From the Department of Clinical Sciences, Division of Obstetrics and Gynecology, Danderyd Hospital

Karolinska Institutet, Stockholm, Sweden

LONG-ACTING REVERSIBLE CONTRACEPTION (LARC) AFTER PREGNANCY AND CHILDBIRTH

Karin Lichtenstein Liljeblad

Karolinska Institutet

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Cover illustration: picture of a hormonal IUD. Reprinted by permission Bayer AB Sverige.

Long-Acting Reversible Contraception (LARC) after pregnancy and childbirth

Thesis for Doctoral Degree (Ph.D.)

By

Karin Lichtenstein Liljeblad

The thesis will be defended in public at Aulan, Danderyd Hospital, Stockholm, 10th of March 2023 at 09.00 am.

Principal Supervisor:
Associate Professor Helena Kopp Kallner
Karolinska Institutet
Department of Clinical Sciences Danderyd Hospital
Division of Obstetrics and Gynaecology

Co-supervisor:
Professor Jan Brynhildsen
Örebro University
Department of Obstetrics and Gynaecology
Division of Medicine and Health

Opponent:
Professor Paul D. Blumenthal
Stanford University Medical Center
Department of Obstetrics and Gynecology
Division of Family Planning Services and Research

Examination Board:
Professor Ove Axelsson
Uppsala University
Department of Women´s and Children´s Health

Associate Professor Henrik Falconer
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Neonatology, Obstetrics and Gynecology

Professor Ellika Andolf
Karolinska Institutet
Department of Clinical Sciences Danderyd Hospital
Division of Obstetrics and Gynecology

“Not All Those Who Wander Are Lost” – J.R.R Tolkien

To Emelie, Cajsa and Lovisa

Popular science summary of the thesis

Most women have a need to control fertility at some point in life. The intrauterine devices and the implant are so called long-acting reversible contraceptives (LARCs). The LARC-method can be used for years without having to remember a contraceptive during sexual intercourse or, in case of hormonal contraception, every day, week or month. Placing an IUD as soon as possible after abortion or childbirth carries the advantage that the device is placed before fertility is restored without need for a follow-up visit to initiate contraception. Pain at device placement is usually neglectable, and when placed during caesarean section, no pain is possible because of the epidural analgesia.

In **study I**, we aimed to investigate the attendance to follow-up at Maternity Health Care 6-12 weeks postpartum, choice of contraception, and associated risk of abortion within 12-24 months of childbirth. We included 11,066 women. Among attendants, 2.1 % had an abortion, compared to 3.6 % of women who did not attend follow-up. Women who chose LARC and who exclusively breastfed at the time of follow-up had the lowest risk of abortion. Smoking and having had an earlier abortion were associated with a higher risk of abortion during the study follow-up.

In **study II** we aimed to investigate if having a hormonal IUD placed before discharged from hospital after vaginal delivery (within 48 hours of birth) was as good as having the device placed at follow-up at Maternity Health Care about 6-8 weeks postpartum in a randomised controlled study. We aimed to compare the risk of unintended pregnancy (measured as abortion), safety, and patient satisfaction between groups. A safety analysis showed unacceptable expulsion rates after early IUD placement. We therefore stopped inclusion after 101 women. No abortion occurred. Of the 52 early placed intrauterine devices, 23/52 (44.2%) were expelled compared to none in the standard group. There were no differences regarding efficacy, safety, satisfaction or pain at device placement.

In **study III** we aimed to investigate if placement of an IUD within 48 hours of completed medical abortion of up to 63 days´ gestation led to higher user rates at 6 months after the abortion compared to placement at 2-4 weeks after abortion (control) in a randomised controlled trial. We also aimed to compare safety, and patient satisfaction between groups. We randomised 240 women who were seeking medical abortion before 9 weeks gestation and opting for an IUD as postabortion contraception. There was no difference in continued IUD use. In the early group 82 % and in the control group 77.7% used IUD at 6 months after abortion. Expulsion rates did not differ between groups. IUD placement within 48 hours seemed safe, preferred by the women, and associated with lower pain scores during placement.

In **study IV** we aimed to explore women´s experiences, thoughts, and preferences regarding antenatal contraceptive counseling in general, and specifically, with focus on the possibility of IUD placement during caesaren section. We interviewed 20 women using a semi-structured interview guide with open-ended questions. We found three main themes: *Receptivity to contraceptive counseling during pregnancy; Communication and decision-making of postpartum contraception during pregnancy* and *needs to navigate in the Maternal Health Care System to receive contraceptive services before and after ceasarean section*. Women generally expressed a lack of antenatal counseling for postpartum contraception and up-to-date knowledge on contraceptive methods. They expressed positive attitudes to antenatal counseling for postpartum contraception from about 25 weeks gestation. Being informed and involved in the decision of contraception was described as central. Some women felt that they needed to navigate in the contraceptive services seeking medical advice and information by themselves.

ABSTRACT

Background and aims

Unmet need of contraception is a global challenge. The need of additional visits to initiate contraception is found to be a barrier for postpartum and postabortion contraceptive care. The IUDs and the implant are called long-acting reversible contraception (LARC). The LARC-method can be used for years without having to remember a contraceptive during sexual intercourse or, in case of hormonal contraception, every day, week or month.

The overall aim of this thesis was to add knowledge to the field of long-acting reversible contraception after pregnancy in Sweden in our effort to improve the quality of contraceptive care after pregnancy and childbirth.

Methods and main results

Study 1 was a retrospective cohort study including 11,066 women. Data was extracted from medical records regarding attendance to the postpartum visit and choice of contraception, breastfeeding, and abortion during 12-24 months after delivery. The primary outcome was the proportion of induced abortions during follow-up, with the outcome measure of abortion being a surrogate for unintended pregnancy.

Among attendees to the follow up 2.1 % had an abortion compared to 3.6 % among non-attendants. A decision to use LARC was associated with a lower risk of abortion (OR 0.74; 95% CI 0.60-0.91; p = .005), as was exclusive breastfeeding (p < .001). Smoking and having had an earlier abortion were associated with a higher risk of abortion during the follow-up.

Study **II and III** were open-label, prospective, randomised, controlled, multicenter studies. In **study II,** 101 women were either allocated to early placement (52/101) of a hormonal IUD within 48 hours after vaginal delivery or to standard placement (49/101) at 6-8 weeks postpartum. Follow-up was one year after IUD placement. Inclusion was prematurely stopped after an interim analysis due to high expulsion rate in the early placement group, and instead of 600 women only 101 were included. In the early placement group 23/52 (44.2 %) of devices were expelled within a year and 10 women had the hormonal device replaced. In the standard placement group there were no expulsions. The IUD continuation rate for the early group was 37/52 (71.2%), compared to 41/49 (83.7%, p = .13) for the standard placement group at study closure.

In **study III,** 240 women seeking medical abortion up to 63 days´ gestation were randomised to either IUD placement within 48 hours (120/240) after completed abortion or to IUD placement at 2-4 weeks (120/240) after abortion. Follow-up was one year after

abortion. The primary outcome was IUD use at 6 months postabortion. In the early placement group (intervention), 91/111 (82%) women used IUD at 6 months compared to 87/112 (77.7%) in the later placement (control) group (p= .51) Pain scores at IUD placement (measured by the visual analogue scale) were lower in the intervention group (p= .002). Women in the intervention group preferred the allocated time significantly more often compared to the control group (p= .03). There was no difference regarding expulsion.

In **study II and III** there were no differences regarding safety profile between groups.

Study IV was a qualitative study where 20 women who had undergone elective caesarean section (CS) were interviewed within 6 weeks of CS, to enable deeper understanding of women´s preferences and needs regarding contraceptive services at the time of pregnancy. Ten of the interviewees had chosen IUD placement during the latest CS. Three themes were identified; *Receptivity to contraceptive counseling during pregnancy; Communication and decision-making of postpartum contraception during pregnancy and Needs to navigate in the Maternal Health Care System to receive contraceptive services before and after caesarean section*. Women were generally positive to contraceptive counseling from about 25 gestational weeks and expressed positive attitudes about the concept of antenatal counseling. Feeling involved and informed was important, but few women had been involved in antenatal counseling. Women who had chosen IUD placement during CS were usually satisfied with the decision. Some interviewees expressed a need to navigate in the contraceptive services by themselves. The communication and coordinating units that should integrate around the woman have not sufficiently adapted to new evidence, needs and conditions.

