LONG-ACTING REVERSIBLE
CONTRACEPTION (LARC) AFTER
MEDICALLY INDUCED ABORTION

Riina Korjamo

ACADEMIC DISSERTATION
To be presented, with the permission of the Medical Faculty of the University of Helsinki, for public examination in the Seth Wichmann Auditorium, Department of Obstetrics and Gynaecology, Helsinki University Hospital, on 28 September 2018, at 12 noon.

Helsinki 2018
To my family
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


The publications are referred to in the text by their Roman numerals. The original publications are reproduced with permission of the copyright holders.
# Abbreviations

## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>Cu-IUD</td>
<td>Copper intrauterine device</td>
</tr>
<tr>
<td>ENG</td>
<td>Etonogestrel</td>
</tr>
<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate</td>
</tr>
<tr>
<td>FDA</td>
<td>The Food and Drug Administration</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>LARC</td>
<td>Long-acting reversible contraception</td>
</tr>
<tr>
<td>LNG</td>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>LNG-IUS</td>
<td>Levonorgestrel-releasing intrauterine system</td>
</tr>
<tr>
<td>MTOP</td>
<td>Medical termination of pregnancy</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PID</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>RU-486</td>
<td>Mifepristone, 17β-hydroxy-11β-(4-dimethyaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one</td>
</tr>
<tr>
<td>TOP</td>
<td>Termination of pregnancy</td>
</tr>
<tr>
<td>WHO</td>
<td>The World Health Organization</td>
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</table>
ABSTRACT

The total number of induced abortions has declined in many countries, but the 32–45% proportion of repeat abortions has remained stable. Medical abortion performed by the antiprogestogen mifepristone followed by prostaglandin misoprostol 1–3 days later has replaced the surgical method in many countries. Up to 97% of abortions are medically induced today in Finland.

Long-acting reversible contraception (LARC), i.e., intrauterine devices and contraceptive implants, is very effective. Initiation of LARC methods at the time of the surgical abortion results in better initiation and long-term continuation rates and prevents both subsequent unplanned pregnancies and induced abortions compared to delayed initiation of LARC. In clinical practice, insertion of an intrauterine device after medical abortion is typically delayed a few weeks or until the next menstruation; thus, a woman is likely to have been exposed to the risk of a subsequent, unplanned pregnancy. Furthermore, up to half of the women do not attend the post-abortion follow-up visit. Shortening the delay between medical abortion and intrauterine device insertion has increased LARC initiation rates, but insertion of an intrauterine device at the time of the medical abortion was not studied before this thesis study.

The first aim of this thesis study was to assess the feasibility and safety of immediate (0–3 days after misoprostol) and delayed (2–4 weeks after misoprostol) insertion of a levonorgestrel-releasing intrauterine device (LNG-IUS, Mirena®) in a randomized controlled trial (KILKE study). The primary outcomes were a three-month expulsion rate and a one-year continuation rate. The secondary outcomes were the rate of adverse events, three-month bleeding profiles and one-year expulsion, subsequent pregnancy and abortion rates. The second aim of this thesis study was to analyze the effect of planned LARCs and LARCs initiated shortly after a medical abortion on subsequent, unwanted pregnancies and abortions in a retrospective cohort setting (CHOICE study).

The participants in these studies were adult (≥18 years) women requesting a medical abortion at up to 20 weeks of gestation in Helsinki University Hospital, Finland. A total of 264 women participated in the randomized controlled trial; 133 women were randomized in the immediate-insertion group and 131 in the delayed-insertion group. The retrospective cohort comprised 666 women.

In the randomized controlled trial, the LNG-IUS was inserted more often in the immediate-insertion group compared to the delayed-insertion group (127 [95.5%] vs. 111 [84.7%]), p<0.004). Per-protocol insertions (only after an uncomplicated medical abortion and in a predefined timeframe) occurred in 116 (87.2%) vs. 101 (77.1%) cases, p=0.82. In per-protocol analysis, three-month expulsion rates were 24 (20.7%) vs. 4 (4.0%), p<0.001, of which the
total expulsion rates were similar between the groups (3 [2.6%] vs. 2 [2.0%], p=1.00). More partial expulsions occurred in the immediate-insertion group (21 [18.1%] vs. 2 [2.0%], p<0.001, respectively). One-year expulsion rates were 26 (22.4%) vs. 12 (11.9%), p=0.049. A better one-year continuation of LNG-IUS was verified following immediate insertion in 83 (62.4%) vs. 52 (39.7%) cases, p<0.001.

Adverse event rates between immediate- and delayed-insertion groups were similar. No difference was seen in the rates of early (9 [6.8%] vs. 8 [6.1%]) or later surgical evacuation (5 [3.8%] vs. 10 [7.6%]), retained products of conception (7 [5.3%] vs. 15 [11.5%]) and infection (17 [12.8%] vs. 12 [9.2%]), bleeding problems (8 [6.0%] vs. 15 [11.5%]), or any problem associated with abortion (32 [24.1%] vs. 38 [29.0%]). The first bleeding or spotting episode following an abortion was longer due to increased spotting days in the immediate-insertion group compared to the delayed-insertion group (24 [IQR 16–56] vs. 18 [IQR 13–40] days, p=0.04), but the total number of bleeding or spotting days during the 90-day reference period was similar between the groups.

A total of 22 (8.3%) subsequent pregnancies occurred during the one-year follow-up in the randomized controlled trial. A total of 11 (42.3%) pregnancies were detected in the group of women (n=26) who never received LNG-IUS, and only 11 (4.6%) pregnancies were detected in the group of women who initiated LNG-IUS during the trial (n=238) (RR 9.15 [95% CI 4.41–19.02]). Nine women ended up with a subsequent abortion: 4 (15.4%) in the group of women who did not receive LNG-IUS vs. 5 (2.1%) in the group of women who initiated LNG-IUS (RR 7.32 [95% CI 2.10–25.25]).

In the retrospective cohort study, 360 (54.1%) women planned LARC for post abortion contraception, but only 177 (26.6%) women initiated LARC during a one-month following abortion. Subsequent unwanted pregnancies during the median of 21 (IQR 20–22) months follow-up occurred in 59 (8.9%) cases, of which 25 (8.2%) cases were in the group of women who planned contraception other than LARC. Most of the pregnancies (30 [16.4%]) were detected in the group of women who planned but did not initiate LARC, and least (4 [2.3%]) were detected in the group of women who initiated LARC (RR 7.25 [95% CI 2.61–20.17]). The number of abortions in the groups of ‘planned, but not initiated’ vs. ‘planned and initiated LARC’ was 29 (15.8%) vs. 4 (2.3%), RR 7.01 (2.52–19.54).

In conclusion, insertion of LNG-IUS immediately after a medically induced abortion is feasible and safe. Even if the LNG-IUS expulsion rate may be elevated, immediate insertion compared to delayed initiation results in better up-take and long-term continuation rates as well as decreased subsequent unwanted pregnancy and abortion rates. Immediate or short-delay LARC insertion with minimal barriers should be liberally available to all women choosing contraception after medical abortion today.
Maailmanlaajuisesti raskaudenkeskeytysten kokonaismäärä on vähentynyt, mutta toistuvien keskeytysten osuus on pysynyt samalla 32–45% tasolla. Lääkkeellinen raskaudenkeskeytys antiprogestiini mifepristonin ja prosta-glandiinianalogi misoprotolin yhdistelmällä on syrjäyttänyt kirurgisen keskeytysmenetelmän monissa maissa. Suomessa lähes kaikki (97%) keskeytykset tehdään lääkkeellisesti.


Tämän kaksiosaisen välitöstimuksen tarkoituksena oli selvittää välittömän (0–3 päivää misoprostolilääkityksestä) ja myöhemmin (2–4 viikon kuluttua) aloitetun hormonikierukkaehkäisyn (Mirena®) käytöskelpoisuutta ja turvallisuutta lääkkeellisen raskaudenkeskeytyksen jälkeen sekä kuukauden sisällä aloitetun pitkääikaisen ehkäisyn vaikutusta uusien raskauksien ja uusin-takeskeytysten ilmanopisto- vaikutukseen. Jopa puolet naisista ei kuitenkaan tule sovitettua keskeytyksen jälkeen.

Kliinisen satunnaisetun KILKE-tutkimuksen (Kierukka Lääkkeellisen KEskeytyksen jälkeen) päätavoitteena oli verrata välittömästi ja myöhemmin asetetun hormonikierukan poistumisten määrää kolmen kuukauden kuluessa ja kierukkaehkäisyyn käytöönotetta vuoden kuluttua keskeytyksen jälkeen. Lisäksi tutkimuksessa selvitettiin välittömän kierukkaehkäisyn vaikutusta keskeytyksen jälkeisen ongelmien ilmanopistuvuuteen ja verenkuohututkimuksiin, sekä kierukan poistumisten, uusien raskauksien ja keskeytysten määrää vuoden seuranta-aikana.

Takautuvan CHOICE-kohorttitutkimuksen tavoitteena oli arvioida kuukauden kuluessa aloitetun pitkääikaisen ehkäisyn vaikutusta ei-toivottujen raskauksien ja raskaudenkeskeytysten ilmanopistuvuuteen.

Kaikki tutkitut naiset olivat aikuisia ja hakivat lääkkeellistä raskaudenkeskeytystä (raskauden kesto ≤20 viikkoa) Helsingin yliopistollisesta sairaalasta. KILKE-tutkimukseen osallistui 264 naista, joista 133 arpoutui välittömän kierukan asetukseen ryhmään ja 131 myöhemmän asetukseen ryhmään. CHOICE-kohortti koostui 666 naisesta.
KILKE-tutkimuksessa hormonkierukkaehkäisy aloitettiin useammin välittömän asetuksen kuin myöhemmän aloituksen ryhmässä (127 [95.5%] vs. 111 [84.7%], p=0.004). Tutkimusprotokollan mukaisesti kierukka asetettiin 116 (87.2%) vs. 101 (77.1%) naiselle, p=0.82. Näissä tapauksissa välittömästi asetetuista kierikoista kolmen kuukauden aikana poistui kokonaan tai osittain 24 (20.7%) ja myöhemmin asetetuista 4 (4.0%), p<0.001. Kokonaan poistuneiden kierukoiden määrä oli samanlainen molemmissa ryhmissä, mutta välittömän asetuksen ryhmässä osittain poistuneita kierukoita oli enemmän (21 [18.1%] vs. 2 [2.0%], p<0.001). Vuoden seurannassa kierukoiden poistumisia oli 26 (22.4%) vs. 12 (11.9%), p=0.049. Vuoden kuluttua keskeytyksestä välittömästi asetettu kierukka oli kuitenkin paremmin käytössä kuin myöhemmin asetettu, 83 (62.4%) vs. 52 (39.7%), p<0.001.

KILKE-tutkimuksen osallistujista 26 naista ei koskaan aloittanut kierukkaehkäisyä ja heistä 11 (42.3%) tuli uudestaan raskaaksi vuoden seurantaiikana. Vain 11 (4.6%) naista raaskaaksi tuli aloittaneita hormonkierukkaehkäisyn, tuli uudestaan raskaaksi (RR 9.15 [95% CI 4.41–19.02]). Uuteen raskaudenkeskeytykseen päätyi näistä 4 (15.4%) vs. 5 (2.1%) naista, RR 7.32 (95% CI 2.10–25.25). CHOICE-kohorttitutkimuksessa 360 (54.1%) naista suunnittelit kierukkaa tai kapselia keskeytyksen jälkeiseksi ehkäisyksi, mutta ainostaan 177 (26.6%) naiselle se aloitettiin. Seuranta-aikana (mediaani 21 kk [IQR 20–22]) todettiin yhteensä 59 (8.9%) ei-toivotta raskautta, joista suurin osa todettiin naisilla, jotka suunnittelivat, mutta eivät aloittaneet pitkäaikaista ehkäisyä (30 [16.4%]) ja vähiten naisilla, joille pitkäaikainen ehkäisy aloitettiin (4 [2.3%], RR 7.25 [95% CI 2.61–20.17]). Uuteen raskaudenkeskeytykseen päätyi näistä 29 (15.8%) vs. 4 (2.3%) naista, RR 7.01 (2.52–19.54).

Välitön hormonkierukkaehkäisy aloitus lääkkeellisen raskaudenkeskeytyksen jälkeen on toteutettavissa ja turvallista. Vaikka välittömästi asetettu kierukka poistuukin useammin kuin myöhemmin asetettu, välitön asetus lisää kierukkaehkäisen aloitusten määrää ja pitkäaikaista käyttöä. Välittömästi tai lyhyellä viiveellä aloitettu kierukka- ja kapseliaehkäisy vähentää ei-toivotta raskauksia ja uusia raskaudenkeskeytyksiä. Pitkäaikaisten ehkäisyjen tulisi olla helposti ja joustavasti saatavilla kaikille lääkkeellisen raskaudenkeskeytyksen jälkeistä ehkäisyä pohtiville naisille.
1 INTRODUCTION

A woman’s access to safe and voluntary family planning and her ability to control if and when she wants to have children is a human right (1). If a woman becomes pregnant and the pregnancy is unwanted, what kind of options to choose, except continuing her pregnancy, have women had in the last century or last decades? What are her options today or in the future?

In the last century, before the 1950s, induced abortion was illegal in Finland, as it was and continues to be in many countries globally. The first law and act permitting induced abortion in Finland were introduced in 1950 (2, 3). Abortion was permitted only on the grounds of serious medical, eugenic or ethical reasons. New, and still valid, abortion laws and acts were announced in 1970, and induced abortion became legal for social reasons (4, 5). The abortion law demands physician to give contraceptive counselling to all women requesting abortion (5). The first act from 1950 even included a strategy to prevent subsequent abortions. In those days, prevention did not mean decreasing the unplanned pregnancies, as we think today. On the contrary, abortions should have been prevented to ensure population growth by serving counselling, financial and social support to women not to end up in an abortion but to continue her pregnancy (6).

Before the 1960s, coitus interruptus (withdrawal method), fertility awareness methods, the lactational amenorrhea method and some spermicides, pessaries and condoms were available for Finnish women for contraception. However, lack of knowledge, availability and high costs, combined with a conservative atmosphere, were barriers to their use (6, 7). In 1958, Pincus et al. published that orally administered synthetic hormones (progestogen combined with varying amounts of estrogen) effectively lowered pregnancy rate (8). The first combined oral contraceptives also became available in Finland in the early 1960s, and their usage increased quickly (7).

The concept of intrauterine contraception was already described in 1909, when Richter inserted a ring made of silkworm gut into a uterus (9, 10). The first commercially sold intrauterine device (IUD) was Graefenberg’s silver spring wire ring in the late 1920s (10). Development of intrauterine devices was slow during the following decades, and plastic intrauterine devices were developed in the 1960s. The safety and efficacy of the intrauterine method became so clear that the U.S. Food and Drug Administration (FDA) approved intrauterine devices in 1968 (9, 10).

University of Helsinki has a long tradition in the field of contraception research. The Population Council formed the International Committee for
Introduction

Contraception Research (ICCR) in 1970, a network of distinguished scientists and clinical investigators who conducted clinical trials to test the safety, efficacy, and acceptability of Council-developed products. Researchers at the University of Helsinki, led by Professor Tapani Luukkainen, were part of this international network. Progestogens and intrauterine contraception were studied in Helsinki, and this work resulted in the development of the levonorgestrel-releasing intrauterine system (LNG-IUS) and the copper intrauterine device (Cu-IUD) (11). LNG-IUS, which was first called Levonova® and today is Mirena®, is still manufactured today by Bayer AG in Turku, Finland.

