.

The proportion of patients treated in the study area was 29% of nationwide-identified cases, which is equal to the proportion of IUDs sold in the area and to the proportion of the Finnish population living within the study area. Incidence calculations therefore represent a reliable estimate of nationwide numbers and symptoms, and surgical findings a good population-based overview of the clinical course of IUD-related perforations.

The study is limited by its retrospective nature. With IUDs inserted mainly outside hospitals and no access to records outside treating hospitals, analysing factors at insertion (both physician- and subject-related) possibly predisposing individuals to perforation was limited to notes made at the hospital where treatment was carried out. In addition, the lack of controls weakens the analysis of patient characteristics. With IUDs inserted in multiple healthcare settings and with reliable information on the insertion lacking among some of the subjects, identifying appropriate controls could not be achieved.
10. CONCLUSIONS

IUD use in nulligravid women

- Nulligravid women are satisfied IUD users. The majority of insertions are easy and uneventful, but pain is common. Continuation rates are similar to those in parous women. Days with bleeding and pain as well as adverse events are similar to those in parous women.

- Dysmenorrhoea is the only predictor of pain. Severe dysmenorrhoea predicts severe pain at insertion and women with dysmenorrhoea experience more pain during IUD use, especially during the first months. Counselling and sufficient analgesia at insertion in these women should be emphasized.

Uterine size and intrauterine contraception

- Small uterine length may increase risk of insertion difficulties, but not pain at insertion. Nevertheless, the majority of insertions in women with small uteri are uneventful and cervical tightness is the main reason for difficulties.

- Smaller uterine size in nulligravid and nulliparous women is not a barrier to modern intrauterine contraception. Instead, LNG-IUS users benefit from small size in long-term use as regards both bleeding profile and pain.

- Ultrasonographic evaluation of uterine size prior to insertion is not necessary to make clinical decisions. Clinical evaluation including pelvic examination and sound measure are sufficient.
Uterine perforation

- The perforation rate is low and similar with the LNG-IUS and copper IUDs.

- A large proportion of perforations occur during the post-partum period. However, the risk is small and this should not limit the use of intrauterine contraception in these women.

- Symptoms associated with a perforating modern flexible T-shaped polyethylene device are rarely severe. Abnormal bleeding and abdominal pain are the most common symptoms, but many women are asymptomatic.

- Pregnancy is a common symptom of a misplaced copper device, but it is rare with a misplaced LNG-IUS.

- Misplaced devices are commonly found in the omentum, if not around the uterus. Adhesions are rare in connection with the LNG-IUS and if found, mainly filmy. A misplaced copper device is commonly surrounded by local adhesions.

- Surgical treatment of asymptomatic perforation has been questioned. However, as the device may act as a contraceptive, the LNG-IUS in particular should be removed if pregnancy is desired.
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