Conclusions

The choice of LARC postpartum is associated with lower risk for unintended pregnancy compared to the choice of other contraceptives or no choice at all. Attendance to the postpartum visit is a prerequisite to initiate LARC when provision of early/immediate LARC initiation postpartum is not part of the established contraceptive health care. Placement of a hormonal IUD within 48 hours after vaginal delivery seems safe, accepted by patients but associated with much higher expulsion rates compared to placement 6-12 weeks postpartum. Early placement of an IUD within 48 hours after completed medical abortion does not lead to higher continuation rates at one year after abortion compared to standard placement 2-4 weeks after abortion when devices are provided free of charge. Early placement seems safe, preferred by patients, and associated with lower pain scores compared to standard IUD placement postabortion. Antenatal counseling for contraceptive method to use postpartum seems acceptable to women from around 25 gestational weeks. To have the opportunity to discuss contraception antenatally and enable placement during planned CS is generally considered valuable.

List of scientific papers

I. Risk of abortion with 1-2 years after childbirth in relation to contraceptive choice: a retrospective cohort study.
Lichtenstein Liljeblad, K, Kopp Kallner, H, Brynhildsen, J.
Eur J Contracept Reprod Health Care. 2020 Apr;25(2):141-146.

II. Effectiveness, safety and overall satisfaction of early postpartum placement of hormonal IUD compared with standard procedure: An open-label, randomised, multicenter study.
Lichtenstein Liljeblad, K, Kopp Kallner, H, Brynhildsen, J.
Acta Obstet Gynecol Scand. 2022 Apr;101(4):424-430.

III. Placement of an intrauterine device within 48 hours after early medical abortion – a randomised controlled trial.
Hogmark, S, **Lichtenstein Liljeblad, K**, Envall, N, Gemzell-Danielsson, K, Kopp Kallner, H.
American Journal of Obstetrics & Gynecology (AM J OBSTET GYNECOL), Jan2023; 228(1): 53.e1-53.e9.(1p)

IV. Womens´ experiences of contraceptive counseling and provision services when elective caesarean section is the method of birth – a qualitative study.
Lichtenstein Liljeblad, K, Kopp Kallner, H, Brynhildsen, J, Kilander, H.

Contents

List of abbreviations

COC	Combined oral contraception
CS	Caesarean section
Cu-IUD	Copper intrauterine device
ICD-10	International statistical classification of diseases and related health problems
IQR	Interquartile range
ITT	Intention-to-treat
IUD	Intrauterine device
LARC	Long-acting reversible contraception
LNG-IUS	Levonorgestrel-releasing intrauterine system
mITT	Modified intention-to-treat
PI	Pearl index
POP	Progestin-only pill
PPIUCD	Postpartum intrauterine contraceptive device
RCT	Randomised controlled trial
SARC	Short-acting reversible contraception
VAS	Visual analog scale

1 INTRODUCTION

Contraception has the potential to provide every human being the possibility to plan one´s own fertility in a life perspective. This is a human right for all people regardless of culture, religion, economy, or politics. The long-acting reversible contraceptives enable effective control of fertility with few side-effects. It is therefore important to make these methods easily available for everyone who wishes to use them. The time after pregnancy is a unique timepoint when contraception should be easily available and possible to initiate for every person who wants to avoid future pregnancy. Therefore, immediate provision of effective contraception after pregnancy is an important public health concern.

2 BACKGROUND

2.1 Contraception in general

Contraceptive methods can be divided into permanent contraception, long-acting reversible contraception (LARC), short-acting reversible contraception (SARC), barrier methods and other methods (cycle-based methods, withdrawal, periodic abstinence). Efficacy and effectiveness of contraception is described as Pearl Index (PI), representing the number of pregnancies among one hundred women using the method during a year. When comparing the efficacy of different contraceptive methods, it is important to distinguish "perfect use" (efficacy) from "typical use" (effectiveness). The effectiveness is influenced by real-life circumstances including incorrect and inconsistent use of the method. Effective contraception can be defined as a typical use where PI ≤ 9 (≥91% effective) and highly effective contraception as having a typical use where PI ≤ 1 (≥99% effective) (1).

2.2 Long-acting reversible contraception

The intrauterine devices and subdermal implants constitute the LARC group. There are two main kinds of intrauterine devices- those containing and releasing copper (Cu-IUDs) and those containing and releasing the progestin levonorgestrel, hormonal IUDs, previously referred to as LNG-IUS. All intrauterine devices are highly effective in preventing pregnancy, are safe to use and associated with few side-effects (2).

Due to the lack of user dependency the LARC methods are associated with lower contraceptive failure rates compared to other methods. The typical-use failure rate for the IUDs is 0.2-1.4 % and for the implant 0.05-0.6 % (3, 4). The lowest failure rates are seen in high-income countries such as the U.S, and the higher rates are seen in the low-income countries of the world (4). The effectiveness of the IUDs and the implant is comparable to that of permanent contraception. When using LARC, the cumulative pregnancy rate in the first three years is 0.9/100 women-years, which is significantly lower compared to the corresponding first three years cumulative pregnancy rate of 9.4/100 women-years for users of SARC (2, 5). With one single intervention at the time of placement, the LARCs provide a high contraceptive effectiveness, independent of user age, parity, and body mass index. The methods can be used for a long time and are associated with several additional health benefits aside from contraception. Furthermore, fertility is quickly and easily restored after removal of the device or implant (2).

2.2.1 Mechanism of action of IUDs

The main mechanism of action of the copper device is release of copper ions and induction of a local sterile inflammatory process causing a spermicidal environment around the device (6). This is the only effective reversible contraceptive method that does not contain hormones. The Cu-IUDs cause an increase in menstrual blood flow and the method is not recommended for women with heavy menstrual bleeding and/or dysmenorrhea. The Cu-IUD is associated with a reduced risk of endometrial- and cervical cancer, however the mechanisms involved is still unknown (2, 7, 8).

The hormonal IUD is a highly effective contraceptive not only for prevention of unplanned pregnancies, but also associated with several added health benefits, making the hormonal IUD the contraceptive with the highest satisfaction rates and the highest acceptability rates on the market (9, 10). The system is estrogen free and suitable when medical conditions constitute a contraindication to exogenous estrogen. The mechanism of action is primarily the thickening of the cervical mucus and impaired sperm penetration (11, 12). Ovulation is partly suppressed in a dose dependent manner and at different rates according to the daily levonorgestrel-release rate. The local effect of levonorgestrel is far more significant than the systemic one, and the level of levonorgestrel in the endometrium is a thousand-fold higher than in the serum for the device containing 52 mg of levonorgestrel (11, 12). Hormonal IUDs containing 52 mg levonorgestrel have profound morphologic effects on the endometrium, including gland atrophy and decidual transformation of the stroma (13). This endometrial effect reduces menstrual blood loss in women with heavy menstrual bleeding more effectively than other hormonal therapies and tranexamic acid. The effect of the hormonal IUDs containing 52 mg levonorgestrel on heavy menstrual bleeding is comparable to surgical endometrial ablation and is cost-effective with high quality-of-life measurements compared to endometrial ablation and hysterectomy (14). These hormonal IUDs may be a satisfying therapeutic option for patients suffering from menorrhagia and dysmenorrhea associated with fibroids (15) as well as patients with endometriosis (16, 17). Furthermore, a hormonal IUD containing 52 mg of levonorgestrel has been found effective in reducing the occurrence of hyperplastic endometrial polyps (18) and reducing the risk of endometrial- and cervical cancer (8, 19). Thus, hormonal IUDs with 52 mg of levonorgestrel may be a therapeutic option for reducing the need of surgical interventions or other medical treatments for selected women.

During recent years, two other hormonal IUDs containing lower doses of levonorgestrel than Mirena® and Levosert®/Liletta® been introduced; Jaydess®/Skyla® containing 13.5 mg and Kyleena® containing 19.5 mg of levonorgestrel (2). These newer hormonal IUDs have an inserter of 3.8 mm-diameter which is narrower compared to the 4.4 mm-diameter of Mirena® and might benefit especially nulliparous women (20). The low-dose

hormonal IUDs work with a very high contraceptive efficacy but with a lower grade of amenorrhea compared to the device containing 52 mg of levonorgestrel (2).

2.3 Short-acting reversible contraception

The pill, the vaginal ring, the injection, and the transdermal patch constitute the SARC group available in Sweden. The injectable available in Sweden is a high dosed progestin-only method and the only method which is not immediately reversible (21).

The oral contraceptive pill is available as a combined estrogen-progestin formulation i.e. combined oral contraception (COC) and as progestin-only pills (POP). COCs thicken the cervical mucus and inhibit ovulation by feedback to the hypothalamic-pituitary-ovarian axis (21). The progestin-only pill works primarily by thickening the cervical mucus and inhibits ovulation in a dose-dependent fashion with the low dosed POPs usually not inhibiting ovulation, whereas the medium dosed pills inhibit ovulation. The vaginal ring and transdermal patch are combined non-oral methods.