Concomitantly to contraception method development, abortion care has also changed over the last decades. Surgical abortion has been replaced by the medical method in many countries (12–14). Indeed, at 97%, Finland has the highest medical abortion rate. The milestones of medical abortion development are presented in the ‘Review of the literature’ section.

All contraceptive methods can be initiated immediately following a surgical abortion (15, 16). Today, according to clinical practice, insertion of an intrauterine device after a medical abortion is often delayed for a few weeks or until the next menstruation, mainly because of fear of adverse events and expulsions and because of the structure of the health care system. One of the problems is that up to half of the women will not attend the follow-up visit, thus missing an opportunity to obtain effective contraception and, thus, being at an increased risk for a subsequent unplanned pregnancy and abortion (17). Before conducting this thesis study, only a few publications were available on shortening the IUD insertion delay after a medical abortion, and no research was available on immediate initiation of intrauterine contraception.

Today, a woman has opportunities to decide her family size and prevent an unplanned pregnancy by numerous contraceptive methods. If an unwanted pregnancy occurs, the woman has some legal options from which to choose, including easy access to an early, safe medical abortion.

The literature review in this thesis describes in detail the development of the medical abortion procedure, of long-acting contraception during the last decades, and of women’s options to choose post-abortion contraception today. Furthermore, this thesis study investigates if immediate initiation of intrauterine contraception following a medical abortion would be feasible and effective and whether or not this immediate initiation could be a new option and choice for women who request a medical abortion in the future.
2 REVIEW OF THE LITERATURE

2.1 INDUCED ABORTION

2.1.1 INCIDENCE OF INDUCED ABORTION

Induced abortion concerns annually more than 50 million women worldwide (18-20). Approximately 88% of them are performed in developing countries and only 12% in developed countries (20). The global incidence of abortion is estimated to be 35/1000 among 15–44-year-old women. Figure 1 presents the incidence of abortion on global and regional levels. Table 1 presents the incidence of abortion in selected developed countries.

Figure 1. Global and regional abortion incidence rate estimates (per 1000 women aged 15–44 years), 1990–94 to 2010–14. Shaded areas are 90% uncertainty intervals. (Figure is reprinted from Sedgh et al. 2016 (20), with permission from Elsevier.)
Table 1. Incidence of induced abortion in selected developed countries. Data derived from (12, 14, 21-25).

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of abortions</th>
<th>Incidence / 1000 women</th>
<th>Age group</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>926 000</td>
<td>14.6</td>
<td>15–44*</td>
<td>2014</td>
</tr>
<tr>
<td>England and Wales</td>
<td>190 000</td>
<td>16.0</td>
<td>15–44</td>
<td>2016</td>
</tr>
<tr>
<td>Scotland</td>
<td>12 000</td>
<td>11.6</td>
<td>15–44</td>
<td>2016</td>
</tr>
<tr>
<td>France</td>
<td>212 000</td>
<td>13.9</td>
<td>15–49</td>
<td>2016</td>
</tr>
<tr>
<td>Finland</td>
<td>9 500</td>
<td>8.3</td>
<td>15–49</td>
<td>2016</td>
</tr>
<tr>
<td>Sweden</td>
<td>38 000</td>
<td>20.8</td>
<td>15–44</td>
<td>2016</td>
</tr>
<tr>
<td>Denmark</td>
<td>15 473</td>
<td>12.3</td>
<td>15–49</td>
<td>2015</td>
</tr>
<tr>
<td>Norway</td>
<td>12 700</td>
<td>10.6</td>
<td>15–49</td>
<td>2017</td>
</tr>
<tr>
<td>Iceland</td>
<td>921</td>
<td>11.8</td>
<td>15–49</td>
<td>2015</td>
</tr>
</tbody>
</table>

* Year-old women

A significant proportion of women requesting abortion have a history of a previous abortion: the figure in the United States was 45% in 2014, whereas in 2016 the figure in other abovementioned countries varied between 32% and 44%. Even if the total number of abortions declines in these countries, the proportion of repeat abortions seems to be quite stable.

2.1.2 RISK FACTORS FOR SUBSEQUENT INDUCED ABORTIONS

Young age, history of a previous pregnancy or induced abortion, and a previous second trimester abortion are risk factors for subsequent induced abortions (26, 27). Furthermore, contraceptive choices at the time of the abortion have an effect on subsequent abortions; intrauterine devices and implants are the most effective methods for preventing subsequent, unplanned pregnancies and abortions (26, 28-30).

2.2 FROM SURGICAL ABORTION TO MEDICAL TREATMENT

Surgical abortion by means of vacuum aspiration or sharp curettage is a traditional way to terminate an unwanted, first trimester pregnancy. Second trimester abortions have been mainly induced medically (by combining oxytocin or other uterotonics and cervix dilatating laminaria) in Finland, but the most commonly used method worldwide to terminate a second trimester pregnancy (above 14 weeks of gestation) has been the dilatation and evacuation procedure (12, 31, 32). This is technically more difficult than vacuum aspiration, but if the surgeon’s caseload is sufficient, the method is safe and effective (31-33). However, if this criterion is not fulfilled, the medical method is preferable (31, 33).
Among the disadvantages of a surgical abortion are the need for general or local anesthesia, immediate adverse events such as uterine perforations and bleeding problems due to cervical lacerations, and the long-term effects on perinatal outcomes in subsequent pregnancies (34, 35). For example, according to a meta-analysis published in 2009, a previous surgical abortion was associated with low birth weight and preterm birth in subsequent pregnancies, and the risk increased with multiple abortions (36).

Medical abortion has been studied and developed over several decades to reduce the adverse events from surgical abortion and to increase abortion availability by reducing the need for specialized facilities. The sections below will describe the milestones of medical abortion development during the last decades.

### 2.2.1 PROSTAGLANDINS

Researchers had already discovered during the 1909–1920 period that human prostate secretion and sperm had a contractive effect on smooth muscle (37, 38). Von Euler from Sweden named this organic acid, extracted from seminal fluid, ‘prostaglandin’ in 1935, and he showed that prostaglandin caused uterine contractions \textit{in vitro} (38). Asplund, also from Sweden, published in 1947 that when prostaglandin was supplied intravenously or intraperitoneally, it caused uterine contractions \textit{in vivo} in a rabbit model, but the effect lasted only 15–20 minutes after administration (37). Furthermore, intramyometrial and intravaginal administration of prostaglandin was found to be effective (37). The occurrence of prostaglandin in different organs and fluids, both in male humans and different animals, was studied during the 1950s, which increased the knowledge of prostaglandin (39). This seminal fluid-derived prostaglandin was thought to enhance emptying the accessory genital glands, increase the motility of spermatozoa and facilitate the migration of sperm in the female genital tract.

Bergström and Sjövall extracted two compounds from a sheep’s prostate gland, which they called prostaglandin E\textsubscript{1} and F\textsubscript{1} (Figure 2), in the late 1950s and thought them to be different from the previously studied prostaglandin (40, 41). These subtypes were found to have different effects on various organs (42), and the effect on the uterus was found to depend on whether the female was pregnant or not. Other, slightly different, forms of these prostaglandins were characterized by Bergström \textit{et al.} and van Dorp \textit{et al.} in the early 1960s (43). It was known in 1970 that human seminal fluid was a mixture at least 13 different prostaglandins, including the first-found E\textsubscript{1} and F\textsubscript{1} (44). Characterization of the different prostaglandins made it possible to synthesize them from essential fatty acids (45, 46).
Prostaglandins were studied from at least three different viewpoints in the late 1960s and early 1970s: medical induction of abortion, menses induction in the case of missed (or late) periods, and as postcoital use to interrupt normal zygote transport and thereby to prevent pregnancy (47). Prostaglandins E₁, E₂ and F₂α (Figure 2) had the strongest effect on gravid myometrium (48), so they were studied for medical induction of first and second trimester abortion (44, 49-51). Prostaglandins were administered by intravenous infusion (52-55) or subcutaneous injections (54). The results were promising; following intravenous infusion, up to 82-93% of women completed their abortion, and side effects were rare, apart from vomiting and diarrhoea. Extra-amniotic administration of prostaglandins was studied by Embrey et al. (56). Prostaglandin solution was administered to the extra-amniotic space through the cervix by catheter every 1 or 2 hours. The rate of complete abortion without surgical evacuations was 60%, but fewer side effects were detected compared to intravenous administration of prostaglandins.

Several prostaglandin analogues were synthesized and studied in the early 1970s. Their advantages, compared to natural prostaglandins, were a prolonged duration of action permitting even single-dose intravenous administration, increased potency to stimulate the uterus, and the possibility of intramuscular and intravaginal administration (34, 57-59). Intravaginal administration had fewer side effects compared to other routes of administration.

Prostaglandin E₁ analogue misoprostol (SC-29333) (Figure 2) was introduced in 1976 as a potent, long-acting and orally effective inhibitor of canine gastric secretion (60). This stable, orally active and well-tolerated drug
was widely introduced in 1985, following pharmaceutical modifications (61-63). Conversely to animal experiments, clinical studies found that misoprostol had an effect on a pregnant human uterus (64). Since the first approval in June, 1984, misoprostol (Cytotec®, Pfizer) was available as a treatment for peptic ulcer in 12 countries in 1987 (65). It was available in 43 countries by October 1988, when the U.S. Food and Drug Administration (FDA) was considering approval of misoprostol (66). Since then, misoprostol has been widely used off-label (without registered indication) as an uterotonic drug for medical induced abortion or miscarriage, induction of labour, and treatment of postpartum haemorrhage. However, the safety and effectiveness of misoprostol is well documented in all these indications (67-69).

### 2.2.2 MIFEPRISTONE COMBINED WITH PROSTAGLANDINS

Progesterone (Figure 3) has been known to be an essential hormone in maintaining normal pregnancy for a long time. Animal experiments had already shown in the 1930s that progesterone maintains early pregnancy and inhibits uterine contractions (70, 71).

![Figure 3. Formulas of natural progesterone and antiprogestogen mifepristone.](image)

The French pharmaceutical company Roussel-Uclaf synthesized and introduced the antiprogestogen mifepristone (RU-486, Figure 3) in 1980. Mifepristone blocks progesterone receptors, binding to them at higher affinity than natural progesterone (72). Herrmann et al. published an observation in 1982 that mifepristone interrupted the luteal phase of the menstrual cycle and early pregnancy (73). Kovacs et al. assessed the effect of different doses of mifepristone (50 to 200 mg per day for four days) on termination of a pregnancy of less than 8 weeks (74). Complete abortion was achieved by this medication in 22 out of 36 cases (61%), and its success rate did not differ between different mifepristone doses.

Haspels et al. conducted a clinical trial in 1985 of 33 women seeking termination of pregnancies with less than 12 weeks of gestation (75). Women
took 200 mg of mifepristone orally for eight days. If their pregnancy was under 9 weeks of gestation, 19 out of 24 (79%) women had a complete abortion. However, only 3 out of 9 women having a pregnancy of 10–12 weeks completed their abortion. Vervest and Haspels published the results of their other clinical trial of 44 women requesting abortion before 12 weeks of gestation in 1985 (76). In this latter trial, mifepristone was administered orally (100 mg or 200 mg per day) for four days. Five women were administered an additional intramuscular prostaglandin (sulprostone) injection to increase uterine contractions. The mifepristone success rate was 71%, but adding prostaglandin to the treatment enabled 29 out of 35 women (83%) to achieve complete abortion if the gestation duration was less than 9 weeks. Similarly, as in the first study, the success rate was disappointing if the gestation duration was 10 to 12 weeks; then, only 3 out of 9 women completed their abortion.

Bygdeman and Swahn simultaneously showed in their 1985 clinical trial, in which they directly measured uterine contractibility, that when prostaglandin (sulprostone) was added to the mifepristone pretreatment, it increased uterine tone, contraction amplitude and frequency (Figure 4). Furthermore, the complete abortion rate increased to 94% compared to a 71–79% success rate for mifepristone-only treatment. Additionally, fewer bleeding problems were detected if prostaglandin was added to mifepristone treatment (75-77).

Figure 4. Uterine contractility and response to prostaglandin (sulprostone) without (A) and with (B) previous mifepristone treatment. (Figure is reprinted from Bygdeman et al. 1985 (77) with permission from Elsevier.)
Several different mifepristone doses combined with different prostaglandins (i.e., intramuscular sulprostone, vaginal gemeprost, oral/buccal/sublingual/vaginal misoprostol) have been studied since the 1980s. The World Health Organization was an active organizer, among others, of the international multicenter trials (78, 79). The most effective combination for first trimester medical abortions seems to be a combination of a single dose of mifepristone 200 mg p.o. combined with misoprostol 24–48 hours later (80, 81). Sulprostone injection as a prostaglandin component was abandoned because of its association with serious cardiovascular complications (even fatal myocardial infarcts) in addition to its impractical invasive administration route (82). Additional advantages favoring misoprostol compared to gemeprost and other prostaglandins have been misoprostol’s easy and useful administration routes, possibility of storing the drug at room temperature, and low price (80, 83). The oral administration route for misoprostol was the first one studied, but the vaginal route was found to be more effective with fewer side effects when compared to buccal or sublingual routes (80, 84, 85).

Only a few women in the abovementioned studies requested an abortion during the late first trimester (9–12 weeks of gestation). Ashok et al. published a cohort study of 120 women in the Lancet 1998 in which mifepristone 200 mg was followed by misoprostol 800 mcg vaginally 36–48 hours later, and additional misoprostol 400 mcg doses were administered if needed (86). The median misoprostol dose was 1200 mcg; the time from the first misoprostol dose to abortion was 4.3 hours, and the success rate was 95%. Immediate heavy bleeding needing medication occurred in 3%, curettage due to incomplete abortion was needed in 5%, and infection occurred in 3% of cases. A randomized controlled trial published in 2002 by Ashok et al. comparing medical and surgical abortion in late first trimester confirmed previous observations that medical treatment was as effective as surgical treatment with similar complication rates (87).

Second-trimester medical abortions were studied following the successful studies on first trimester medical treatments. Rodger and Baird presented their results in 1990 from a double-blind, randomized, placebo-controlled trial of 100 women, in which mifepristone given 36 hours before the gemeprost pessary decreased the median time from the first pessary to abortion from 15.8 to 6.8 hours. The median number of pessaries needed also reduced from 5 to 3 (88). A retained placenta was common in both groups (53% vs. 72%) and almost all women (92% vs. 96%) underwent surgical evacuation of the uterus. El-Refaey et al. showed in 1993 that mifepristone combined with oral misoprostol was at least as effective as vaginal gemeprost (89), and in 1995, an oral and vaginal misoprostol treatment success rate as high as 97% was achieved (90). Median induction to abortion time was 6.4 hours. A mifepristone dose of 200 mg has been as effective as a higher 600 mg dose (91) in the second trimester.
2.3 MEDICAL ABORTION TODAY

Medical abortion by using mifepristone was first approved for clinical use in France in September 1988. The pharmaceutical company Roussel-Uclaf stopped the distribution of mifepristone in October 1988 because of pressure from pro-life protests. However, the French government ordered the company to resume distribution of mifepristone only two days later (92). Mifepristone was approved in the United Kingdom and China in 1991 and Sweden in 1992, followed by several European countries, including Finland and the U.S. in 2000 (93). Today, mifepristone combined with misoprostol is included in the WHO's complementary list of essential medicines with the addendum 'where permitted under national law and where culturally acceptable' (94). Misoprostol could be used alone if mifepristone is unavailable, but it is not as effective as when it is combined with mifepristone (16).

Several high-class, systematic reviews written on methods of medical abortion (80, 95, 96) exist today, and clinical guidelines are similar in different countries (16, 33, 97-101).