With perfect use COCs are very effective with a failure rate of 0.3 %, but with typical-use the effectiveness declines to failure rates between 6-9 % (4, 22). Especially women younger than 21 years who use SARC have significantly higher contraceptive failure rates than older women, probably due to higher risk of incorrect or inconsistent use (5).

2.4 Barrier methods and other methods

The typical-use failure rate for the male condom, withdrawal and periodic abstinence is found to range between 5-18, 13-22 and 14-24 % respectively (4, 22). These methods are highly user dependent and require consistent use at every intercourse. Because of the nature of these methods there are no contraindications to use them, which is an advantage of these otherwise relatively unreliable methods regarding protecting from pregnancy.

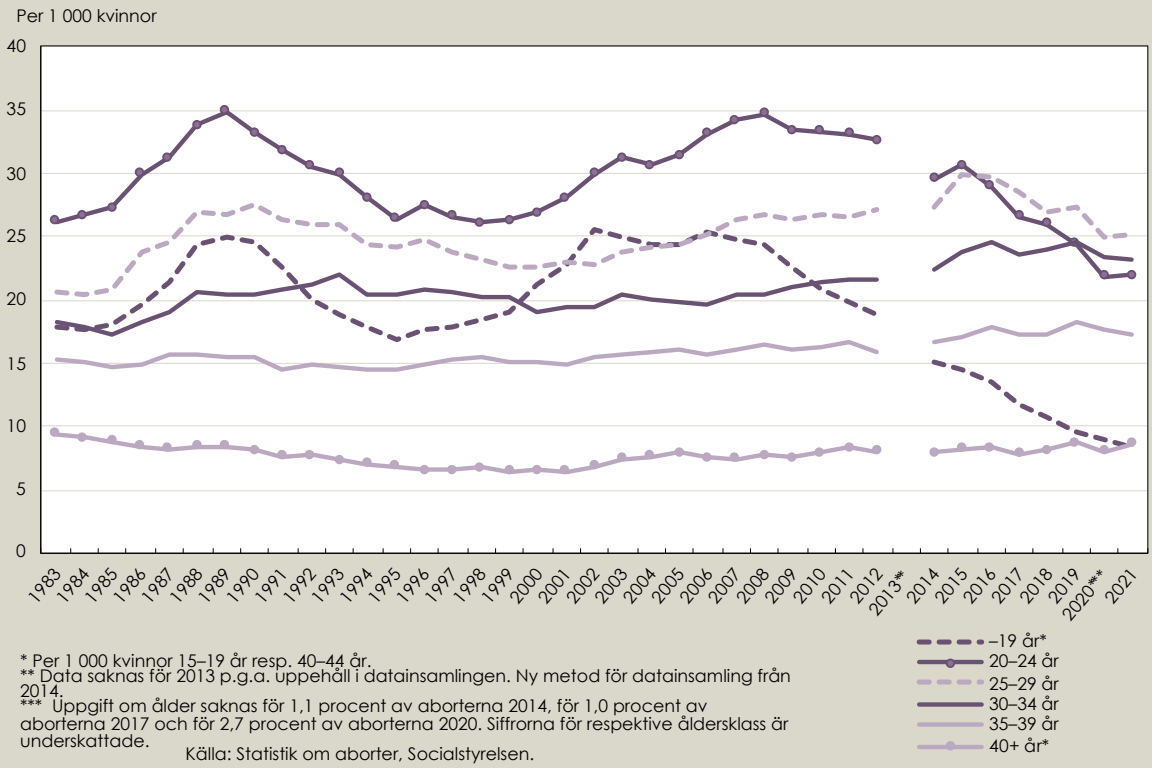
2.5 Unmet need of contraception

Unintended pregnancy remains a huge challenge for families and societies around the world connected to complex interactions with politics, economics, health care systems and traditions. In a global perspective, around 80 million pregnancies yearly are estimated to be unintended (23) and in low- and middle-income countries up to 24 % of pregnancies end up in abortion (24). Globally, insufficient provision of safe abortion care counts for 8-18 % of maternal deaths, and almost all deaths related to unsafe abortion occur in low-and middle-income countries (25-27). Unintended pregnancy in low- and middle-income countries, might be associated with low access to contraception and low availability of sufficient contraceptive care. In contrast, high-income countries would in comparison have a theoretically significant better possibility of a high-quality contraceptive service to match the expectations and needs of

contraceptive care. Despite this, also in high-income countries, and in high-resource settings, there seem to be underlying and not always easily understood factors that challenge the availability, provision, and use of contraceptives. The unmet need of contraception, also in high-income countries, is likely multi-factorial but a sufficient person-centered concept including systems promoting an informed choice of contraception may be important (28, 29). Thus, beside availability and easily accessed information, the process of actively involving the patient in the decision is likely to be crucial to meet expectations and demand of contraception. In the United States 45% of pregnancies from 2008 to 2011 (30) and 38 % of births from 2017 to 2019 (31) were estimated to be unintended, and approximately 40 % of unintended pregnancies were estimated to end up in induced abortion (30). Sweden has a relatively high and constant annual number of induced abortions since the middle of the 1990s (32). Most induced abortions are performed in women between the age of 18 to 44 years. In 2021, the rate of induced abortion was nearly 18 per 1000 among women 18 to 44 years, accounting for 33 700 induced abortions. Despite easy access to contraceptives, Sweden still has an unmet need for contraception. Sexually active women are not using contraception even though they do not plan for pregnancy (33). Additionally, a high number of women are using methods with high typical-use failure rate (34).

The figure below shows the abortion rate/1000 women in Sweden dependent on age from the national abortion statistics (The Swedish National Noard of Health and Welfare)

Figur 2b. Antal aborter per 1 000 kvinnor efter ålder, 1983–2021



* Per 1 000 kvinnor 15–19 år resp. 40–44 år.
** Data saknas för 2013 p.g.a. uppehåll i datainsamlingen. Ny metod för datainsamling från 2014.
*** Uppgift om ålder saknas för 1,1 procent av aborterna 2014, för 1,0 procent av aborterna 2017 och för 2,7 procent av aborterna 2020. Siffrorna för respektive åldersklass är underskattade.

Källa: Statistik om aborter, Socialstyrelsen.

A meta-analysis published in November 2022, showed that unintended pregnancy was significantly associated with higher odds of maternal depression during pregnancy and the postpartum period, and maternal experience of interpersonal violence in the U.S. Furthermore, the study showed a higher incidence of preterm birth and low birth weight for births following unintended pregnancy in the U.S. Earlier studies have likewise showed that mothers with unintended births suffer more from depression and disturbance in the early bonding between the mother and the child with risk of a long-term, lower quality relationship (35). The risk of postpartum depression remains elevated up to at least one year after childbirth (36). Furthermore, unintended pregnancy is associated with short interpregnancy intervals (37, 38) usually defined as an interpregnancy interval of less than 18 months. Studies have shown that in some settings, a short interpregnancy interval may be an independent risk factor for premature birth, low birth weight and small-for-gestational age (39-42). Women who are not using reliable contraception in the extended postpartum period seem to conceive sooner (43-45). The American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO) recommend pregnancy spacing of at least 6–24 months between a delivery and conception. Postpartum initiation of long-acting reversible contraception is highly effective for the prevention of short interpregnancy intervals and should be considered a first-line recommendation for women who wish to retain fertility but to avoid early repeat pregnancy. Long-acting reversible contraception is superior in effectively preventing pregnancy in combination with quick resumption of fertility after removal of the LARC-method (46). Despite this, it is yet not known if immediate postpartum initiation of LARC leads to a decrease in the number of induced abortions. Thus, the effect of PPIUDC on unwanted pregnancy rate is still to be explored.

2.6 LARC after surgical and medical induced abortion

Contraceptive counseling is free for women of all ages in Sweden and several hormonal contraceptives (including subdermal implants and hormonal IUDs) are subsidized up to the age of 25 (47). Despite good access to contraceptive services, almost half of women who seek an abortion in Sweden have a history of previous abortion(s) (48). Long-acting reversible contraceptives are associated with the lowest need for subsequent abortion (49, 50, 51) and should be available for placement by the time of a surgical abortion or up-take within a week after a first-trimester medical abortion (52, 53, 54, 55). According to recommendations from the World Health Organization, IUDs can be placed immediately after a first- or second trimester abortion. Placement after first trimester abortion is considered safe with no restrictions, and placement after second trimester abortion is considered beneficial and that the advantages generally outweigh the risk. The recommendations lacks referral to specific trials studying the timing of IUD-placement after medical abortion (56).

A study from Sweden reported that 24 % of women return for induced abortion(s) within 3-4 years after an index abortion (57). Women who chose LARC after the index induced abortion had a significantly lower risk of a new abortion compared to women who used other contraceptive methods. Long-acting reversible contraceptives were chosen more frequently ahead of surgical abortion compared to medical abortion which might be associated with the convenience of having an IUD placed during the surgical procedure whereas LARC-initiation after medical abortion requires an additional visit (53, 57, 58). Another Swedish study showed that 40 % of patients choose placement of an IUD at the time of surgical abortion (59). Immediate placement of an intrauterine device during surgical abortion has been proven effective, safe, and acceptable (60-62). There are several advantages of immediate placement compared with delayed placement, including high motivation, less discomfort, assurance the woman is not pregnant and reduced burden for the patient and the health care system. In a Swedish trial aiming to study IUD-placement after first-trimester medical induced abortion, women attended the placement visit significantly more often in the early placement group compared to the delayed placement group. In this study IUDs were not provided free of charge (54).

Studies show that up to 50 % of women do not attend a follow-up appointment after induced abortion, with the consequence of missing out of effective contraception (63, 64). Easy access to immediate LARCs after an unintended pregnancy and/or abortion is an important fundament to improve up-take of effective contraception.

2.7 LARC after childbirth

It is increasingly acknowledged that the need of effective contraception after childbirth is underestimated (65) with up to 62% of women globally having an unmet need for contraception in the postpartum period (66).

Among women not breastfeeding, fertility may return as early as four weeks after delivery (67) and close to half of women have resumed sexual activity and have unprotected intercourse before 6 weeks postpartum (68). In Sweden, contraception is currently not provided as part of routine care in hospital after delivery. The antenatal health care program recommends a follow-up visit at 6–12 weeks postpartum (69) in accordance with other countries (70) to provide contraceptive counseling, prescription, and initiation of LARC. To place an IUD or implant, one more visit is sometimes required. In Sweden, a plan for postpartum use of contraception is sometimes discussed antenatally but this is not mandatory and thus depends on the working routine for the midwife or doctor, along with the woman´s preferences and time available.

Although the postpartum visit is an ideal time to discuss and provide family planning services, approximately 20 percent of postpartum women in Sweden do not attend the postpartum follow-up visit, with large local variations (71). Furthermore, studies have shown that the need of multiple appointments for postpartum contraception increases

the risk of unintended pregnancy (72). Consequently, women in the postpartum period are at potential risk of an unintended pregnancy soon after delivery. Additionally, studies have reported barriers for giving contraceptive advice during the postpartum period (73). Women may have all focus on their child, leading to a temporary lack of interest for discussing contraception (74), or may not want to think about "having sex again" (75). Hence, there are several fundamental advantages for women and couples to have easy access to individualized counseling antenatally, provided the woman and couple are interested in using contraception postpartum.

2.7.1 Timing of contraceptive counseling and LARC provision for women giving birth

There are few studies available regarding the optimal time to discuss and commit to a postpartum contraceptive plan. An American study from 2019 investigated the attitudes among pregnant women regarding readiness, capability, and confidence in discussing and committing to a postpartum contraceptive plan. Most patients considered the second or third trimester as an optimal timepoint for contraceptive counseling. Despite that, women reported significantly higher levels of readiness and capability to discuss and to choose contraception after delivery (76). One interpretation of the results may be that counseling before delivery could have played a role in preparing the women to feel ready and confident to make a choice of contraception once delivery was over. Another study investigated the relation between timepoint of contraceptive counseling and the continuation rate of postpartum intrauterine contraceptive device (PPIUCD) placed during caesarean section or within 48 hours of a vaginal delivery. All included women participated in counsel-sessions regarding different methods of contraception during antenatal checkups, early labor and/or immediately postpartum (within 48 hours). The highest success rate of PPIUCD-continuation was noted in patients counseled thoroughly both antenatally and at early labor (77).

It has been shown that antenatal counseling is fundamental to have the time to consider and decide upon placement of an IUD during a cesarean section, immediately after vaginal delivery or before leaving the hospital postpartum (78). Women who wish to use an IUD postpartum with an antenatal decision upon that, are more likely to receive the PPIUCD. Women´s preferences, needs and attitudes regarding antenatal contraceptive counseling is not fully explored, and a deeper and more insightful understanding would be of great value and importance when looking into future development of contraceptive services.

There are several barriers to receiving immediate LARC after delivery even when there is a plan for postpartum contraception. In Scotland, prenatal contraceptive counseling, and provision of postpartum contraception to first-time teenage mothers was investigated. The study showed that most patients found prenatal counseling and planning for

postpartum contraception helpful. Approximately 70 % were planning to use a LARC-method, and 80% wished to receive LARC before discharged from hospital. In the end though, only 32% received the contraceptive method before leaving hospital. The busy workload at the maternity ward was stated as the main reason (79).

Most women do not plan another pregnancy within the first year postpartum. A Scottish study showed that almost none of postpartum women were planning another pregnancy within the first year after childbirth, but only a few were planning on using LARC postpartum. Despite that, more than 40% of women stated they would likely choose LARC if the implant or IUD could be placed before leaving the hospital (80). This indicates that women are interested in using effective, safe, long-acting methods postpartum and that easy access to the methods is important.

2.7.2 Immediate and early placement of an IUD after vaginal birth.

Evidence strongly indicates that placement of LARC within hours after vaginal childbirth is safe for the mother and the child and enables uptake of a highly effective contraceptive method by a single intervention before fertility is restored (7, 81, 82). Placement of an IUD at this time may cause the woman less pain and discomfort, because women may be under pain relief from a delivery associated epidural analgesia, and the cervix is soft and dilated.

Studies of postpartum placement of IUDs usually define three time-intervals for IUD-placement: 1. immediate placement i.e. placement within ten minutes after removal of the placenta, 2. early placement i.e. placement from ten minutes after removal of the placenta and within 48 hours after delivery, and 3. standard/interval placement i.e. placement within six to twelve weeks after delivery (during a postpartum visit). An alternative definition of "immediate postpartum" is the period between delivery and hospital discharge (83).

A Cochrane review from 2015 compared immediate postpartum Cu-IUD and hormonal IUD placement with standard placement and found immediate placement to be as safe, with no higher risk of perforation or infection, than standard/interval placement. Higher expulsion rates were found after immediate placement, but the overall evidence was presented as limited because of the small sample sizes from full-report studies. Despite the associated higher expulsion rate, the Cochrane report found the benefit of immediately placed contraception to probably outweigh the risk of expulsion. The Cochrane report thus found support for placement of an IUD within ten minutes after removal of the placenta after a spontaneous vaginal delivery or uncomplicated instrumental delivery (81). Furthermore, the report found support for IUD placement within 48 hours after a vaginal delivery while still in hospital (84, 85).

A Cochrane review published 2022 aimed to compare the initiation rate, utilization rates at six- and 12 months after delivery, effectiveness, and adverse effects of immediate versus delayed postpartum placement of implants and IUDs for contraception (86). Eleven RCT-studies of IUDs (1894 participants) were included. The difference in rate of unintended pregnancy at 12 months postpartum was uncertain but suggested to be lower after immediate IUD-placement. Immediate placement was found to improve the initiation rate compared with delayed placement, independently of the type of IUD used. The chance of receiving a postpartum IUD by immediate placement was found to be between 66% and 93%, compared to a 61 % chance to receive an IUD by delayed placement. However, the evidence was very low for estimating the utilization rate for IUDs at six and 12 months postpartum and thus concluded as uncertain if immediate IUD-placement improved utilization rate within the first year postpartum compared with delayed placement. Furthermore, the review found that expulsion rate for IUDs at six months postpartum may be higher after immediate placement compared to delayed placement. The expulsion rates at 12 months were not possible to evaluate because of lack of low follow-up rates at 12 months postpartum (86).

Immediate postpartum placement of IUDs is supported by The American College of Obstetricians and Gynecologists and the World Health Organization (56, 87), but has not been established as a best practice in Europe or in the U.S. In Sweden, immediate placement of IUDs is not yet recommended. A few years ago, immediate postpartum IUD placement was mainly available and evaluated in low-resource settings, often using the Cu-IUD. However, during the last years studies on PPIUCD have been conducted also in Europe and in the U.S., representing high-resource settings. In accordance with the Cochrane report (81), expulsion rates have been higher compared to standard placement postpartum also in high-resource settings. The device can be completely expelled or partially expelled, the latter meaning finding the device partly or completely positioned in the cervical canal. Studies report a wide range of expulsion rates probably representing different methods for placement, types of devices, study settings, quality of design, use of ultrasound to detect IUD position, and time of follow-up. Furthermore, the method to diagnose expulsion and how expulsion is defined differ in reports. The use of ultrasound as a method to determine IUD-position and detect partial and complete expulsion differ. Lack of consensus could possibly explain the wide range of expulsions reported.