The most effective and widespread practice for conducting medically induced abortion is to give the woman

- mifepristone 200 mg orally followed by
- misoprostol 800 mcg vaginally 36–48 hours later (102-104).

Oral, sublingual or buccal misoprostol administration could be used, especially if the woman has bleeding. A woman could self-administer misoprostol herself at home in early pregnancy (≤9 weeks of gestation) in many countries, depending on the legislation. Additional misoprostol of 400 mcg doses could be added every three hours until foetal expulsion in late first trimester and second trimester.
Medical abortion has become common, especially in Nordic countries and Scotland, during the last 30 years (Figure 5).

![Figure 5](image)

**Figure 5.** Proportion of medically induced abortions from all abortions in selected countries during the years 1990 to 2016. Data derived from the references (12-14, 21, 23, 105, 106).

### 2.3.1 SUCCESS RATE

Medical abortion is safe and effective today. Ongoing pregnancies are rare (0.5%), and they can be detected by good follow-up practices (107).

Rates of complete abortion without the need for surgical evacuation are
- in early first trimester (≤9 weeks) 95–97%
- in late first trimester (9–12 weeks) 95%
- in second trimester (12–24 weeks) 63-75% (108).

### 2.3.2 ADVERSE EVENTS

**Severe adverse events** (hospital admission, blood transfusion, intravenous antibiotic treatment, thromboembolic complications, surgical procedures other than evacuation) of medical abortion are rare (0.02–0.26%). The mortality rate is very low (0.4 / 100 000) (107-109).
Some adverse event was experienced, according to a register-based study, by 20% of women when gestational age is ≤9 weeks by 29% when gestational age was 12–24 weeks (108, 110).

- **Haemorrhage** (15.6–17.2%) and **incomplete abortion** (6.7–7.9%) occur more often following a first-trimester medical abortion compared to surgical methods (2.1% and 1.6%, respectively) (108, 109).

- **Bleeding over 500 ml** after a second-trimester abortion occurs in 6.3–7.0% cases (104).

- **Retained products of conception** are seen in 4% of cases when gestational age is below 9 weeks, and it increases when gestational age grows (79, 109, 111).

- **Risk for surgical evacuation** is 5.9% in early medical abortion (≤9 weeks), 7.9% in the first trimester and 25–38.5% in the second trimester (104, 108, 109).

- **Infection rates** vary according to gestational age, diagnostic criteria used, and clinical practice on infection prophylaxis. Infection prophylaxis is not included in the Finnish Current Care Guideline on Induced Abortions when sexually transmitted diseases have been screened before treatment (97).

  Infection rates according to register-based studies have been 1.7% when gestational age is ≤9 weeks, 1.9% after first trimester medical abortion and 4.0% after second trimester abortion. Infection rates are similar to those seen after surgical abortion (109). According to clinical trials, infection rates following second trimester abortion have been 8.9–11.3% (104, 108).

**Long-term adverse events** are difficult to study. Thorp et al. reviewed studies on adverse events following surgical abortion in 2002 (35). They found no association between induced abortion and subsequent miscarriage, subfertility or breast cancer. However, surgical abortion had some association between subsequent placenta previa, ectopic pregnancy and preterm birth. Conversely, one previous medical or surgical abortion was not a risk factor for any perinatal outcomes in the next delivery in the Finnish register-based study (112, 113). Furthermore, uncomplicated medical abortion was not a risk for intrauterine adhesions, but surgical re-evacuation following either medical or surgical abortion was (114). KC et al. published 2017 results from the Finnish register-based study of 420 000 first-time mothers in which they could differentiate perinatal outcomes according to method of previous induced abortion; surgical abortion increased the risk of preterm birth, but medical abortion did not have an effect on perinatal outcomes (115). Mental health may be influenced by induced abortion, but confounding factors make it difficult to interpret the results (35, 116, 117).
2.4 LONG-ACTING REVERSIBLE CONTRACEPTION (LARC)

2.4.1 PROGESTOGENS AS CONTRACEPTIVES

The idea of hormonal contraception has been studied since the 1930s. Kurzrok declared that ‘The potentialities of hormonal sterilization are great’ in The Journal of Contraception in 1937 (118). Different estrogens and progestogens combined with estrogen were studied, and knowledge of their ovulation-inhibiting potential increased from the 1940s to the 1960s. Combined oral contraceptives turned out to be effective, but side effects (e.g., thromboembolic complications) mainly caused by the estrogen component were recognized.

The idea of progestogen-only contraception was studied, and in 1958 Pincus et al. reported that large oral doses of progestogens (norethynodrel and norethindrone) may inhibit ovulation (8). These progestogens were synthesized from estrogens, and there was a suspicion that these preparations were not totally estrogen-free (119). Rudel, Martinez-Manautou et al. from Mexico discovered in 1965 that small daily doses of synthetic, estrogen-free progestin chlormadinone acetate had an effect on fertility (119, 120). According to, i.e., endometrial biopsies and urinary pregnanediol levels, they stated that low-dose progestin did not regularly inhibit ovulation, but an antifertility effect was most likely due to endometrial or cervical mucus changes (120). Only bleeding problems were detected as side effects during continuous low-dose progestine therapy. The contraceptive effect was good: The pregnancy rate was only 0.2–3.3 / 100 woman-years (120, 121).

Previous studies with chlormadinone acetate were conducted mainly in South America, and Foss et al. wanted to test this type of method in the British population (122). They conducted their trial using norgestrel, one of the newer synthesized, most potent progestines (123). The chlormadinone acetate dose in the abovementioned studies was 0.5 mg, but the same effect on fertility could be achieved by a norgestrel dose of only 50 mcg. A total of 188 British women received 50 mcg of norgestrel daily, resulting in 2 250 completed menstrual cycles. The pregnancy rate due to method failure was 1.1 / 100 women-years. Again, any side effects other than bleeding disturbances were rare.
2.4.2 IMPLANTS

The method failure rates for oral low-dose progestogens were low, but pregnancies occurred if medication was forgotten or gastrointestinal diseases impaired drug absorption (122). Subcutaneous capsules were innovated to achieve long-term, constant progestogen plasma levels.

Silicone rubber (dimethylpolysiloxane, Silastic®, Dow Corning Corporation) was found in the late 1960s not to cause foreign body reactions if inserted subcutaneously. Diffusion of different steroids through this Silastic membrane, including natural progesterone and two synthetic progestines, was tested in vitro, and one synthetic progestin was tested in vivo by subcutaneous insertion of a capsule in ewes (female sheep) (124). All steroids passed through the membrane in vitro and subcutaneously released progestogen had an effect on the ewes' heat in vivo (124, 125). Lifchez et al. studied the release rates of four progestogens (natural progesterone, medroxyprogesterone acetate, chlormadinone acetate and norgestrel) from subcutaneous Silastic capsules in female rats (126). The results were published in 1970; natural progesterone was found to diffuse quickly from a capsule, but the other three synthetic progestines were released more slowly and constantly, norgestrel having the lowest diffusion rate.

Megestrol acetate containing subdermal Silastic implants were found in clinical trials to be quite effective contraceptives, but several implants had to be inserted, and efficacy was restricted for approximately one year (127, 128). Jackanicz et al. studied a different biodegradable polylactic acid implant as a carrier for contraceptive steroids in parallel with the abovementioned studies, but it was found to release norgestrel too quickly for long-term contraception (129).

Several different synthetic progestins, such as norgestrel, were tested in the 1970s, and the release rate from Silastic implants was found to be well tolerated and effective (130). Levonorgestrel, the biologically active isomer of norgestrel, had the highest contraceptive efficacy, and the Population Council registered trademark Norplant® for levonorgestrel containing subcutaneous Silastic capsules in the early 1980’s (131-133). Norplant® consisted of six capsules (levonorgestrel at 36 mg each for a total of 216 mg levonorgestrel) (Figure 6) and contraceptive effectiveness lasted for five years. Its contraceptive effect was very good at 0.27 / 100 women-years, and the 5-year cumulative pregnancy rate was as low as 1.1 / 100 women-years. Norplant® was first approved in Finland in 1983, and the U.S. Food and Drug Administration (FDA) approved Norplant® in December 1990 (134, 135).

The next generation of the Norplant® implant was Norplant-II, which consisted of only two capsules containing levonorgestrel 75 mg each but had
as good efficacy, safety and continuation rates as the original Norplant® and was easier to remove due to a fewer number of implants (136). However, the Norplant-II capsule material was unavailable for large-scale production, and a new formula for implants was developed (133, 136, 137). This new 2-rod implant containing a similar amount of levonorgestrel (150 mg) as Norplant-II was called Jadelle® and was manufactured by Leiras (Turku, Finland) (Figure 6) (137). Jadelle® was first approved in the mid-1990s in Finland and the USA for a three-year period, but prolonged use for five years was approved first in Finland in 2000. The cumulative five-year pregnancy rate for Jadelle® was as low as 0.8–1.1 / 100 women-years (138). Jadelle® is still available in Finland but is seldom used today.

The other implant available today in Finland is Nexplanon® (previously Implanon®, manufactured by NV Organon, Oss, The Netherlands), which contains 68 mg etonogestrel (3-ketodesogestrel, the biologically active metabolite of progestin desogestrel). The implant consists of only one rod, is made of ethylene vinyl acetate copolymer instead of Silastic material and is effective for three years (Figure 6) (133, 134, 139, 140). Recent studies suggest that efficacy remains high for up to 5 years of use (141, 142). Its advantage, if compared to Jadelle®, is Nexplanon®'s easier insertion and removal due to the implant material and single rod. The FDA approved Implanon® in 2006 (135). The main contraceptive effect of this etonogestrel implant seems to be by ovulation inhibition (143). The efficacy of the etonogestrel implant is excellent; in the first clinical studies, no pregnancies were detected at all, but the typical-use failure rate has been 0.1 / 100 women-years in later studies (135, 140). Bleeding disturbances are the most typical side effects of implant contraception, but the continuation rate is usually high, despite these.

![Figure 6](image-url)  
*Figure 6.* Visualization of three different contraceptive implants. A. Norplant®, B. Jadelle®, C. Nexplanon®. Modified from Croxatto, 2002 (133).  
LNG = levonorgestrel, EVA = ethylene vinyle acetate, ENG = etonogestrel.
2.4.3 INTRAUTERINE CONTRACEPTION

Rapid population growth, especially in developing countries, challenged the need for fertility control in the 1950s and 1960s. New forms of intrauterine devices (IUDs) were studied (47) in the 1960s in parallel to research being done on oral anti-ovulatory steroid therapy. New types of intrauterine devices, made of nylon thread, polyethylene or stainless steel at that time, were inserted into parous women only (144). Pregnancy rates for the first 12 months with these devices varied between 1.8–7.5 / 100 women-years. One-year expulsion rates were somewhat high depending on the device, 1.1–21.8 / 100 women, and removals were common, 10–25 / 100 women. The most common reasons for removals were bleeding problems and pain. Pelvic inflammatory disease was common during the first year of IUD usage; its incidence was 1.7–3.9 / 100 women. One-year continuation rates varied from 58% to 83%. The antifertility mechanism of intrauterine devices was suggested to be mainly mechanical; a bigger device had better contraceptive effectiveness but also had more side effects. A smaller device, the plastic T-shaped IUD called Tatum T, that easily fitted into the uterine cavity, was developed toward the end of the 1960s to reduce these side effects (Figure 7) (145).

Figure 7. Illustration of different types of T-shaped intrauterine devices (IUDs): A. plain Tatum T, B. copper containing Tatum T and C. Nova T®.

Zipper et al. found in 1969 that copper wire in a rabbit’s uterus prevents implantation of a blastocyst (146), and the same effect of intrauterine copper was also observed in rats and hamsters in 1970 (147, 148). The contraceptive effect seemed to be due to changes in the intrauterine environment that prevented implantation (147). The recently developed, inert Tatum T device had a poor contraceptive effect, but it served as a good carrier for copper wire (145). Copper-containing Tatum T (Figure 7) had low one- and two-year pregnancy (2.2–9.8%) and expulsion rates (4.9–6.6%) in clinical trials and a high continuation rate (76.5–77.6%) when compared to previous IUDs (145, 149, 150).
The Nova T®, a more flexible T-shaped device with an easier and safer insertion technique compared to the Tatum T device, was developed and manufactured by the Outokumpu Company (Pori, Finland) in the 1970s in cooperation with Leiras (Turku, Finland) (Figure 7) (151). The first Nova T® had the same amount of copper (200 mm²) as the Tatum T, but its copper wire was strengthened by a silver core. The first-year pregnancy rate for the Nova T® was only 0.7%, and the expulsion rate (5.8%) and continuation rate (72.6%) were comparable to the copper-containing Tatum T (151).

Several different copper-containing IUDs were developed and tested (152) during the next decades. Increasing the copper surface from 200 mm² to over 300 mm² increased contraceptive effectiveness, leading to pregnancy rates below 1 / 100 women-years (153). More copper (380 mm²) was also added to the Nova T® device, and the pregnancy rate was lowered to 0.4 / 100 women-years (154). Today several different copper IUDs are available. Women can choose from four different copper-containing IUDs in Finland: Nova T 380® (Bayer, Berlin, Germany), Flexi-T300® (Azanta, Denmark) (155), Flexi-T380® (Azanta, Denmark) and GyneFix® (Williams Medical Supplies Ltd, Great Britain) (156). All of these Cu-IUDs are approved for five years' use, but there is good evidence that their contraceptive effectiveness remains high up to ten years or more (157, 158).
2.4.4 LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM (LNG-IUS)

Intrauterine progestogen was expected, from the beginning, to increase long-term contraceptive effectiveness and to decrease uterine contractility (decrease expulsions) and vaginal bleeding.

The first report on intrauterine progestogen administration in animal studies (rats, rabbits and monkeys) was published in 1968 by Doyle et al. (159). Medroxyprogesterone acetate in Silastic rubber capsules prevented expulsions and inhibited mating.

Simultaneous with the development of subcutaneous capsules, Scommegna et al. published their results from studies with rhesus monkeys and human volunteers in 1970: A Silastic capsule filled with natural progesterone was added to an S-shaped intrauterine Lippes Loop device (Figure 8) (160). Clinical trials following the monkey experiment observed changes in the endometrium as early as 18 hours post insertion, and endometrial suppression was found from almost all endometrial samples taken during three months period post insertion. No systemic hormonal changes were detected, but the capsule was found to be empty approximately 12–14 weeks post insertion. The expulsion rate was 13%, and 23% of the volunteers experienced some adverse events. Additionally, several other intrauterine devices with different shapes and progestogens were tested in the early 1970s, but the clinical results were poor (11).

Pharris and Martinez-Manatou added a natural progesterone reservoir on the vertical arm of the T-shaped inert Tatum T device in 1974 and registered the device as trademark Progestasert® (Alza Corp, Palo Alto, California) (Figure 8) (161, 162). Natural progesterone was suspended as microcrystals in a fluid medium and put into an ethylene polymere capsule. This capsule was designed to release progesterone constantly over one year. Progestasert® had impressive contraceptive effectiveness (pregnancy rate 1%) and a low expulsion rate (2.8%) compared to the inert Tatum T device (pregnancy rate 18.3% and expulsion rate 5.9%). Even when Progestasert® users had more bleeding than the controls, the one-year continuation rate was 83.2% compared to 68.7% in the controls.