A systematic review and meta-analysis from 2020 identified 48 trials and a total of 7661 IUD placements. The authors found rates of complete IUD expulsion to vary according to the time of placement: 10.2% (range 0.0-26.7) for immediate, 13.2% (3.5-46.7) for early, and 1.8% (0.0-4.8) for standard placement. Compared to interval placement, immediate- and early postpartum placements were associated with a higher risk of complete expulsion (88). Another systematic review found similar results, with a pooled

expulsion rate for immediate and early placement after vaginal delivery of 14.9% (range 3.3–46.7%; n 51,543), representing a six-fold higher risk of expulsion compared to interval placement (89). Furthermore, there are indications that early postpartum placement is associated with a higher rate of expulsion compared to immediate placement (90).

Considering the higher rates of expulsions reported after immediate- and early placements, focus has gradually come to shift from solely rating expulsions to a broader perspective focusing more on IUD continuation. Studies indicate that expulsion rates may be balanced by a higher continuation rate of the IUD-method in the longer perspective (91). Recent studies have shown high continuation rates among women receiving immediate postpartum IUDs, as well as cost-effectiveness, despite higher expulsion rates (92-94). This shift in focus of interest has not only added power to the research field but also eased implementation of the method of immediate and early placement of IUDs in health services (43).

Different elements in the process of IUD-placement that might be connected to the risk of expulsion have naturally been of interest, such as the insertion technique, the impact of experience of the involved staff and type of health profession, the type of device used and the impact of parity. The IUD placement can be accomplished by the hand of the obstetrician or midwife (for immediate insertion), by a Kelly- or ring forceps, or the insertion device from the manufacturer (43). There are also dedicated postpartum intrauterine device inserters available, specifically designed for the immediate post-delivery setting (95, 96). There is evidence that the dedicated postpartum Cu-IUD inserters are safe, with high acceptability among the participants and providers with no higher incidence of complications (96). There is no consensus about any insertion technique being superior in comparison, but some studies indicate that training of the practitioner lowers the risk of device expulsion (90, 97). Furthermore, the type of intrauterine device might affect the risk of expulsion. A systematic review and meta-analysis found the expulsion rate of hormonal IUDs to be 27.4% (18.8-45.2) and of Cu-IUDs to be 12.4% (4.8-43.1) after immediate postpartum placement. The hormonal IUD was thus associated with a higher risk of expulsion compared to the Cu-IUD (88). Additionally, some studies have found an association between multiparity and a higher risk of expulsion (91, 98).

2.7.3 Immediate placement of an intrauterine device during caesarean section

An IUD of any sort can be placed in the fundal part of the uterus after removal of the placenta during an elective cesarean section (99-101). In accordance with immediate placement after vaginal birth, this strategy provides immediate uptake of LARC during caesarean section with several advantages over standard device placement. Advantages of the method includes painless placement, convenience, high patient

motivation, immediate up-take without need of additional appointments and up-take of LARC prior to resumption of ovulation. The proportion of women using IUD at long term follow-up is higher after placement during caesarean section compared to standard placement, due to the high proportion of women not attending a scheduled appointment for placement (102). There is high evidence that the method is safe and effective, without higher risk of infection compared to standard placement, and without risk of perforation of the uterine wall (81, 97). Because the uterine wall of the fundal part is thick and the positioning of the device is visualized, the risk of perforation during procedure is extremely low.

The device can be positioned in the fundal part of the uterus by the hand of the obstetrician, by using a dedicated applicator, or by a forceps through the uterine incision (103). A trial comparing the risk of expulsion between the different insertion techniques found no difference between manual and forceps placement (104), and a study comparing the dedicated applicator with the forceps found no difference in complete expulsion rates for these placement methods (102). A weakness in several studies is the lack of description about placement method used, thus making comparison difficult.

Before placement during caesarean section, the threads of the device can either be cut and shortened or left at the original length. In a few studies the threads have been left in the cavity (103) but usually the threads are gently directed through the cervix by the applicator or by forceps before closing the hysterotomy.

The risk of expulsion of an intrauterine device placed at a timepoint unrelated to pregnancy is approximately 0-4 % (85, 102, 105, 106). The risk of expulsion after placement during a caesarean section is higher compared to standard placement, but considerably lower compared to placement after vaginal birth (90, 99, 107). A systematic review and meta-analysis found a complete IUD expulsion rate of 3.8 % (0.0-21.1) after caesarean deliveries, with a lower risk after caesarean placement than after immediate placement following vaginal delivery (88). The reason for the lower expulsion rate after caesarean section compared with immediate placement after vaginal delivery is not defined, but placement during caesarean section may have several advantages such as true fundal IUD placement, a less dilated cervix at the timepoint of placement, and the uterus being more momentarily contracted after caesarean delivery than within 10 minutes of placental removal after vaginal delivery (43).

The IUD threads are more likely not to be visualized through the cervical canal at follow-up when the IUD has been placed during caesarean section compared to immediate or early IUD placement after vaginal delivery (90). A check-up within the first four weeks after placement is recommended to confirm that the threads are visible through the cervical canal as an assurance that the device is still in the uterus. If no threads are

visible at the examination, a vaginal ultrasound scan is recommended. In most cases, the IUD will still be in the cavity of the uterus even if the threads are not visualized at the cervical os during a gynecological examination. If the IUD threads are not visualized through the cervical canal, they are most likely retained in the uterine cavity, but a vaginal ultrasound is needed to confirm that the IUD is still in the cavity and not expelled (108).

The method of IUD placement during caesarean section thus opens for the possibility to choose PPIUCD also for women delivering by caesarean section. The woman´s preferences, needs and attitudes towards antenatal counseling and use of postpartum contraception is thus fundamental and important to explore for implementation of a user-friendly, professional, and easily available contraceptive service that meets modern needs. There is a knowledge gap regarding preferences, expectations, and attitudes of PPIUDC and hopefully further research will help to design initiated services for information, counseling, and availability of PPIUCD for everyone who wants to use it.

3 RESEARCH HYPOTHESES AND AIMS

The overall aim of this thesis was to add knowledge to the field of long-acting reversible contraception after pregnancy in Sweden in our effort to improve the quality of contraceptive care after pregnancy and childbirth. We aimed to do this by applying both clinical and epidemiological methodologies and using both a quantitative and a qualitative dimension to address the complexity of contraceptive care after pregnancy.

3.1 Hypotheses

- Choice of LARC postpartum is related to a lower number of abortions than choice of other contraceptional methods or no method at all, within 24 months after delivery (Study I).

- Placement of a hormonal IUD (Mirena®) immediately (within 48 hours) after vaginal delivery is as effective as standard placement 6-12 weeks postpartum in reducing the number of abortions during the first year postpartum (Study II).

- Immediate placement of IUD after medical abortion results in higher use of IUD at six months post abortion compared to the current routine of delayed IUD placement at 2-4 weeks post abortion (Study III).

3.2 Aims

- To investigate if the choice of using long-acting reversible contraception (LARC) postpartum is associated with the risk of induced abortion over a period of 24 months postpartum, and to analyse other significant factors that affect the risk of abortion during this period (Study I).

- To study the risk of induced abortion within 1 year postpartum, the safety profile and patient acceptability after early postpartum placement of a hormonal IUD (Mirena®) compared with standard placement 6–8 weeks postpartum.

- To investigate if placement of an IUD within 48 hours of completed medical abortion at up to 63 days' gestation leads to higher user rates at 6 months after the abortion compared with placement at 2 to 4 weeks after abortion, and to compare continued use of IUD, safety, and patient satisfaction between allocation groups (Study III).

- To identify and describe women´s experiences of contraceptive services before, during and after an elective CS (Study IV).

4 MATERIALS AND METHODS

4.1 Reflection and ethical considerations

All studies in this thesis were approved by the Regional Ethical Review Boards in Stockholm, Linköping and/or Uppsala or by the Swedish Ethical Review Authority.

Study I: Linköping (2016/84-31)

Study II: Linköping (2017/339-31, 2018/56-32)

Study III: Stockholm (2016/1685-31/1, 2018/48-32, 2018/962-32, 2019-03183, 2020-02925, 2021-02625)

Study IV: (2021-00065)

Considering **Study I,** there were ethical dilemmas common to all studies that use data from medical records. Data was accessed from medical records without patient consent. Extraction of data and analysis was approved by ethical review boards before access to data. The accessed data was pseudonymized and only available to the research team. Data was presented on a group-level, and thus impossible to relate to any identifiable participant.