Nilsson et al. from Finland added a levonorgestrel-containing polylactate film in 1975, first around the horizontal arms of the inert Tatum T device (163). Hydrolysis of the polylactate film increased during bleeding periods. The polylactate film was replaced by Silastic rubber capsules to achieve a more stable hormone release (164). These Silastic capsules released levonorgestrel at a steady rate (50 mcg/day), and the rate was unaffected by bleeding episodes. The amount of bleeding decreased and dysmenorrhea seemed to
disappear. Endometrial and ovulatory suppression was also found with a displaced IUD.

The Nova T® copper IUD was developed as previously described in parallel with the abovementioned studies. Levonorgestrel was added to the vertical arm of the plain Nova T® device to improve the hormone-releasing ability and decrease bleeding problems (165). With this improved levonorgestrel-releasing intrauterine system (LNG-IUS), the amount of bleeding was reduced and the endometrium was suppressed, but ovulation was not inhibited in every woman (165, 166). The results from the first randomized clinical one-year performance trial of two LNG-IUSs (releasing levonorgestrel 20 mcg/day or 30 mcg/day) and Nova T® was published in *The Lancet* in 1981; a total of 483 women were randomized in an allocation ratio of 1:1:1 (167). Only one (0.6%) (ectopic) pregnancy was detected in the LNG-IUS groups compared to 4 (2.6%) in the Nova T® group. The LNG-IUS one-year continuation rates were good, 84.1% and 81.4%. LNG-IUS significantly decreased the bleeding days, but more spotting days were detected compared to the Nova T® group. However, the overall bleeding profile was favorable to LNG-IUS. The two-year results from the study showed that a release rate of 20 mcg/day levonorgestrel was sufficient (168). The five-year results from the first study showed that the cumulative pregnancy rate for LNG-IUS was 0.0–0.8%, the expulsion rate was 2.0–4.3%, and the continuation rate was 50% (169).

![Illustration of different types of progestogen releasing intrauterine systems](image)

**Figure 8.** Illustration of different types of progestogen releasing intrauterine systems. A. Lippes Loop, B. Progestasert®, and C. Mirena®.

Subsequent studies performed both globally and in the Nordic countries confirmed the safety and efficacy of the LNG-IUS (170, 171). Furthermore, its continuation rates increased after the first years, because removals due to amenorrhea diminished. Even the intracervical LNG-IUS was found to be effective (172-176). But fertility returns quickly, if needed, after LNG-IUS removal (177).
An LNG-IUS releasing 20 mcg/day was first approved for contraception in Finland in 1990, and it was first called Levonova®, later Mirena® (Figure 8). The FDA approved Mirena® in December 2000 (134). Today, Mirena® is not only an effective contraceptive, but it is also approved as treatment for heavy menstrual bleeding. Furthermore, it is used as treatment for, i.e., dysmenorrhea, endometriosis, endometrial hyperplasia and endometrial protection during hormone replacement therapy (178). Smaller and reduced amount of levonorgestrel-releasing intrauterine systems Jaydess®/Skyla® (8 mcg/day for three years) and Kyleena® (9 mcg/day for five years) were developed from Mirena® and are available for contraception today. A competing device available in some countries in Europe and the USA is called Levosert®/Liletta®. It releases 18.6 mcg/day levonorgestrel, has a different inserter and is cheaper compared to the original Mirena®.

2.4.5 EFFICACY OF LONG-ACTING REVERSIBLE CONTRACEPTION

Table 2 shows how the WHO has categorized different contraceptives according to their efficacy during a one-year, typical use, pregnancy rate [73].

<table>
<thead>
<tr>
<th>Table 2. Different contraceptives according to their efficacy.</th>
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<td><strong>Very effective methods (1-year typical use pregnancy rate &lt;1%)</strong></td>
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<td>Sterilization</td>
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<td>Intrauterine devices</td>
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<td>Implants</td>
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<td><strong>Effective methods (1-year typical use pregnancy rate 1-9%)</strong></td>
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<td>Pills</td>
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<td>Rings</td>
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<td>Patches</td>
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<td><strong>Moderately effective methods (1-year typical use pregnancy rate 10-25%)</strong></td>
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<td>Diaphragms with spermicide</td>
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<td><strong>Less effective methods (1-year typical use pregnancy rate 26-32%)</strong></td>
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</table>
Contraception effectiveness is commonly measured as Pearl’s index, which describes how many women out of 100 become pregnant during one-year of contraceptive use. Pearl’s index is low for the WHO’s effective methods during perfect use, but failure rates increase during typical use. On the contrary, Pearl’s index for long-acting reversible contraceptives (LARC: implants and intrauterine devices) is as good with typical use as with perfect use. Therefore, LARC methods are recommended if effective contraception is needed, as is usually the case after an induced abortion.

2.5 LONG-ACTING REVERSIBLE CONTRACEPTION FOLLOWING ABORTION

2.5.1 IMPLANT AND INTRAUTERINE CONTRACEPTION AT THE TIME OF SURGICAL ABORTION

According to several guidelines and reviews, initiation of intrauterine contraception and an implant is safe and effective during a surgical abortion procedure (15, 16, 179-182). Expulsion rates may be somewhat increased after immediate insertion of an intrauterine device (1.9–6.8% vs. 0.9–2.3%), especially in advanced gestational ages (15, 183-185). However, an increased initiation rate compared to delayed insertion compensates for this, and immediate insertion of an IUD results in a better six-month continuation (52–69% vs. 23–56%) and decreases subsequent unplanned pregnancies and abortions (15, 28, 184-188).

2.5.2 IMPLANT AT THE TIME OF MEDICAL ABORTION

Contraceptive implant insertion during misoprostol treatment is feasible. However, in many countries a woman can administer misoprostol herself at home in an early medical abortion, and a second visit for implant insertion is required. Inserting the implant at the same visit as the mifepristone is administered would remove this barrier. Theoretically, concomitant progestine treatment could have an effect on antiprogestine mifepristone efficacy. Raymond et al. and Hognert et al. conducted clinical trials in which an etonogestrel implant was inserted after mifepristone administration at the same visit (delay not specified) or one hour later, respectively (30, 189). Success rates without surgical intervention in both studies did not differ from the control groups (94–96% vs. 96%), but immediate implant insertion significantly increased both initiation (99–100% vs. 72–83%) and verified six-month continuation rates (72–86% vs. 58–77%).
Guidelines recommend that intrauterine contraception could be initiated after medical abortion as soon as completion of the abortion is confirmed (97, 179-181, 190). However, the insertion has been delayed up to several weeks (i.e., 3-4 weeks after an abortion or until the next menstruation) in clinical practice. Ovulation may return after abortion as soon as 8-10 days, and up to 83% of patients ovulate during the first menstrual cycle (191, 192). Also, sexual activity seems to return quickly after an abortion; 51% resumed coitus within two weeks and 87% within 8 weeks after an induced abortion (193). Obviously, delaying IUD insertion several weeks after abortion exposes a woman to a subsequent unplanned pregnancy and abortion.

Only a few studies had been published before this thesis study on shortening the delay for IUD insertion following a medical abortion. Verified IUD insertion 2–3 weeks after or the next menstruation following an early medical abortion prevented subsequent abortions (26). Table 3 summarizes the results from more recent studies assessing the safety and efficacy of a short delay between a medical abortion and IUD insertion. A short delay increased IUD uptake (91–97% vs. 24–86%), but a difference in the six-month continuation rate is not statistically significant. Expulsion rates following a short insertion delay has varied between 5.5–12%, and these rates have been comparable to delayed insertion.
Table 3. Summary of previous studies assessing safety and efficacy of intrauterine contraception initiation following medically induced abortion. Primary outcomes of the studies are indicated in **bold font**.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Prospective observational study</td>
<td>RCT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Retrospective case note review</td>
<td>RCT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RCT&lt;sup&gt;a&lt;/sup&gt; subanalysis</td>
</tr>
<tr>
<td><strong>Gest. age</strong></td>
<td>≤ 9 weeks</td>
<td>≤ 9 weeks</td>
<td>≤ 9 weeks</td>
<td>≤ 12 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>IUD type</strong></td>
<td>LNG-IUS or Cu-IUD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cu-IUD&lt;sup&gt;c&lt;/sup&gt;</td>
<td>LNG-IUS or Cu-IUD</td>
<td>LNG-IUS or Cu-IUD&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Insertion after mifepristone</strong></td>
<td>7-10 days</td>
<td>1 week vs. 4-6 weeks</td>
<td>Median of 21 days (range 0-54)</td>
<td>5-9 days vs. 3-4 weeks</td>
<td>1-4 weeks vs. control (&gt;2-4weeks)</td>
</tr>
<tr>
<td><strong>No of patients</strong></td>
<td>n=118</td>
<td>n=156</td>
<td>n=237</td>
<td>n=129</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-LNG-IUS n=77 (65%)</td>
<td>Early insertion n=71</td>
<td>Early insertion n=66</td>
<td>Early insertion n=66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Cu-IUD n=41 (35%)</td>
<td>Delayed insertion n=85</td>
<td>Delayed insertion n=63</td>
<td>Delayed insertion n=63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LFU&lt;sup&gt;e&lt;/sup&gt; n=21 (18%)</td>
<td>LFU&lt;sup&gt;e&lt;/sup&gt; 14 (9%)</td>
<td>LFU&lt;sup&gt;e&lt;/sup&gt; 8(13%) vs. 8(15%)</td>
<td>LFU&lt;sup&gt;e&lt;/sup&gt; n=14 (9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-ups</strong></td>
<td>Enrollment and insertion visit 7-10 days</td>
<td>Visit, randomization and early insertion 1-week</td>
<td>Insertion visit asap after abortion</td>
<td>Insertion visit 5-9 days or 3-4 weeks</td>
<td>Intervention group:</td>
</tr>
<tr>
<td></td>
<td>Telephone call 6 weeks after insertion</td>
<td>Delayed insertion 4-6 weeks</td>
<td>Visit 6 weeks post-abortion</td>
<td>Visit 4 weeks after insertion</td>
<td>-Insertion visit 1-4 weeks</td>
</tr>
<tr>
<td></td>
<td>Visit 3 months after insertion</td>
<td>Visit 8-9 weeks after insertion</td>
<td>Contact 3 months</td>
<td>Telephone call 6 months after insertion</td>
<td>-Follow-up visit 3 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visit 6 months</td>
<td></td>
<td>Control group:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Advised to schedule visit 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Electronic patient files review by 3 months</td>
</tr>
<tr>
<td><strong>IUD initiation</strong></td>
<td>Insertion 69 (97%) vs. 65 (76%), p&lt;0.001</td>
<td>Insertion visit attendance 126 (53%)</td>
<td>Insertion 62 (94%) vs. 54 (86%)</td>
<td>Insertion by 3 months: 280 (91.2%) vs. 72 (24.1%), OR 32.7 (95%CI 20.3–52.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Devices chosen -LNG-IUS 113 (90%)</td>
<td>IUD inserted 113 (90%)</td>
<td>Devices chosen -LNG-IUS 64 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Cu-IUD 49 (43%)</td>
<td></td>
<td>-Cu-IUD 49 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continuation</strong></td>
<td>3-month continuation 80%</td>
<td>6-month continuation 49 (69%) vs. 51 (60%), p=0.24</td>
<td>6-week post-insertion follow-up attendance 55 (49%)</td>
<td>6-month continuation 42 (67.7%) vs. 39 (72.2%), p= 0.55</td>
<td></td>
</tr>
</tbody>
</table>
| Expulsion | Expulsion at 3 months  
- Total 4 (4.1%)  
- Displaced 6 (6.2%) | Expulsion at 6 months  
8 (12%) vs. 7 (11%),  
p=0.88 | Total or partial expulsion  
at 6 weeks 4 (7.2%) | Expulsion at 6 months  
6 (9.7%) vs. 4 (7.4%)  
p=0.54f  
-LNG-IUS 4 (12.5%) vs. 4  
(13.8%), p=0.99  
-Cu-IUD 2 (6.7%) vs. 0  
(0%), p= 0.25 | Expulsion at 3 months  
Intervention groupf:  
- Total 5 (2.3%)  
- Partial 7 (3.2%)  
Control group: no data |
| --- | --- | --- | --- | --- | --- |
| Removal | 9 (9.3%) | 10 (14%) vs. 5 (8%)  
p=0.21 | 2 (3.6%) | 6-month discontinuation  
12 (19%) vs. 7 (13%)  
p=0.37 |
| Infection | No infections  
(No infection prophylaxis,  
women having PID were  
excluded) | No serious infections  
(Infection prophylaxis  
doxycycline 100mg x2 for  
1 week p.o.) | 4 (7.2%)  
(Infection prophylaxis  
Azithromycin 1g +  
metronidazole 1g p.o.) | No infections  
(Excluded if infection at  
insertion visit) | 29 (9.4%) vs. 17 (5.7%)  
OR 1.73 (95%CI 0.93–  
3.22)  
(Antibiotic treatment after  
IUD insertion n=5) |
| Bleeding | No difference in bleeding patterns,  
p=0.11 | No difference in bleeding patterns.  
LNG-IUS users: more  
bleeding days  
immediately after  
insertion, but less heavy  
bleeding during first 4  
weeks and 6 months | Extra visit due to bleeding  
20 (6.5%) vs. 23 (7.7%),  
OR 0.83 (95%CI 0.45–  
1.56) | No difference in adverse  
events due to bleeding |
| Other results | No perforations  
No pregnancies | Insertion pain  
VAS 10 mm vs. 13 mm,  
p=0.13  
Subsequent pregnancy  
0 (0%) vs. 4 (4.7%),  
p=0.09 | No perforations  
Insertion pain no  
difference  
Unprotected intercourse  
prior IUD insertion  
10 (16%) vs. 22 (44%)  
p=0.015  
No pregnancies | No perforations  
Residual tissue  
72 (23.5%) vs. 30 (10%),  
OR 2.75 (95%CI 1.73–  
4.35)  
Surgical evacuation  
40 (13.0%) vs. 24 (8.0%)  
p=0.045 |

*a Randomized controlled trial, b Copper T380, c ParaGard, d Nova T, e Loss to follow-up, f Per-protocol analysis
2.6 BARRIERS TO USING LONG-ACTING REVERSIBLE CONTRACEPTION AFTER ABORTION

Women are interested in long-acting contraception at the time of the abortion (199). However, interest and clinical practice do not meet, and several barriers prevent initiation of this highly effective contraception.

2.6.1 COUNSELLING

According to Finnish law, women requesting abortion should receive contraceptive counselling by their doctor before leaving the hospital (4, 5). Counselling is not easy and should be done nonjudgmentally (200). Evidence of the effectiveness of contraceptive counselling alone is controversial.

Langston et al. published in 2010 a RCT of 222 patients comparing additional structured, non-directive, non-physician contraceptive counselling among women seeking a first trimester surgical abortion (94% induced, 6% spontaneous abortion) (201). Additional counselling had no effect on the contraceptive method chosen, initiation or three- and six-month self-reported (phone calls) continuation rates. Contraceptives were free of cost. All women also received counselling from their specialized physician, which might have reduced the efficacy. A very effective method (implant, IUDs, sterilization) was chosen by 50-58% women; the three-month continuation rates were 77-85% and six-month continuation rates were 67-68%.

2.6.2 COST OF CONTRACEPTION

Long-acting reversible contraception can be quite expensive in many countries. A Cu-IUD costs 93–134 Euros, the LNG-IUS costs 146–153 Euros and an implant costs 162-175 Euros in Finland if the woman must buy it herself. Furthermore, inequality exists between different communities and between women in different age-groups. For example, since 2013, women residents of Vantaa (city in the Helsinki metropolitan area) have had an opportunity to have a free-of-cost LARC from their primary health care provider any time, not only after induced abortion. A free-of-cost LARC and easy access to contraception services increased the LARC initiation rate and the reduced abortion rate when compared to Espoo, a city next to Vantaa in the Helsinki metropolitan area without similar contraception services (202). Adolescent women are especially likely to benefit from these services.