Study II and III were randomised controlled studies that used intrauterine devices (IUDs) with well-known effects and few side-effects, and the IUDs were free of charge for the study participants. The randomised studies were conducted according to Good Clinical Practice and the World Medical Association Declaration of Helsinki. Participation was voluntary and could be discontinued at any time without further explanation. Participation was dependent on signed informed consent. Eligible participants were informed by written- and oral information and had the opportunity to ask questions before and after signing consent in good time ahead of IUD placement. In **study II** pregnant women were informed of the study during pregnancy and eligible women were informed again after delivery during the hospital stay. In **study III** eligible women were informed during the medical appointment before an abortion was initiated.

Care was taken not to put pressure to participate, and it was emphasized that a decline to participate would not affect medical care. If the study participant chose another method after signing of the informed consent, she was still included in the follow-up within the study but received counseling according to clinical practice. Also, if the participant was not prepared to make any decision regarding further use of contraceptives, this was respected.

The women were assured that we did not know the difference in outcome of the study in advance, so that they would not get disappointed when allotted to delayed

placement. Furthermore, it was important not to make the women afraid of pain related to the delayed placement, which could make her refrain from attending the placement visit.

It could not be excluded that there was a higher risk of expulsion with immediate IUD placement soon after pregnancy, and especially after vaginal delivery compared to standard placement. Previous studies have shown that expulsion usually happens within the first weeks of IUD placement. Women were therefore informed of the risk of expulsion. As part of the study plan, for the early placement group in **study II,** an early follow-up including speculum examination was performed at 2 weeks after placement, and in **study III** women were contacted by 3 months after placement. In the event of an expulsion the woman would receive support with contraceptive care according to preference. Because of earlier findings indicating a higher risk of expulsions (81), pre-defined safety analyses were part of the study plan for both study **II and III,** including a pre-defined stopping of recruitment according to the proportion of expulsions.

In **study II** the main outcome measure was abortion as a surrogate for unwanted pregnancy. In **study III** the main outcome of use of IUD at six months post abortion was a surrogate for risk for unintended pregnancy which is a risk for unwanted pregnancy. As IUD is a highly effective method compared to other methods it was assumed that a higher use of IUD would lead to fewer unintended pregnancies compared to all other methods except sterilization and the implant. This was evaluated through follow-ups and questionnaires but also by review of medical records. Abortion could be a very personal question and there might have been a risk that the women could feel a threat to personal integrity. The women were however informed by written- and oral information before they gave informed consent. Moreover, all data was pseudonymized and at the time of analysis there was no possibility to link the information to a specific woman without accessing the code key. Data was presented on group-level for both **study II and study III**. According to Swedish law, IUDs provided in trials must be available without any cost for the participants. Otherwise, women pay slightly above 100 Euro for a hormonal IUD. The regulation of cost-free drugs in trials, including hormonal IUDs, is a fundament for ethical dilemma. There might be a risk that women feel forced to participate in a trial because they cannot afford the IUD outside the trial. Furthermore, there is a dilemma regarding the trustworthiness of the outcome in trials studying adherence to follow-up and IUD placement visits when the IUD is provided for free. The setting will differ from real life circumstances and might affect the outcome of what is intended to study, and even jeopardize the generalizability of the results. In **study II and III** we had to adept to these regulations and conducted both studies being aware of this dilemma.

Study IV was a qualitative study based on 20 interviews. Eligible women were informed of the study after CS but while still in hospital. The women were informed by written and

oral information and had the opportunity to ask questions before and after signing the informed consent. It was important that the women did not feel forced to enter the study and that it was easy to decline participation. The free choice to enter and drop out of the study without having to motivate the decision were emphasised.

Contraception might be a sensitive issue, and it was important that the women did not feel any harm or threat to integrity. Moreover, there could have been a risk that a woman felt pushed to answer in a positive way. However, the questions were neutral and open-ended, and the research team is experienced with qualitative methodology interviews. Every woman was informed about the study before signing informed consent and then again before the interview. Interviews were performed with only the interviewer and the interviewee present to secure safety and confidentiality. Confidentiality was carefully kept throughout the whole process including the report of results. Interview sound files and transcripts were saved on secure servers. All personal identifiers were removed, and the data was pseudonymized. At the time of analysis there were no possibility to link the information to a specific woman except for the research team.

4.2 Study I Method and statistical analyses

4.2.1 Method

Study 1 was a retrospective cohort study. We included all women with a live birth at Linköping, Norrköping, and Västervik hospitals in Sweden from January 1, 2013, to December 31, 2014. The catchment areas of these hospitals covered both urban and rural populations. We excluded women with an intrauterine fetal death, women who had moved out of the catchment area, who had a missing personal identification number or who had been re-registered for antenatal care because of another pregnancy during the follow-up period (n = 1081), (figure I:I).

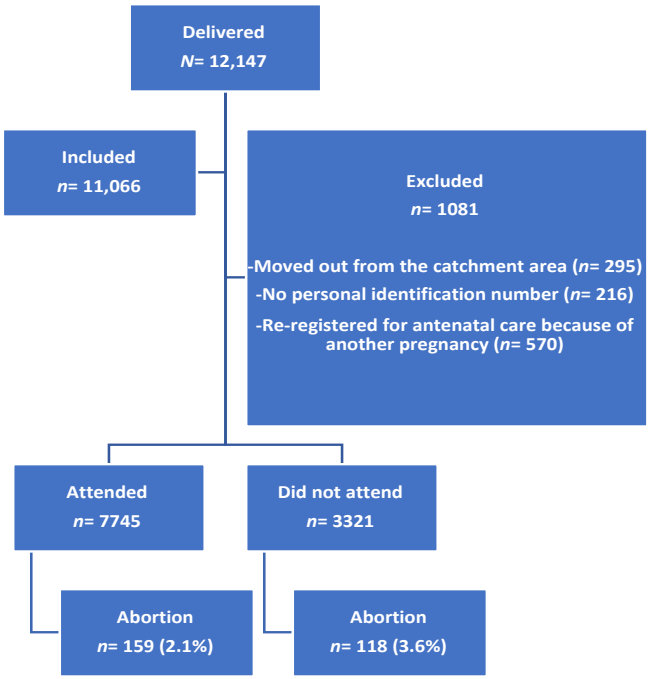
From the obstetric electronic medical record (Obstetrix; Cerner, Lund, Sweden) we identified demographic data, attendance to the postpartum visit, choice of postpartum contraception and self-reported breastfeeding status at the postpartum visit at the Maternity Health Care units. Data regarding placement of LARC could not be extracted. Through the medical record system (Cosmic; Cambio, Stockholm, Sweden) we identified women with possible need for abortion by ICD-10 diagnosis code Z64.0 (definition ICD-10, problems related to unwanted pregnancy).

Our primary outcome was the proportion of induced abortions 12-24 months after delivery for each contraceptive method, with the outcome measure of induced abortion being a surrogate for unwanted pregnancy. We verified abortion in women with ICD-10 diagnosis Z64.0 by reading every one of the medical records with this diagnosis. Registration of diagnosis codes is mandatory in Sweden and reported to the Swedish National Board of Health and Welfare. According to Swedish guidelines, code Z64.0

should be used for all women requesting counseling for or provision of induced abortion. Depending on the time of delivery during the index year (2013 or 2014), the follow-up period varied between 12 and 24 months.

Our secondary outcomes were the proportion of women attending the postpartum follow-up visit at Maternity Health Care 2-3 months after delivery, and the relation between the demographic characteristics of the included women and the choice of postpartum contraception.

Figure I:I Flowchart of study population, attendance to the postpartum visit and number of induced abortions during follow-up



4.2.2 Statistical analyses

We calculated the sample size based on the results of a pilot study of 350 postpartum women. The pilot study revealed that 6% had had an appointment for induced abortion within 1–2 years after childbirth. We expected that close to 30% of participants would choose a LARC method, and we expected 50% fewer abortions in the LARC-group compared with the group of women who had chosen other contraceptive methods or no method at all. Based on assumptions from the pilot study, and to achieve 80% power and a 5% significance level, the study needed to include 10,000 postpartum participants.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY). The analyses used the full dataset, and all results were based on observed outcomes without imputation of missing data.

Demographic characteristics were calculated and presented as medians with minimum and maximum values and differences between groups were analysed by the Mann–Whitney U test. The proportions of women who attended versus not attended the postpartum visit at Maternity Health Care were calculated. The proportion of women who had at least one abortion during follow-up in relation to the choice of contraceptive method was analysed and presented as a proportion. Differences between groups were analysed by the $\chi 2$ test or Fisher's exact test, as appropriate. Differences in odds ratios (ORs) for induced abortion were presented. For analyses of significant factors affecting the risk of abortion, continuous variables were dichotomised and used in a backward elimination method for logistic regression as follows: age <25 and ≥25 years, body mass index (BMI) <30 and ≥30 kg/m2, postpartum visit <13 and ≥13 weeks after childbirth. Results were presented as adjusted ORs with 95% confidence interval. All differences between groups were considered as statistically significant if they had a p-value ≤.05.

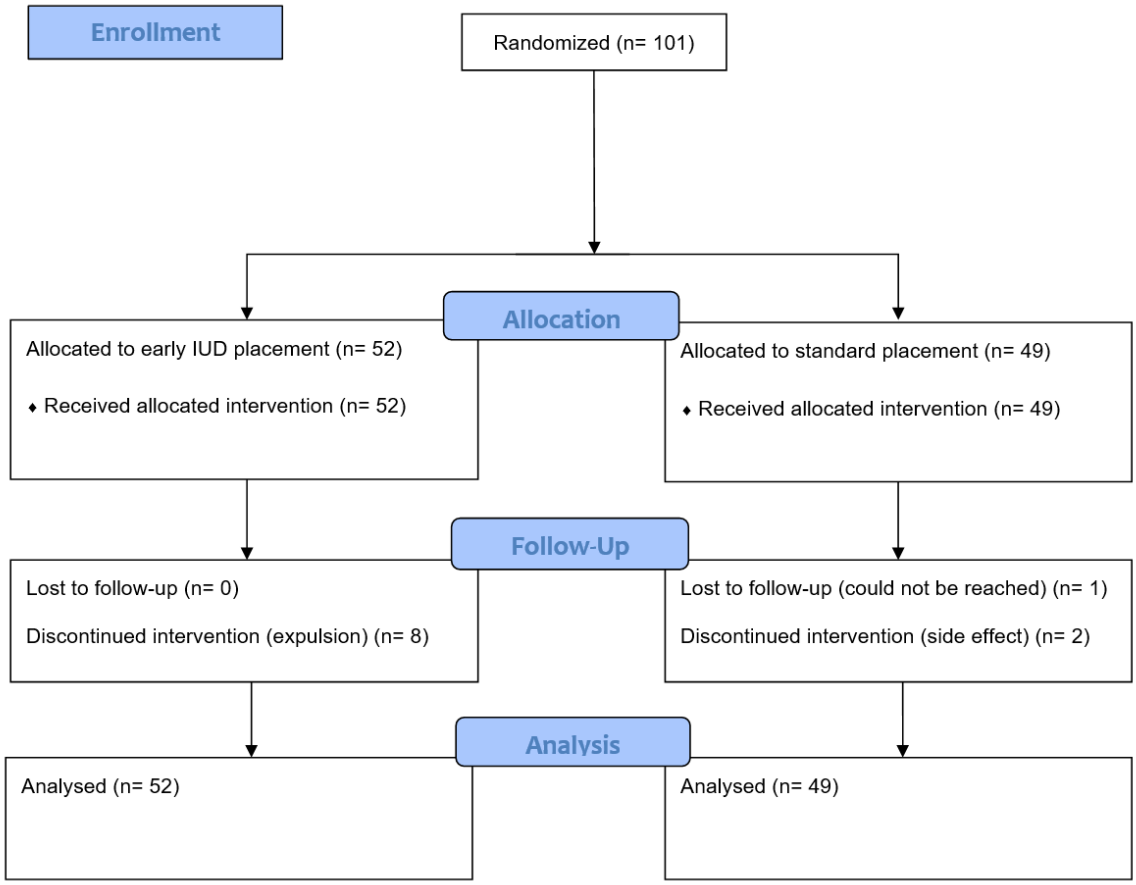
4.3 Study II Method and statistical analyses

4.3.1 Method

Study II was an open-label, randomised controlled, non-inferiority, multicenter study (phase 3). From April 2018 to January 2020 eligible women with uncomplicated vaginal delivery who fulfilled the inclusion and were without exclusion criteria were recruited at the delivery clinics of Danderyd, Linköping, Norrköping and Jönköping Hospitals in Sweden. Written information about the study was available antenatally at the Maternity Health Care units and at the delivery wards. Eligible women were again informed of the study prior to delivery or within hours after delivery. Informed consent was obtained by a designated medical doctor within the first day postpartum. Included women were then randomised at a ratio of 1:1 in consecutive order and in parallel groups, to placement of a hormonal IUD (Mirena®, Bayer AB) either early within 48 h after delivery (early group) or at standard time 6–8 weeks postpartum (standard group). All women were included in the study for 12 months, with follow-up at 2, 4 and 8 weeks after IUD placement, and at 6 and 12 months postpartum. The standard group had a final follow-up at 12 months after IUD placement.

An interim analysis was performed after inclusion of 100 women with the predefined decision to prematurely stop inclusion of women if the rate of expulsion were to exceed 20% within 28 days after IUD placement in either of the two study groups. The interim analysis showed the rate of expulsion in the early placement group to widely exceed the predefined value, and thus the inclusion of women was stopped. No expulsions were found in the standard placement group (figure II:I).

Figure II:I Flowchart of study population



We used a standardised protocol for hormonal IUD placement according to the recommendations for standard placement. All devices were placed by the same midwives/gynecologists at each center. The inserter provided by the manufacturer of the hormonal IUD was used to place the device in both the early and the standard group. During the early placement, the device was placed in a fundal position as judged by the healthcare personnel performing the placement. Placement of the hormonal IUD in the standard group were performed according to the manufacturer's instructions. No ultrasound examination was performed before or after placement. Immediately after the IUD placement, participants were asked to estimate the worst pain experienced during the placement procedure, using a visual analog scale (VAS) ranging from 0–100, where 0 was equal to no pain and 100 was equal to the worst imaginable pain. Bleeding patterns were determined by descriptions of how many continuous days after delivery, and after IUD placement, the participant experienced fresh and/or brown bleeding and/or spotting's.

The primary outcome was the proportion of abortions in each group within 1 year after IUD placement. The secondary outcomes were the rate of expulsions, assessment of reasons for discontinuation of the hormonal IUD method, rate of continuation with the

method, successful placements of the hormonal IUD, assessment of reasons for non-application of the hormonal IUD as planned, pain reported at the time of placement, number of days and amount of postpartum and menstrual bleeding, and questions of acceptability. Furthermore, we compared safety parameters by studying the number of complications as well as infant growth and duration of breastfeeding.

4.3.2 Statistical analyses

The power calculation was based on the same pilot study as in Study I. We expected 50% fewer abortions than in the pilot study among women using the hormonal IUD with standard placement time and assumed that early placement most probably would lead to fewer abortions compared with the standard group. Based on that theory, we predicted approximately 1% abortions in the early group and 3% in the standard group after one year. Given a non-inferiority limit of 1% (Δ), 80% power (1–β) and 5% significance level (α) we had to include 259 participants in each group. To compensate for an estimated 15% drop-out rate, we decided to include 300 participants in each group. Due to the premature stopping of inclusion after the interim analysis, we included 101 women instead of 600.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM). The analyses used the full dataset. Baseline characteristics, i.e. age, parity, vaginal deliveries and CS, as well as reported pain during placement of the hormonal IUD measured by the VAS, the period of bleeding after delivery and infant growth in terms of weight, length and head circumference at the age of 12 months, were presented as medians with minimum and maximum values. Differences between groups were analysed by Mann–Whitney U-test. The continued use of long-acting reversible contraception at study closure 1 year after IUD placement, the number of women preferring the allocated time of IUD placement, the number of women that would recommend the hormonal IUD method to a friend based on the current experience and the number of women partially or exclusively breastfeeding at 6- and 12-months follow-up were presented as proportions with differences between groups analysed by the $\chi 2$ test or Fisher's exact test, as appropriate. All differences between groups were considered statistically significant if they had a $p \leq .05$.

4.4 Study III Method and statistical analyses

4.4.1 Method

Study III was an open-label, randomised, controlled, multicenter, superiority trial (phase 3). We recruited women aged ≥18 years requesting medical abortion with gestation of ≤63 days and opting for postabortion IUD at the gynecology clinics of Danderyd, Stockholm South General, Falun/Mora, Uppsala University, and Helsingborg hospitals in Sweden. Exclusion criteria were contraindications for medical abortion or IUD use,

inability to give informed consent, and abortion-related complications. Eligible women received written- and oral information about the study and had the opportunity to ask questions, before signing informed consent. Women were, at the time of taking mifepristone, randomised at a ratio of 1:1 in permuted blocks of 4 to 8, to placement of an IUD within 48 hours after complete abortion (intervention group), or to IUD placement at a scheduled follow-up visit 2 to 4 weeks after abortion according to routine care (control group). The induced abortion was carried out according to the World Health Organization guidelines (109). Ultrasound verification of complete abortion was not mandatory according to protocol, except in the case of doubt concerning complete abortion. The abortion was defined as complete after the women had reported bleeding with clots and cessation of heavy bleeding without reason to suspect an incomplete abortion based on patient history.