Rose et al. conducted a prospective intervention study in New Zealand in 2010 in which they offered an LNG-IUS free of cost (previously 360 dollars) or a Cu-IUD or an injectable depot medroxyprogesterone acetate (DMPA) (but
Review of the literature

not implant), and counselled both patients and staff (203). The study population comprised 1020 women, of whom 92-94% requested surgical abortion and 90% first trimester abortion. LARC uptake increased from 45% to 61% and LNG-IUS uptake from 6% to 36%. The highest uptake was reached among women from the most deprived socioeconomic status group. Self-reported (phone calls) continuation rates among LARC patients were 89% (6 weeks post abortion) and 78% (6 months post abortion), and LNG-IUS continuation rates were 89% and 81%, respectively. A prospective cohort study in Travis County (Texas, the U.S.) reported that 143 (28%) low-income women out of 518 women had an opportunity to receive free-of-cost LARC at the time of the induced abortion (204). A free-of-cost IUD or implant was chosen by 65% of them compared to 6-25% of women who had to pay it themselves. The continuation rates following immediate LARC initiation were high, according to phone calls: 91–94% at 6 months and 86–90% at 12 months.

2.6.3 ACCESS TO LONG-ACTING REVERSIBLE METHODS

Abortion and contraception services are often offered separately, or all contraceptives are not available during abortion service in many countries (205, 206). Women in Finland are also in an unequal position depending on where they live: Some communities offer different free-of-cost contraceptives to women in different age groups, and women have different accessibility to those services. According to a small survey, the time needed for an additional visit was the principal barrier to returning for a follow-up visit and IUD insertion (207). The same phenomenon has been seen in many other studies: Loss-to-follow up rates are high even if scheduling has been made flexibly at the time of the abortion and the cost barrier was removed.

2.6.4 REDUCING ALL BARRIERS

The Contraceptive CHOICE Project was a large cohort study project performed in the St Louis region in the U.S. during 2007–2011. It was designed to promote the use of LARC methods in three different ways: offering structured counselling that emphasizes the most effective LARC methods, removing the cost barrier with free-of-cost contraception for two to three years, and reducing the access barrier (208, 209). The primary objectives of the project were to reduce teen pregnancies and abortions. The study population comprised 9256 women, of whom approximately 1500 (16%) women were recruited at the abortion facilities and the others at family planning clinics or by different advertisements.

Among the CHOICE study participants, three out of four (75%) chose the LARC method during the intervention, most often the LNG-IUS (46%) (208). Among the women recruited at abortion clinics, up to 85% chose the LARC
method for post-abortal contraception. The difference in contraceptive failure rates between LARC users and other contraceptive users was remarkable; at one year 0.3% vs. 4.8%, at two years 0.9% vs. 7.8%, and at three years 0.6% vs. 9.4% (adjusted HR 21.8, 95% CI 13.7–34.9) (209). Furthermore, abortion and teen pregnancy rates decreased significantly (208, 210).
Aims of the study

3 AIMS OF THE STUDY

This thesis study was designed to assess the feasibility of immediate initiation of the levonorgestrel-releasing intrauterine system (LNG-IUS) following a medical first- and second-trimester-induced abortion and the effect of long-acting reversible contraception on subsequent unplanned pregnancies and abortions.

Specific objectives of the study were to:

1. compare the expulsion rates of the LNG-IUS following immediate (0–3 days after misoprostol) vs. delayed insertion (2–4 weeks after misoprostol) of the device (I, II);

2. assess the three-month complication rates and bleeding profiles following immediate and delayed LNG-IUS insertion (I, II);

3. assess one-year continuation rates following immediate and delayed LNG-IUS insertion (III); and

4. analyze the effects of long-acting reversible contraception on the rate of subsequent unwanted pregnancies and induced abortions (III, IV).
4 MATERIALS AND METHODS

This thesis consists of two parts:

**KILKE**, prospective clinical randomized controlled trial
(KIerukka Lääkkeellisen KEskeytyksen jälkeen i.e. Intrauterine system following medical abortion)

**CHOICE**, retrospective cohort study

Table 4 summarizes the main information on the KILKE and CHOICE studies. Detailed information on both studies is described in the original publications: the KILKE study in publications I, II and III, and the CHOICE study in publication IV.

**Table 4.** Summary of the thesis’ KILKE and CHOICE studies on women requesting a medical abortion.

<table>
<thead>
<tr>
<th></th>
<th>KILKE</th>
<th>CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>I, II, III</td>
<td>IV</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized contr. trial</td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>264</td>
<td>666</td>
</tr>
<tr>
<td>≤ 63*</td>
<td>108</td>
<td>507</td>
</tr>
<tr>
<td>64–84*</td>
<td>102</td>
<td>136</td>
</tr>
<tr>
<td>85–140*</td>
<td>57</td>
<td>23</td>
</tr>
<tr>
<td>Contraception</td>
<td>LNG-IUS</td>
<td>All methods</td>
</tr>
<tr>
<td>Follow-up(s)</td>
<td>2–4 weeks</td>
<td>Until subsequent abortion or unplanned pregnancy or Dec 31, 2014</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td></td>
</tr>
<tr>
<td>Main outcomes</td>
<td>LNG-IUS expulsion rate at 3 months</td>
<td>Risk factors affecting the selection and initiation of LARC</td>
</tr>
<tr>
<td></td>
<td>LNG-IUS continuation rate at 1 year</td>
<td>Effect of planned or initiated LARC on the risk of subsequent unwanted pregnancy and induced abortion</td>
</tr>
</tbody>
</table>

*Duration of gestation, days
4.1 PERMISSIONS AND ETHICAL APPROVALS

We obtained the approvals from the Hospital District of Helsinki and Uusimaa (December 21, 2012) and from the Ethics Committee for gynaecology and obstetrics, paediatrics and psychiatry (November 21, 2012, 355/13/03/03/2012) before initiating the KILKE clinical trial. We followed principles of the Declaration of Helsinki, and the study was web-posted at www.clinicaltrials.gov on Dec 13, 2012 (NCT01755715). We received the approvals for the CHOICE retrospective cohort study from the Hospital District of Helsinki and Uusimaa (October 25, 2013), and National Institute of Health and Welfare.

4.2 SUBJECTS

We recruited the KILKE population from January 30, 2013 to December 31, 2014. The CHOICE population comprised women requesting a medically induced abortion from January 17 to May 20, 2013. Both studies were conducted at the Department of Obstetrics and Gynaecology of the Helsinki University Hospital, Finland. The Department is a tertiary referral center and is responsible for performing practically all abortions in the Helsinki metropolitan area. All study subjects were adult (≥ 18 years) women undergoing medical abortion up to 20 weeks of gestation.

4.2.1 KILKE POPULATION (I, II, III)

We recruited women planning to have an LNG-IUS for post-abortal contraception and who were willing to participate in the KILKE trial. We excluded women under 18 years, those with a structural uterine abnormality, submucosal fibroid, suspected uterine or cervical neoplasia, or acute pelvic inflammatory disease. Other contraindications for the LNG-IUS, such as acute liver disease or prior breast cancer, did not exist among the women assessed for eligibility. Written informed consent was obtained from all patients before enrolment. A dedicated research nurse enrolled the participants. We had three separate patient groups of different gestational ages: ≤ 63, 64–84, and 85–140 days of gestation. As regards the group with the most advanced pregnancies (85–140 days of gestation), patient enrolment was halted on Dec 31, 2014 after inclusion of 57 patients because of a slow enrolment rate.

4.2.2 CHOICE POPULATION (IV)

We identified the CHOICE population from the hospital electronic outpatient and inpatient records by searching for all women requesting an induced abortion. Women choosing surgical abortion were excluded after reviewing the electronic patient files.
4.3 METHODS

4.3.1 RANDOMIZATION

The KILKE study compared immediate (0–3 days after misoprostol) and delayed insertion (2–4 weeks after misoprostol) of LNG-IUS (Mirena®, purchased from Bayer, Turku, Finland) after a medical abortion. The participants were randomized at the time of the abortion in a 1:1 allocation ratio to immediate or delayed insertion of an LNG-IUS by using a computer-generated list. Block randomization was performed with block sizes of four and six, and sequentially numbered opaque envelopes were used. The personnel responsible for generating the randomized list and sealing the envelopes did not take part in the enrolment.

4.3.2 COLLECTION OF DEMOGRAPHIC DATA

We collected demographic factors in the KILKE study by structured questionnaire from patients and supplied from hospital electronic records. In the retrospective CHOICE study, all demographics and contraceptive plans and initiations were collected from hospital electronic patient files.

4.3.3 MEDICAL ABORTION PROCEDURE

All abortion-related procedures were carried out according to current Finnish national guidelines on induced abortions (97). All women were screened for Chlamydia trachomatis infection and treated, if positive, before the medical procedure. Gestational age was determined by ultrasonography. All women orally received 200 mg of mifepristone (Mifepristone Linepharma®, Linepharma France) and received misoprostol (Cytotec®, Pfizer, Great Britain) 24–72 hours later. The women in the group with the shortest pregnancies (≤63 days of gestation) had an opportunity to self-administer 800 mcg misoprostol vaginally at home. When the gestational age was 64–84 or 85–140 days, patients received 400 mcg misoprostol vaginally at the clinic (orally in cases of heavy bleeding) every three hours until foetal expulsion.

4.3.4 CONTRACEPTION FOLLOWING ABORTION

Among the women randomized for immediate insertion in the group with the least advanced pregnancies (≤63 days of gestation), we inserted the LNG-IUS within three days (i.e., on the next normal working day) of misoprostol administration in the KILKE study. The LNG-IUS insertion occurred after foetal expulsion before leaving the hospital in the next group (64–84 days of gestation). Identifiable placental expulsion was awaited at the ward before
Materials and methods

LNG-IUS insertion and discharge from the hospital in cases of 85–140 days of gestation. We recorded a uterine sound measure and the uterine content thickness, measured by transvaginal ultrasonography, at the time of LNG-IUS insertion. We used the insertion technique recommended by the manufacturer of the LNG-IUS, and a fundal location was verified using vaginal ultrasonography. We recorded a pain score immediately after insertion using a numeric rating scale of zero (no pain) to ten (the most severe pain imaginable). The LNG-IUS was inserted during the procedure if uterine curettage was performed at the time of abortion and the woman was randomized to the immediate insertion group.

Among the women randomized to delayed insertion, the LNG-IUS insertion occurred at the 2–4-week follow-up using a similar technique to the other group. Insertion of the LNG-IUS was carried out during the procedure if uterine curettage was performed at the time of follow-up. The three investigators performed all the per-protocol insertions.

The LNG-IUS, Cu-IUD (Nova T380®, Bayer Pharma AG, Berlin, Germany), or contraceptive implant (Nexplanon®, N.V. Organon, Oss, Netherlands) was offered from the hospital free of cost in the CHOICE population (others than KILKE participants), if a woman had a history of previous induced abortions. An implant was inserted during the abortion procedure if abortion was conducted at the hospital ward. An IUD or implant insertion could have been scheduled in the outpatient clinic 2–4 weeks after medical procedure; otherwise, all women were prescribed some hormonal contraceptives at the time of the abortion. However, if these women would have obtained LARC, they were responsible themselves to contact either their primary health care center or private gynaecologist.

Two major cities of the Helsinki metropolitan area, namely Helsinki and Vantaa, were offering the first contraceptive LNG-IUS, Cu-IUD, or implant free of cost during the study period. The insertion occurred at the primary health care facility during a separate visit scheduled by the woman herself. These visits may have occurred up to three months after the first contact. We had no access to information on these insertions; thus, all verified LARC insertions in this study were free of cost.

4.3.5 FOLLOW-UPS

The KILKE study scheduled follow-ups at 2–4 weeks, three months and one year after an abortion. The women met one of the researchers in the first follow-up. A clinical examination and ultrasound were performed and possible complications were recorded. An LNG-IUS was inserted if woman had been randomized to a delayed-insertion group.
The research nurse performed a speculum examination at the three-month visit to check for the presence and appropriate length of the LNG-IUS threads in the cervix. If the threads were not visible or appeared too long, the researcher performed ultrasonography.

The researcher also examined the women at a one-year follow-up when a clinical examination and ultrasound was performed again. The patients also answered a questionnaire concerning menstruation, contraception and quality of life at the beginning of the study, at the three-month and one-year visits. We recorded possible complications at every follow-up visit. If the patient did not attend the follow-up visit, the research nurse tried to contact her by calling or text messaging two to three times, and if contacted, a new appointment was scheduled if desired. The electronic patient files of the hospital district of Helsinki and Uusimaa were revised to minimize the drop-out rate and maximize the information.

The CHOICE study followed patients by electronic patient files and from the Abortion Register until a subsequent abortion, an unplanned pregnancy, or to the end of year 2014.

4.3.6 EXPULSIONS AND ADVERSE EVENTS

An LNG-IUS was recorded as being “expelled” in the KILKE study when it was spontaneously and completely expelled from the uterus and “partially expelled” if any part of the LNG-IUS was visible in the cervix or the stem of the LNG-IUS was seen to be in the cervix in ultrasonography. A new LNG-IUS was offered if it was partially or totally expelled.

No pre-existing criteria for other adverse events were defined, and diagnoses and treatment were based on clinical judgement and practice.

4.3.7 BLEEDING DATA

Women in the KILKE study recorded their uterine bleeding during a 90-day reference period by using a bleeding chart. A three-point scale of heavy bleeding, bleeding, and spotting was used. Heavy bleeding was described as a need for the largest sanitary towels during the day or overflow at night; bleeding was described as a need for a normal sanitary towel or tampon; and spotting was described as a need for a panty-liner or small tampon or no need for sanitary protection.
4.3.8 STATISTICAL ANALYSIS

Calculation of sample size in the KILKE study was based on the reported expulsion rate of 8% following post-abortal insertion (194, 196, 211). We considered a difference of $\leq 20\%$ to be clinically insignificant to show that expulsion rates are not different. Assuming an alpha level of 0.05 for a two-sided test, a number of 48 subjects per group would result in 90% power. As loss in the follow-up visit of 4% was anticipated, we thus planned to recruit 50 patients per group. We had three subgroups; ≤ 63, 64–84 and 85–140 days of gestation as we wanted to assess the rate of expulsion at different gestational ages. We thus aimed to recruit 100 women to each subgroup (total of 300 patients).

We performed intention-to-treat analyses regarding the primary outcome and all secondary outcomes in the KILKE study. Per-protocol analyses were also carried out if appropriate.

Both studies analyzed categorical data by cross tabulation and calculated statistical significance by using Fisher’s exact test (KILKE) and Chi-square test (CHOICE). The Mann–Whitney $U$-test was used for continuous variables. Risk ratios were calculated by logistic regression, and the Kruskall–Wallis test was performed to detect differences between the subgroups. Kaplan-Meier analysis and Log-Rank test were used to describe subsequent unwanted pregnancies and abortions. Survival analysis and hazard ratios were analyzed by Cox’s regression model in the CHOICE study. Analysis of bleeding diaries was modified from the method described by Belsey et al. (212) – the numbers of bleeding and spotting days, length of first bleeding episode and numbers of bleeding and/or spotting episodes were calculated. At least two days of no bleeding or spotting were required between episodes. All analyses were performed with IBM SPSS statistical software versions 22 and 24.
5 RESULTS

5.1 STUDY POPULATION

Figure 9 shows the formation of the KILKE and CHOICE study populations among women requesting medical abortion during January, 2013, to December, 2014. A total of 267 women were recruited to the KILKE study. Three women were excluded after randomization because of continuing pregnancy (1 woman, immediate-insertion group) and suspected cervical neoplasia (2 women, delayed-insertion group). The immediate-insertion group comprised 133 women and the delayed-insertion group had 131 women after these exclusions. Figure 10 presents the KILKE study flowchart.

Out of 722 women requesting an induced abortion during the CHOICE inclusion period, 666 out of them requested medical abortion. A total of 159 women in the CHOICE population were also KILKE study participants. Table 5 summarizes the demographics of both study populations.

Table 5. Demographics of the 264 KILKE (I, II, III) and 666 CHOICE (IV) study participants undergoing a medically induced abortion between January 30, 2013 – December 31, 2014 (KILKE) and January 17–May 30, 2013 (CHOICE) in Helsinki University Hospital. Data are presented as median (interquartile range), or n (%).

<table>
<thead>
<tr>
<th>KILKE population</th>
<th>CHOICE population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate insertion</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>27.3 (23.1–32.3)</td>
</tr>
<tr>
<td><strong>Age &lt; 25 years</strong></td>
<td>48 (36.1%)</td>
</tr>
<tr>
<td>≥ 25 years</td>
<td>85 (63.9%)</td>
</tr>
<tr>
<td><strong>BMI</strong>a</td>
<td>23.6 (21.7–26.5)</td>
</tr>
<tr>
<td>History of pregnancy</td>
<td>89 (66.9%)</td>
</tr>
<tr>
<td>History of delivery</td>
<td>71 (53.4%)</td>
</tr>
<tr>
<td>History of abortion</td>
<td>57 (42.9%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>70 (52.6%)</td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>47 (35.3%)</td>
</tr>
<tr>
<td>Divorced</td>
<td>12 (9.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>69 (51.9%)</td>
</tr>
<tr>
<td>Regular use of alcohol</td>
<td>88 (66.7%)</td>
</tr>
<tr>
<td>Duration of gestation, days</td>
<td>67 (51.5–78.5)</td>
</tr>
<tr>
<td>≤ 63</td>
<td>55 (41.4%)</td>
</tr>
<tr>
<td>64–84</td>
<td>51 (38.3%)</td>
</tr>
<tr>
<td>85–140</td>
<td>27 (20.3%)</td>
</tr>
</tbody>
</table>

^ Includes 159 KILKE patients
* BMI = body mass index (kg/m^2)
# Body mass index (kg/m^2) (missing n=90 [13.5%]) (median [IQR])
\^ Regular daily smoking (missing n=17 [2.6%])
\^ Regular weekly use of alcohol (missing n=59 [8.9%])
Figure 9. Formation of the KILKE and CHOICE populations among women requesting medical abortion during January, 2013 to December, 2014.
Figure 10. Flowchart of the randomized controlled KILKE study.
Results

Follow-up 2 to 4 weeks 121
- Did not attend to follow-up 6

Follow-up 2 to 4 weeks 115
- Refused LNG-IUS insertion 3
  - Did not attend to follow-up 13

LNG-IUS inserted after medical abortion 101
  (Included in per-protocol analysis)

LNG-IUS inserted in 2nd follow-up after medication of residua and/or infection 5

LNG-IUS inserted in vacuum aspiration 5

Follow-up 3 months 98
- LNG-IUS removed 1
  - Did not attend to follow-up 22

Follow-up 3 months 78
- LNG-IUS removed 3
  - Did not attend to follow-up 30

Follow-up 1 year 79
  + 10 = 89

Follow-up 1 year 55
  + 8 = 63
5.2 CONTRACEPTIVE PLANS AND INITIATIONS

LARC was planned for all 264 women in the KILKE population and for the 360 (54.1%) women in the CHOICE population (Figure 9). LARC was planned more often in the CHOICE population for women older than 25 years, women with history of pregnancy or induced abortion and women requesting a second trimester abortion (Table 6). LARC was not only planned but also initiated more often for these women except for women older than 25 years. LARC was also initiated more often for women treated in the hospital ward compared to women who administered misoprostol at home. LARC initiation could be verified for a total of 177 (26.6%) cases in the CHOICE population.

Table 6. LARC plans and insertions according to selected demographic factors among the CHOICE population.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LARC planned^</th>
<th>p-value</th>
<th>LARC inserted^</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>283</td>
<td>135 (47.7%)</td>
<td>0.005</td>
<td>66 (23.3%)</td>
<td>0.10</td>
</tr>
<tr>
<td>≥25 years</td>
<td>383</td>
<td>225 (58.7%)</td>
<td></td>
<td>111 (29.0%)</td>
<td></td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>395</td>
<td>256 (64.8%)</td>
<td>&lt;0.001</td>
<td>131 (33.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>271</td>
<td>149 (51.7%)</td>
<td></td>
<td>46 (17.0%)</td>
<td></td>
</tr>
<tr>
<td>Previous induced abortion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>229</td>
<td>149 (65.1%)</td>
<td>&lt;0.001</td>
<td>81 (35.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>437</td>
<td>211 (48.3%)</td>
<td></td>
<td>96 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Gestational-age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤63 days</td>
<td>507</td>
<td>265 (52.3%)</td>
<td>0.04</td>
<td>114 (22.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>64-84 days</td>
<td>136</td>
<td>77 (56.6%)</td>
<td></td>
<td>48 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>≥85 days</td>
<td>23</td>
<td>18 (78.3%)</td>
<td></td>
<td>15 (65.2%)</td>
<td></td>
</tr>
<tr>
<td>Abortion partially at home among gestation of ≤63 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>437</td>
<td>226 (51.7%)</td>
<td>0.53</td>
<td>89 (20.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>39 (55.7%)</td>
<td></td>
<td>25 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Participated in randomized trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>159</td>
<td>159 (100.0%)</td>
<td>&lt;0.001</td>
<td>141 (88.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>507</td>
<td>201 (39.6%)</td>
<td></td>
<td>36 (7.1%)</td>
<td></td>
</tr>
</tbody>
</table>

^ ‘LARC planned’ means that woman was recruited to the randomized study or LARC was planned for post-abortion contraception.

^ ‘LARC initiated’ means that initiation was verified as a part of the randomized study or insertion occurred in a hospital within one month following the abortion.
**Results**

LNG-IUS was inserted more often in the KILKE population for women in the immediate-insertion group compared to the delayed-insertion group (127 [95.5%] vs. 111 [84.7%], RR 1.13, 95%CI 1.04–1.22, p=0.004) (Table 7). Per-protocol insertion (only after an uncomplicated medical abortion and in a pre-defined time-frame) occurred in 116 (87.2%) compared to 101 (77.1%) women (RR 1.01, 95%CI 0.94–1.09, p=0.82), respectively. Only one immediate insertion (0.8%) failed (64–84-day-subgroup), and almost all (106 [91.4%] vs. 94 [93.1%], p=0.80) of the per-protocol insertions occurred without any problems (i.e., LNG-IUS displaced, the need for cervical dilatation, cervical *via falsa* by sound, LNG-IUS extraction by scissors).

**Table 7.** Initiation rates of the levonorgestrel-releasing intrauterine system (LNG-IUS) contraception in the KILKE population following immediate (≤ 3 days) or delayed (2 to 4 weeks) insertion after a medical abortion (intention-to-treat analysis).

<table>
<thead>
<tr>
<th>Duration</th>
<th>Immediate Insertion</th>
<th>Delayed Insertion</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>63b (n=55 vs. 53)</td>
<td>127 (95.5%)</td>
<td>111 (84.7%)</td>
<td>1.13 (1.04–1.22)</td>
<td>0.004</td>
</tr>
<tr>
<td>64–84 (n=51 vs. 50)</td>
<td>50 (98.0%)</td>
<td>47 (88.7%)</td>
<td>1.05 (0.93–1.18)</td>
<td>0.52</td>
</tr>
<tr>
<td>85–140 (n=27 vs. 28)</td>
<td>26 (96.3%)</td>
<td>23 (82.1%)</td>
<td>1.17 (0.97–1.41)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*a* LNG-IUS inserted within trial  
*b* Different subgroups according to duration of gestation (days)

### 5.3 EXPULSIONS

Table 8 presents the LNG-IUS expulsion rates according to the per-protocol analysis. The number of total expulsions did not differ between the study groups, but the partial expulsion rate was higher following immediate LNG-IUS insertion. The difference was significant in the subgroup of 64–84 days of gestation.

Three out of six totally expelled (two in the immediate- and one in the delayed-insertion group) and all partially expelled LNG-IUS were replaced. One woman expelled LNG-IUS totally again and after that she initiated another contraception method.

Endometrial thickness was measured by ultrasound before LNG-IUS insertion (I, II), and thickness did not correlate to either partial or total LNG-IUS expulsions (data not shown).
**Table 8.** Expulsions of the levonorgestrel-releasing intrauterine system (LNG-IUS) by three months and one year (per-protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Three months</th>
<th>One year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate n=116</td>
<td>Delayed n=101</td>
</tr>
<tr>
<td>Expulsion total or partial</td>
<td>24 (20.7%)</td>
<td>4 (4.0%)</td>
</tr>
<tr>
<td>≤ 63*</td>
<td>6 (12.5%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>64–84</td>
<td>13 (30.2%)</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>85–140</td>
<td>5 (20.0%)</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Expulsion total</td>
<td>3 (2.6%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>≤ 63</td>
<td>1 (2.1%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>64–84</td>
<td>2 (4.7%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>85–140</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Expulsion partial</td>
<td>21 (18.1%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>≤ 63</td>
<td>5 (10.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>64–84</td>
<td>11 (25.6%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>85–140</td>
<td>5 (20.0%)</td>
<td>1 (4.5%)</td>
</tr>
</tbody>
</table>

* Different subgroups according to duration of gestation (days)

Numbers of patients in subgroups of different duration of gestation:

- ≤ 63 days: n = 48 vs. 44
- 64–84 days: n = 43 vs. 35
- 85–140 days: n = 25 vs. 22


## 5.4 ADVERSE EVENTS

No cases of uterine perforation occurred during LNG-IUS insertion. Table 9 presents the adverse events observed in the KILKE study.

**Table 9.** Adverse events by three months in the KILKE study according to duration of gestation (days). Intention-to-treat analysis.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Immediate insertion</th>
<th>Delayed insertion</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early surgical operation</strong></td>
<td>9 (6.8%)</td>
<td>8 (6.1%)</td>
<td>1.11 (0.44–2.78)</td>
<td>1.00</td>
</tr>
<tr>
<td>≤ 63 (n=55 vs. 53)</td>
<td>2 (3.6%)</td>
<td>0 (0%)</td>
<td>Not applicable</td>
<td>0.50</td>
</tr>
<tr>
<td>64–84 (n=51 vs. 50)</td>
<td>6 (11.8%)</td>
<td>5 (10.0%)</td>
<td>1.18 (0.38–3.61)</td>
<td>1.00</td>
</tr>
<tr>
<td>85–140 (n=27 vs. 28)</td>
<td>1 (3.7%)</td>
<td>3 (10.7%)</td>
<td>0.35 (0.04–3.12)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Later surgical operation</strong></td>
<td>5 (3.8%)</td>
<td>10 (7.6%)</td>
<td>0.49 (0.17–1.40)</td>
<td>0.19</td>
</tr>
<tr>
<td>≤ 63</td>
<td>1 (1.8%)</td>
<td>4 (7.5%)</td>
<td>0.24 (0.03–2.09)</td>
<td>0.20</td>
</tr>
<tr>
<td>64–84</td>
<td>2 (3.9%)</td>
<td>3 (6.0%)</td>
<td>0.65 (0.11–3.75)</td>
<td>0.68</td>
</tr>
<tr>
<td>85–140</td>
<td>2 (7.4%)</td>
<td>3 (10.7%)</td>
<td>0.69 (0.13–3.82)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Residua</strong></td>
<td>7 (5.3%)</td>
<td>15 (11.5%)</td>
<td>0.46 (0.19–1.09)</td>
<td>0.08</td>
</tr>
<tr>
<td>≤ 63</td>
<td>3 (5.5%)</td>
<td>4 (7.5%)</td>
<td>0.72 (0.17–3.08)</td>
<td>0.71</td>
</tr>
<tr>
<td>64–84</td>
<td>2 (3.9%)</td>
<td>7 (14.0%)</td>
<td>0.28 (0.06–1.28)</td>
<td>0.09</td>
</tr>
<tr>
<td>85–140</td>
<td>2 (7.4%)</td>
<td>4 (14.3%)</td>
<td>0.52 (0.10–2.60)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Residua (medicated only)</strong></td>
<td>2 (1.5%)</td>
<td>5 (3.8%)</td>
<td>0.39 (0.08–1.99)</td>
<td>0.28</td>
</tr>
<tr>
<td>≤ 63</td>
<td>2 (3.6%)</td>
<td>0 (0.0%)</td>
<td>Not applicable</td>
<td>0.50</td>
</tr>
<tr>
<td>64–84</td>
<td>0 (0.0%)</td>
<td>4 (8.0%)</td>
<td>Not applicable</td>
<td>0.06</td>
</tr>
<tr>
<td>85–140</td>
<td>0 (0.0%)</td>
<td>1 (3.6 %)</td>
<td>Not applicable</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>17 (12.8%)</td>
<td>12 (9.2%)</td>
<td>1.40 (0.69–2.81)</td>
<td>0.43</td>
</tr>
<tr>
<td>≤ 63</td>
<td>6 (10.9%)</td>
<td>3 (5.7%)</td>
<td>1.93 (0.51–7.31)</td>
<td>0.49</td>
</tr>
<tr>
<td>64–84</td>
<td>5 (9.8%)</td>
<td>4 (8.0%)</td>
<td>1.23 (0.35–4.30)</td>
<td>1.00</td>
</tr>
<tr>
<td>85–140</td>
<td>6 (22.2%)</td>
<td>5 (17.9%)</td>
<td>1.24 (0.43–3.60)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Bleeding problem</strong></td>
<td>8 (6.0%)</td>
<td>15 (11.5%)</td>
<td>0.53 (0.23–1.20)</td>
<td>0.13</td>
</tr>
<tr>
<td>≤ 63</td>
<td>3 (5.5%)</td>
<td>5 (9.4%)</td>
<td>0.58 (0.15–2.30)</td>
<td>0.49</td>
</tr>
<tr>
<td>64–84</td>
<td>4 (7.8%)</td>
<td>7 (14.0%)</td>
<td>0.56 (0.18–1.80)</td>
<td>0.36</td>
</tr>
<tr>
<td>85–140</td>
<td>1 (3.7%)</td>
<td>3 (10.7%)</td>
<td>0.35 (0.04–3.12)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Any problem</strong></td>
<td>32 (24.1%)</td>
<td>38 (29.0%)</td>
<td>0.83 (0.55–1.24)</td>
<td>0.40</td>
</tr>
<tr>
<td>≤ 63</td>
<td>13 (23.6%)</td>
<td>11 (20.8 %)</td>
<td>1.14 (0.56–2.31)</td>
<td>0.82</td>
</tr>
<tr>
<td>64–84</td>
<td>12 (23.5%)</td>
<td>18 (36.0 %)</td>
<td>0.65 (0.35–1.21)</td>
<td>0.20</td>
</tr>
<tr>
<td>85–140</td>
<td>7 (25.9%)</td>
<td>9 (32.1 %)</td>
<td>0.81 (0.35–1.86)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

*a* Vacuum aspiration / surgical evacuation of the uterus performed immediately at the hospital because of heavy bleeding, failed abortion or incomplete abortion.

*b* Vacuum aspiration or hysteroscopy >4 days of abortion because of incomplete abortion, bleeding problem and/or clinical infection.

*c* Residual tissue treated by means of medication (administration of additional misoprostol) or surgical evacuation.

*d* Bleeding problem resulting in an additional contact or intervention (medication, surgical evacuation, blood transfusion).

*e* Any problem associated with abortion or IUD, leading to additional contact or intervention.
5.5 BLEEDING PROFILES

 Appropriately filled bleeding diaries were returned by 86 (64.7%) women in the immediate-insertion group and by 64 (48.9%) women in the delayed-insertion group (p=0.013). Of these, 79 (59.4%) and 60 (45.8%) (p=0.048), respectively, were filled by women who received the LNG-IUS per protocol. Table 10 presents bleeding patterns and Figure 12 shows the bleeding profiles. The women who returned the diaries were compared with those who did not in regard to their demographic background factors to assess the validity of returned diaries. Both groups were similar: Only the non-smokers (return rates 55.7% vs. 37.9%, p=0.005) and nulliparous women (53.6% vs. 40.3%, p=0.036) were overrepresented in the group who returned their diaries. Insertion problems and pain scores did not affect the return rates.

Table 10. Bleeding profiles during the 90-day reference period calculated from the day of first misoprostol administration (per-protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Immediate insertion n=79</th>
<th>Delayed insertion n=60</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First bleeding or spotting episode (days)</td>
<td>24 (16–56)</td>
<td>18 (13–40)</td>
<td>0.04</td>
</tr>
<tr>
<td>Heavy bleeding</td>
<td>2 (0–4)</td>
<td>2 (0–5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Bleeding</td>
<td>9 (4–15)</td>
<td>7 (4–11)</td>
<td>0.21</td>
</tr>
<tr>
<td>Spotting</td>
<td>12 (6–25)</td>
<td>8 (4–14)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total number of bleeding and spotting days</td>
<td>48 (33–68)</td>
<td>41 (30–59)</td>
<td>0.23</td>
</tr>
<tr>
<td>Heavy bleeding</td>
<td>2 (0–5)</td>
<td>3 (0–6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Bleeding</td>
<td>13 (6–21)</td>
<td>13 (8–19)</td>
<td>0.95</td>
</tr>
<tr>
<td>Spotting</td>
<td>26 (14–46)</td>
<td>22 (13–37)</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of bleeding and/or spotting episodes</td>
<td>3 (2–4)</td>
<td>3 (2–6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of heavy bleeding and/or bleeding-only episodes</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Number of spotting-only episodes</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>0.67</td>
</tr>
<tr>
<td>Number of bleeding or spotting days/episode (days)</td>
<td>12 (8–31)</td>
<td>10 (6–24)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

Heavy bleeding was described as the need for the largest available sanitary towel during the day or overflow at night, bleeding as the need for a normal sanitary towel or tampon, and spotting as the need for a panty-liner or small tampon, or no need for sanitary protection.
Figure 12. Bleeding profiles after medical abortion according to LNG-IUS insertion group.

Heavy bleeding was described as the need for the largest sanitary towel on daytime or overflow on nights, bleeding as the need for a normal sanitary towel or tampons, and spotting as the need for a panty liner or small tampon, or no need for sanitary protection.
5.6 CONTINUATION OF CONTRACEPTION

Table 11 presents the LNG-IUS continuation rates in the KILKE population. The verified one-year continuation rates were 62.4% in the immediate-insertion group compared to 39.7% in the delayed-insertion group (RR 1.57, 95%CI 1.23–2.02). Figure 13 visualizes the results of a sensitivity analysis of continuation rates.

Table 11. Continuation rates of the levonorgestrel-releasing intrauterine system (LNG-IUS) contraception following immediate (≤ 3 days) or delayed (2 to 4 weeks) insertion after medical abortion in the KILKE study at three months and one year (intention-to-treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>Immediate insertion n=133</th>
<th>Delayed insertion n=131</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best-case scenario</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG-IUS use verified at 3 months or LNG-IUS inserted</td>
<td>125 (94.0%)</td>
<td>110 (84.0%)</td>
<td>1.12 (1.03–1.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>≤ 63*</td>
<td>50 (90.9%)</td>
<td>47 (88.7%)</td>
<td>1.03 (0.90–1.16)</td>
<td>0.76</td>
</tr>
<tr>
<td>64–84</td>
<td>50 (98.0%)</td>
<td>41 (82.0%)</td>
<td>1.20 (1.04–1.37)</td>
<td>0.008</td>
</tr>
<tr>
<td>85–140</td>
<td>25 (92.6%)</td>
<td>22 (78.6%)</td>
<td>1.18 (0.94–1.47)</td>
<td>0.25</td>
</tr>
<tr>
<td>LNG-IUS use verified at 1 year or LNG-IUS inserted</td>
<td>113 (85.0%)</td>
<td>88 (67.2%)</td>
<td>1.26 (1.10–1.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>≤ 63</td>
<td>44 (80.0%)</td>
<td>38 (71.7%)</td>
<td>1.12 (0.90–1.38)</td>
<td>0.37</td>
</tr>
<tr>
<td>64–84</td>
<td>45 (88.2%)</td>
<td>33 (66.0%)</td>
<td>1.34 (1.07–1.67)</td>
<td>0.009</td>
</tr>
<tr>
<td>85–140</td>
<td>24 (88.9%)</td>
<td>17 (60.7%)</td>
<td>1.46 (1.06–2.03)</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Worst-case scenario</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG-IUS use verified at 3 months</td>
<td>96 (72.2%)</td>
<td>75 (57.3%)</td>
<td>1.26 (1.05–1.51)</td>
<td>0.014</td>
</tr>
<tr>
<td>≤ 63</td>
<td>41 (74.5%)</td>
<td>31 (58.5%)</td>
<td>1.27 (0.97–1.68)</td>
<td>0.10</td>
</tr>
<tr>
<td>64–84</td>
<td>37 (72.5%)</td>
<td>29 (58.0%)</td>
<td>1.25 (0.94–1.67)</td>
<td>0.15</td>
</tr>
<tr>
<td>85–140</td>
<td>18 (66.7%)</td>
<td>15 (53.6%)</td>
<td>1.24 (0.81–1.92)</td>
<td>0.41</td>
</tr>
<tr>
<td>LNG-IUS use verified at 1 year</td>
<td>83 (62.4%)</td>
<td>52 (39.7%)</td>
<td>1.57 (1.23–2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤ 63</td>
<td>33 (60.0%)</td>
<td>24 (45.3%)</td>
<td>1.33 (0.92–1.91)</td>
<td>0.18</td>
</tr>
<tr>
<td>64–84</td>
<td>35 (68.6%)</td>
<td>21 (42.0%)</td>
<td>1.63 (1.12–2.38)</td>
<td>0.009</td>
</tr>
<tr>
<td>85–140</td>
<td>15 (55.6%)</td>
<td>7 (25.0%)</td>
<td>2.22 (1.08–4.59)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

* Different subgroups according to duration of gestation (days)
** The best-case scenario: LNG-IUS inserted and its use verified or status unknown at 1 year.
*** The worst-case scenario: LNG-IUS inserted and its use verified at 1 year
Figure 13. Continuation rates at three months and one year following immediate or delayed insertion of LNG-IUS, best-case and worst-case scenarios.

The best-case scenario is defined as LNG-IUS inserted, and its use verified or status unknown at three months and one year.

The worst-case scenario is defined as LNG-IUS inserted, and its use verified at three months and one year.
5.7 SUBSEQUENT PREGNANCIES AND ABORTIONS

Information on subsequent pregnancies and induced abortions were collected from all study subjects. The KILKE study’s follow-up time was one year following the index abortion; the CHOICE study’s median follow-up time was 21 months (IQR 20–22).

Altogether, 22 (8.3%) subsequent pregnancies occurred in the KILKE population, of which 9 (3.4%) women ended up with a subsequent abortion. One partial and one total unrecognized LNG-IUS expulsion was diagnosed at the time of the subsequent abortions. One woman requesting a subsequent abortion received an LNG-IUS, but she never returned for her follow-ups. All other subsequent abortions occurred in women who did not receive a LNG-IUS or her LNG-IUS was removed. Of the remaining 13 pregnancies, ten resulted in a delivery and three in a miscarriage.

In the CHOICE population, 54 women (8.1%) requested a subsequent abortion during the follow-up period, and the median time to a subsequent abortion was 11 months (IQR 8–15). An additional five women were observed to have an unwanted pregnancy.

Table 12 presents subsequent pregnancies and abortions in both studies according to LARC initiation status. An initiated LARC prevented subsequent pregnancies and abortions compared to women only planning LARC for their post-abortion contraception in both study populations. The CHOICE population had the lowest subsequent abortion rate following initiated LARC (Figure 14). Furthermore, other prescribed contraception methods (i.e., oral contraceptives, patch, ring, condom, sterilization) had better contraceptive efficacy compared to only planned, not initiated LARC.
Table 12. Subsequent pregnancies (A.) and abortions (B.) among women planning LNG-IUS (KILKE population) or LARC (CHOICE population). All pregnancies occurred in the KILKE population are recorded, but only unwanted pregnancies in the CHOICE population are recorded. Follow-up time is one year for KILKE population and 21 months (median) for CHOICE population.

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy</th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong></td>
<td></td>
<td></td>
<td>Risk ratio (95%CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KILKE</td>
<td>LNG-IUS planned, not inserted (n=26)</td>
<td>11 (42.3%)</td>
<td>9.15 (4.41–19.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LNG-IUS inserted (n=238)</td>
<td>11 (4.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOICE</td>
<td>LARC planned, not inserted (n=183)</td>
<td>30 (16.4%)</td>
<td>7.25 (2.61–20.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LARC inserted (n=177)</td>
<td>4 (2.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Abortion</th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B.</strong></td>
<td></td>
<td></td>
<td>Risk ratio (95%CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KILKE</td>
<td>LNG-IUS planned, not inserted (n=26)</td>
<td>4 (15.4%)</td>
<td>7.32 (2.10–25.58)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>LNG-IUS inserted (n=238)</td>
<td>5 (2.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOICE</td>
<td>LARC planned, not inserted (n=183)</td>
<td>29 (15.8%)</td>
<td>7.01 (2.52–19.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LARC inserted (n=177)</td>
<td>4 (2.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 14. Survival without subsequent abortion according to contraceptive plans and LARC initiation status. CHOICE population, 666 women.
6 DISCUSSION

6.1 CONTRACEPTIVE PLANS

Women with a recent history of induced abortion are a highly fertile population. LARC should be a real option to choose for post-abortal contraception. Results from the contraceptive CHOICE project from the U.S. showed that the post-abortal LARC was chosen 1.8–3.3 times more often at the time of the abortion compared to women without a recent history of induced abortion (213). If LARC initiation was delayed, the choice of LARC method occurred as often as among women without a recent history of abortion. A large population-based study from England and Wales analyzed the contraceptive method preferences and provision among 211,000 women requesting abortion (214). Young age (<20 years), surgical abortion and option to receive contraception from the same facility as the abortion, in addition to a history of pregnancy and abortion, increased the LARC uptake. LARC was planned more often for women older than 25 years in our CHOICE cohort, but in practice LARC was initiated similarly in both age-groups (<25 years 23% vs. ≥25 years 29%). Moreover, women with a history of a previous pregnancy (65% vs. 38%), with a previous abortion (65% vs. 48%) and with a second-trimester abortion (78% vs. 52–57%) planned LARC for their post-abortal contraception more often compared to women with no such history. It is important to note that we especially planned LARC for the women with these factors in the present study, as they are found to be at risk for a subsequent abortion (26, 27).

6.2 INITIATION OF LONG-ACTING CONTRACEPTION

Immediate IUD insertion during surgical abortion has resulted in initiation rates as good as 91–100% compared to 23–71% after an insertion delay of 2-6 weeks (15, 182). Similarly, after a medical abortion good initiation (90–97%) rates have been detected following short abortion–IUD insertion intervals as Table 3 described in the 'Review of the Literature' section (194-197, 215). More women (96%) in the immediate-insertion group received LNG-IUS compared to the control group (85%) in the randomized KILKE study. This difference was evident in the 9–12-gestational-week subgroup (98% vs. 82%, p=0.008) but was not statistically significant in the other subgroups. The difference was smallest (93% vs. 89%, p=0.52) in the subgroup of earliest pregnancies. This may be partly due to an additional insertion visit required in the immediate-insertion group because the misoprostol administration occurred at home. However, we did not want to change our clinical practice on
Discussion

misoprostol home administration, but usually women were prescribed sick leave for three days; thus, they had an opportunity to attend the insertion visit. The difference in initiation rates (96% vs. 82%, p=0.19) was not statistically significant in the second-trimester subgroup, but the number of subjects was insufficient to make further conclusions.

Overall, our LNG-IUS initiation rates in the immediate-insertion group were comparable to the one seen after surgical abortion and were at least as good as seen in previous studies on quick insertion after medical abortion (Table 3). LNG-IUS insertion among participants in the delayed-insertion group occurred more often than was seen in previous studies. If a woman did not attend her follow-up visit, we actively tried to contact her two to three times and make a new appointment. This increased the LNG-IUS initiation rate in our delayed-insertion group.

Only 177 (27%) women initiated the LARC method one month after their abortion in the CHOICE cohort of 666 women, and the majority of them were KILKE participants. We only had access to our own hospital’s patient records, and some LARC initiations may have occurred in the primary health care or private sector.

We recommended and planned LARC more often for women in the risk groups for subsequent abortion (26, 27), except for young women, as described in the previous section. Planning for LARC also resulted in better LARC initiation rates in these risk groups: Previous pregnancy 33% vs. 17%, previous abortion 35% vs. 22%, late first trimester (9–12 weeks) 35% and second trimester up to 65%. Moreover, young women also received LARC as often as older women (23% vs. 29%). As anticipated, abortion at the hospital increased LARC uptake.

6.3 EXPULSIONS

Expulsion rates within six months after a first-trimester abortion have been 5.0% compared to 2.7% after delayed insertion in randomized controlled studies on insertion of modern T-shaped IUDs during surgical abortion (183). The one-year LNG-IUS expulsion rate following immediate insertion has been 7.1%, and the three-year expulsion rate is 10.5% (211). After a second-trimester surgical abortion, immediate IUD insertion has resulted in an expulsion rate of 3.0–6.8% compared to 0–5% after delayed insertion (184, 185). According to meta-analyses, expulsions occurred more often after immediate insertion compared to delayed insertion (RR 2.64 [1.16–6.00] (15). The majority of these expulsions have occurred during the first few months post insertion.
The cumulative one-year total expulsion rates (2.6% vs. 3.0%) in our KILKE study were comparable to previous studies. However, the partial expulsion rate was high, 19.8%, in the immediate-insertion group compared to 8.9% in the delayed-insertion group. Diagnosis of partial expulsion was made by ultrasonography only in 19 cases out of 32 (59%) [I, II] and may not have significant clinical importance, because intracervical LNG-IUS provides as good a contraceptive effect as a fundally located device (173). In addition, endometrial thickness measured by ultrasound at the time of the LNG-IUS insertion did not correlate to expulsions. Thus, ultrasound should have a minor role in the insertions and follow-up and should be performed on symptomatic women only.

### 6.4 ADVERSE EVENTS

Legal induced abortion is a safe procedure, and ongoing pregnancies are rare (≤ 0.5–1%) after both surgical and medical evacuation (80, 216). The rate for incomplete abortions needing repeat aspiration following a surgical abortion has been ≤3%, the infection rate ≤2% (with infection prophylaxis) and the haemorrhage rate 0–4.7% (108, 217). Vacuum aspiration is needed for an incomplete abortion after a first-trimester medical abortion in 6–8% of cases, and bleeding problems occur in 16% of cases; both of these rates are higher compared to surgical abortions (108). However, the infection rates seem to be similar (≤2%) if infection prophylaxis is used during a surgical method and sexually transmitted diseases are screened before the medical procedures (108). As expected, second-trimester medical abortions have resulted in higher haemorrhage, infection and surgical operation rates (109).

Complication rates following an immediate IUD insertion during a surgical first-trimester abortion are similar to those seen without an IUD insertion (182, 183). Likewise, shortening the medical abortion–IUD insertion interval has had no effect on complication rates when compared to delayed insertion, but the detected infection rate (6–9%) has been higher than that seen in cohort or register studies (Table 3) (198) in a randomized controlled study.

In the KILKE population, 24–29% of the women experienced some adverse event leading to additional contact. This is a somewhat high rate that may reflect the nature of the study and patient counseling emphasizing that they should contact the research nurse if experiencing any signs of complications. Overall, complication rates did not differ between the study groups according to intention-to-treat analysis, which indicates that immediate LNG-IUS insertion did not affect the incidence of complications.
A surgical operation was needed in a total of 10.6% and 13.7% of women in our study groups. These rates were 5.4% and 7.5% in the subgroup of the shortest gestation duration (≤9 weeks), which are comparable to those seen in previous studies. However, surgical evacuation rates in the second-trimester subgroup (11.1% and 21.4%) are lower than reported before, but the limited number of women in this subgroup does not allow further conclusions.

The infection rates seen in our first-trimester subgroups (5.7–10.9%) were higher than reported after IUD insertion during surgical abortion and medical abortion without IUD insertion. However, almost all detected infections were mild and diagnosed because of uterine tenderness and/or purulent cervical discharge and were treated with oral antibiotics only without removal of the LNG-IUS. Infection prophylaxis was used or women with infection at the time of insertion were excluded in previous studies concerning shortening of the medical abortion–IUD insertion interval (Table 3); thus, our results are not comparable to them. Infection rates were 22% and 18% in our second-trimester subgroups. Again, similar rates between the study groups indicates that LNG-IUS insertion did not affect the incidence of infection; rather, the higher gestational age increased the infection rate.

The first bleeding episode was slightly longer in the immediate-insertion group because of an increased number of spotting days. However, no difference was detected in the overall number of bleeding days between the study groups during the 90-day reference period. The visualization of the bleeding profiles (Figure 10) shows the differences in bleeding and spotting profiles during the 90-day period post abortion, even if other statistical differences in the bleeding and spotting numbers were undetected. Immediate LNG-IUS initiation seems to flatten cyclic bleeding profiles during the first months after insertion, while bleeding profiles remain in their cyclic nature longer after delayed insertion (2–4-week post abortion).

Sääv et al. (197) published the only comparable study protocol concerning bleeding profiles after medical abortion and IUD insertion, and our results are comparable to theirs. Early IUD insertion did not have an effect on bleeding profiles compared to delayed insertion, and more bleeding days were detected following LNG-IUS compared to the Cu-IUD group during the first four weeks, but heavy bleeding days decreased. It is well known that bleeding disturbances during the first months after LNG-IUS insertion are common and will gradually reduce or disappear, leading to reduced bleeding in almost every woman or amenorrhea in 20–30% of women (218-220). Counselling women concerning this phenomenon is likely to prevent unnecessary LNG-IUS removals during the first months.
6.5 CONTINUATION OF INTRAUTERINE CONTRACEPTION

Higher IUD initiation rates at the time of the surgical abortion have resulted in better continuation rates. Six-month continuation rates of 82–92% have been reported following immediate IUD insertion, compared to 28–77% if IUD insertion was delayed by 2–6 weeks (risk ratio according to meta-analysis 1.40 [1.24–1.58]) (15, 183–185, 221). The one-year continuation rate following immediate insertion has been 68–71% (211). Similarly, after shortening the medical abortion–IUD insertion interval, six-month continuation rates of 68–69% have been detected (195, 197).

The primary outcome of our KILKE study was a one-year LNG-IUS continuation rate. The verified one-year continuation rate of 62% was significantly higher in the immediate-insertion group compared to 40% in the delayed-insertion group. One-year continuation rates were 85% vs. 67%, respectively, in the best-case scenario (all inserted LNG-IUSs are in use, if not known to be removed). This study’s higher continuation rates are mainly due to better insertion rates (127 [95.5%] vs. 111 [84.7%], p=0.004), as the removal rates (10 [7.5%] vs. 15 [11.5%], p=0.30) (III) were statistically similar or were favoring immediate insertion.

6.6 PREVENTION OF UNPLANNED PREGNANCY AND ABORTION AFTER AN INDUCED ABORTION

Young age, history of a previous pregnancy or induced abortion, and a previous second-trimester abortion are risk factors for a subsequent induced abortion (26, 27). The effect of LARC following an abortion on reducing subsequent pregnancy and abortion rates is well documented (26, 29, 187, 222, 223) and may be cost effective (224). Risks for a subsequent abortion have been reduced by 2.5–20 times in these studies if LARC was initiated at the time of the abortion when compared to initiation of other contraceptives.

Our results underline previous observations that only initiated long-acting contraceptives can prevent subsequent unplanned pregnancies and abortions. Only the inserted LARC methods had the best contraceptive effectiveness in the CHOICE population, followed by other contraceptives (pills, patch, ring, condoms). In contrast the women who planned but did not initiate LARC had the greatest risk for a subsequent abortion. Their relative risk was as high as 7-fold compared to women who initiated LARC. A similar increase in the risk ratio was seen in the KILKE population.
Discussion

Prevention of future unplanned pregnancies is not only in a woman’s personal interest, but it is also a public health issue. For example, up to half of the pregnancies in the U.S. are unplanned, and two out of five end up in an induced abortion (225). Young age and low income and educational levels are risk factors for unplanned pregnancy, and free-of-cost LARC effectively prevents unplanned pregnancies and abortions in this group of women (208). Our results support the idea that LARC should be available easily and free of cost at the time of the abortion.

Today, Finland’s health care system is not equal for every women requesting abortion. More efforts to unify post-abortion contraceptive provision, including LARC methods, should be made, and the barriers between primary and specialist health care should be lowered. Knowledge of the LARC methods should be distributed at all levels of the health-care system. For example, the city of Vantaa has lowered all these barriers (202). In addition to decreased abortion rates, free-of-cost LARC for teenage women seems to be cost effective.

6.7 STRENGTHS AND LIMITATIONS OF THE STUDY

This thesis study’s strengths include the randomized, controlled nature of the KILKE study and the comprehensive cohort of women requesting abortion in the CHOICE study. The KILKE population was older and had a history of more pregnancies and abortions compared to the average woman requesting abortion in Finland (12). However, the women requesting a repeat abortion present as a high-risk group and should, thus, be offered an LARC. We succeeded in reaching this risk population quite well from this viewpoint. The CHOICE population represents well the population of women requesting abortion in the Helsinki metropolitan area, because practically all induced abortions in our area are performed in Helsinki University Hospital.

Dropout rates in the KILKE study were larger than expected, and this may have influenced the results. However, this highlights the low compliance for further follow-ups among women seeking abortion. A follow-up visit a few weeks after an abortion may not be anymore convenient for the woman if she had recovered well, and the time window to affect her contraceptive choices has been closed. Investigating the electronic patient files and the Finnish Abortion Register would have revealed most of the major complications and subsequent abortions. In addition, sensitivity analyses confirmed better continuation rates in the immediate-insertion group compared to the delayed-insertion group; thus, this study’s results can be considered reliable.
The CHOICE population comprised all women requesting a medical abortion during the study period. The real initiated contraception rate is unknown, because of the study’s retrospective nature and the fact that we only had access to registered contraceptive plans and LARC initiations in our hospital. However, it could be presumed that LARC would not be initiated in the near future if it had not been planned at the time of the abortion. Additionally, if LARC would have been initiated in the near future, these additional LARC initiations would have decreased the detected difference in the primary outcome (subsequent unplanned pregnancy or abortion) of the CHOICE study.

### 6.8 FUTURE PERSPECTIVES

The efficacy of intrauterine devices and implants is well documented and recognized. Health-care professionals are familiar with these contraceptive options, but uncertainty of, e.g., their suitability for nulliparous women and timing of initiation during menstrual cycle or after delivery or abortion may constitute an unnecessary barrier between women’s contraceptive needs and the health-care system. In addition, rigid office hours and long queues to contraceptive facilities may be additional barriers, especially for young women. Intrauterine devices and implants are provided mainly by doctors in many countries such as Finland. Task shifting from the doctors to trained nurses or midwives could be one possible option to increase the availability of LARC methods (226).

Discussion of and counselling on not only contraception but all aspects of fertility is needed in western countries. Women should be aware of, i.e., age the limits of their fertility to avoid unnecessary difficulties in attempts to conceive at older ages. The age of women having their first child has increased and the birth rate has decreased in Finland (227); thus, prevention of all pregnancies should not be a goal for contraception facilities. Their main goal should be that a woman can choose liberally the contraception she needs in her current life situation. She should also be counselled that LARC methods can be discontinued before expiration date if her situation changes. The ideal situation would be that no pregnancies would be unplanned or unwanted, but all would be planned and wanted.
SUMMARY AND CONCLUSIONS

In summary:

1. Following insertion after a medically induced abortion, the total LNG-IUS expulsions were rare (3%) and did not differ between immediate- (0–3 days after misoprostol) and delayed-insertion groups (2–4 weeks after misoprostol). However, partial expulsion occurred more often after immediate LNG-IUS insertion compared to delayed insertion (20% vs. 9%, respectively).

2. Three-month complication rates were similar following immediate and delayed LNG-IUS insertion. The first bleeding or spotting episode was longer due to increased spotting days following immediate LNG-IUS insertion, but the total number of bleeding or spotting days during the three months following a medical abortion were similar.

3. The verified one-year continuation rates following immediate LNG-IUS insertion were better compared to delayed insertion (62% vs. 40%, respectively).

4. Initiation of LARC during one month after an abortion decreased the rates of subsequent pregnancies and induced abortions compared to only planned LARC or other contraceptive methods.

In conclusion, insertion of the LNG-IUS immediately after a medically induced abortion is feasible and safe. Immediate initiation results in better uptake and long-term continuation rates compared to delayed insertion, even if the partial expulsion rate of LNG-IUS may be elevated. Furthermore, immediate initiation, or at least quick and easy access to LARC initiation (both intrauterine devices and implants), prevents subsequent unplanned pregnancies and abortions.

Immediate or short-delay LARC insertion following a medical abortion should be liberally available today to women choosing contraception after a medical abortion. The health-care system should enable flexible contraception services in future.
ACKNOWLEDGEMENTS

This thesis study was carried out at the Department of Obstetrics and Gynaecology at the University of Helsinki and Helsinki University Hospital between 2012 and 2018. I wish to express my gratitude to the former and present administrative heads of our institution, Adjunct Professor Jari Sjöberg and Professor Seppo Heinonen, as well as to the former and current academic department heads, Professors Jorma Paavonen and Juha Tapanainen. The environment in the Women’s Hospital has been academically motivating and the work facilities have been great. Thus, my profound thanks belong also to all other chiefs of the clinic: Professor Oskari Heikinheimo, Professor Aila Tiitinen, Adjunct Professor Veli-Matti Ulander, Adjunct Professor Mika Nuutila, Adjunct Professor Aydin Tekay, and Professor Juha Räsänen.

My deepest gratitude belongs to my fabulous supervisors and co-authors:

Professor Oskari Heikinheimo. I thank you for introducing me to the scientific world. I admire your never-ending enthusiasm, ideas and optimism. Your transferable skills and quick answers to all of my questions have been crucial during this project. Your worldwide network and scientific expertise has inspired me.

Adjunct Professor Maarit Mentula. I thank you for your never-failing faith in me. You have always encouraged me during my journey through this project. You have taught me a great part of scientific reading, writing, mathematics and computer work.

My warmest appreciation goes to Associate Professors Helena Kopp Kallner from Karolinska Institutet and Terhi Piltonen from the University of Oulu, the official reviewers of this thesis. Their thorough evaluation, valuable comments and productive conversations have greatly improved this study.

I thank Adjunct Professors Terhi Saisto and Maija Jakobsson for being my thesis follow-up group. You have always encouraged me and shared your versatile scientific expertise throughout this project.

My deepest gratitude goes to our trustworthy, hardworking, warm-hearted research nurse, Pirjo Ikonen. Without you, our clinical trial would have never been possible. You are precious.

Unfortunately, I did not have an opportunity to meet ‘the father’ of the levonorgestrel-releasing intrauterine system (LNG-IUS), Professor Tapani Luukkainen, and Professor Carl Gustaf Nilsson, whose dissertation was the first one written on LNG-IUS. However, I have had the pleasure to meet the
Acknowledgements

‘next pieces of the researcher chain’, Adjunct Professor Pekka Lähteenmäki and Professor Juhani Toivonen, who have been instrumental in the development of the LNG-IUS. Conversations with them during lunches have given me some idea of the ‘good old times’ in the research laboratory. I thank both for inspiring me during my own project.

I express my sincere gratitude to all nurses, midwives and colleagues who have been involved in the recruitment and care of our patients. You are doing a great work in the outpatient clinic and in the hospital ward with warm hearth.

My sincere thanks go to all women who participated in the study.

Over these years, many people have been contributed to this work. Elina Pohjoranta, Suvi Leppälähti, Venla Kemppainen, Janina Kaislasuo, Kati Korhonen and Pia Halonen: We have had great conversations and conference journeys. Tuire Saloranta and Frida Gyllenberg, my future co-authors, always share positive energy with me. Adjunct professor Satu Suhonen has shown that research and clinical work can be done together. Liisu Saavalainen has been a trustworthy companion, both in clinical work and scientific writing; our egg has become a hen! All my former and present colleagues at Helsinki University Hospital deserve my warm appreciation. Clinical work with you has been a huge privilege.

I wish to address my deepest gratitude to my beloved friends and colleagues, Hanne Kuittinen and Anu Hänninen; you have always believed in me. Our family’s dear friends in Nurmijärvi, Järvenpää, Klaaukkala and Espoo, your presence has lightened my life during these years.

The greatest and deepest gratitude belongs to my family. My grandmother, Marjatta, has taught me many things during my life, and I have loved my time in Kuhmo. My father, Risto, passed away too early, but his memory is living strong, especially when I am spending time with my hobbies orienteering and cross country skiing, which he taught me. I am sincerely grateful to my mother, Riitta, for her faith in me. Her optimism and resilience has been an example for me and marked out my life. Her help with the kids and everything has been invaluable. My brothers Riku-Matti and Rikke-Pekka have always enriched my life.

The last and most valuable thank you belongs to my husband, Timo, and our kids, Santtu, Pinja, Aapo and Visa. Timo, you have taken care of most of our dishes and laundry during these years when I specialized and worked with this thesis research. Our life has not been easy, and without you, I could have never done this work. Our kids remind me every day what is important in life. All five of you are the world to me.
Acknowledgements

This work was supported by research grants from The Hospital District of Helsinki and Uusimaa, The Finnish Cultural Foundation (February 2014 and February 2017), Finnish-Norwegian Medical Foundation (June 2016), Instrumentarium Science Foundation (March 2017), and the University of Helsinki Chancellor's travel grants (2015, 2016, 2017, 2018).

Helsinki August 13th, 2018
Riina Korjamo
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