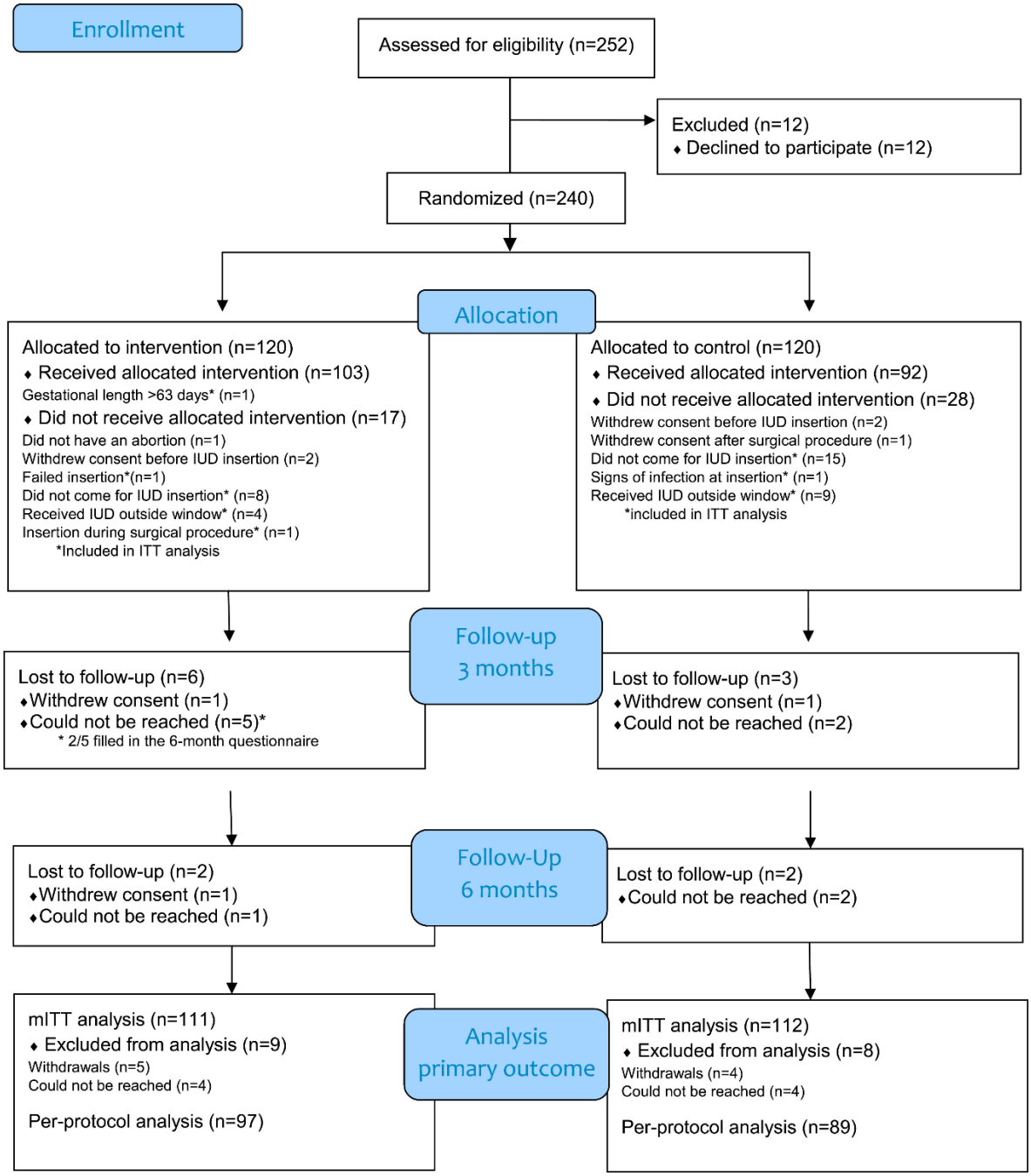
Women who had home administration of misoprostol and were allocated to the intervention group were scheduled for IUD placement within 48 hours of misoprostol administration. Women in the control group were scheduled for an appointment for placement after 2 to 4 weeks. All devices were placed by the same midwives/gynecologists at each center. The IUDs approved for this study were: Mirena® (LNG-IUS, 52 mg), Kyleena® (LNG-IUS, 19.5 mg), Jaydess® (LNG-IUS, 13.5 mg, marketed as Skyla in some countries), and NovaT 380™ (Cu-IUD). All IUDs were placed according to the instructions by the manufacturer and provided at no cost.

Pain scores were measured before, during and after IUD placement using a visual analogue scale (VAS) ranging from 0 to 100, where 0 is equal to no pain and 100 to the worst imaginable pain.

Women were included in the study for 12 months (figure III:I). Follow-ups were conducted at 3, 6, and 12 months, either by a phone call and/or an e-mail with a link to a questionnaire with multiple questions related to the primary and secondary outcomes of the study. There was no mandatory follow-up visit after the IUD placement visit and thus the rate of expulsion was only reported by the women. Reporting was limited to complete expulsion noticed by the women or to partial expulsions reported by women if they had themselves taken initiative to a visit due to perceived problems related to the IUD.

The primary outcome of the study was IUD use at 6 months postabortion, evaluated as the proportion of women using IUD vs not using IUD. The secondary outcomes were rates of IUD placement at allocated time, reasons for non-placement of IUD, expulsion rate, pain at placement, adverse events and complications from the abortion, acceptability, and pregnancies and abortions evaluated at the 3-, 6-, and 12-month follow-up.

Figure III:I Flowchart of study population



ITT , intention-to-treat; IUD , intrauterine device; mITT , modified intention-to-treat.

4.4.2 Statistical analyses

The sample size was calculated based on the hypothesis of 80% IUD use in the intervention group and 60% use in the control group at 6 months after abortion. We estimated 3-5% to need a vacuum aspiration because of incomplete abortion and/or prolonged bleeding. We expected approximately 15% loss to follow-up which is commonly observed in abortion studies. With a power of 90 % and an alpha of 0.05, we needed to randomise 240 women.

An interim analysis was performed when 50% of women had been recruited, with the predefined decision to stop inclusion of women in case the expulsion rates exceeded 20% or if acceptability rates were <50% at the 3-month follow-up in any group. The results of the interim analysis were compatible with continuation of the study according to the study protocol.

We performed statistical analyses using IBM SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, NY). The main analysis for the primary outcome "use of IUD at 6 months postabortion", was performed with a modified intention-to-treat (mITT) analysis including all randomised women with medical abortion and follow-up recorded at 6 months. Hence, also women with no IUD placement or IUD placed outside the allocated time window or during surgery, and women experiencing expulsion, were included in the mITT population but not in the per-protocol population. For the primary outcome and for IUD expulsion rates, we also calculated per-protocol analyses. We added a sensitivity analysis for the primary outcome with imputation of the results with the found proportions of IUD usage, which did not change the results significantly.

Baseline characteristics, i.e. age, number of school years, gestational age at mifepristone intake, parity, previous abortion, misoprostol taken at home, type of IUD placed, and IUD not placed, were presented as medians with minimum and maximum values. The differences between groups were analysed by Fisher's exact test. The pain scores during the procedure of IUD placement were presented as means and differences in distributions were analysed by Mann Whitney U-test. The proportion of women using an IUD at 6 months, attendance rate for placement and rate of successful IUD placement, use of ultrasound at IUD placement, women´ preferences of allocated time of IUD placement and healthcare providers´ rates of ease of IUD placement, were presented as proportions with differences between groups analysed by Fisher's exact test. All differences between groups were considered statistically significant if $p \leq .05$.

4.5 Study IV Method

4.5.1 Method

In **study IV** we used a qualitative design and methodology to study the phenomena of contraceptive services in the context of caesarean section, and to enable deeper

understanding of women´s preferences and needs. Womens´ experiences were gathered by on-line video interviews. The interviews were recorded and transcribed for further analysis. Demographic characteristics were collected via a questionnaire.

The study was conducted from November 2021 to June 2022 at Danderyd Hospital, Sweden. Swedish speaking women >18 years of age who underwent elective CS were invited to participate (n=33). We did not invite women who had complications during or after the caesarean to participate, such as conversion to an emergency CS, complicated CS, blood loss > 1000 ml, or severe neonatal adverse outcome before enrolment. Eligible women received written- and oral information about the study and had the opportunity to ask questions before signing informed consent. Included women were invited for an interview within six weeks of the CS. Before the start of the interview, the woman once again received oral information about the study and had the opportunity to ask questions. Out of 33 invited women, four declined to participate and 29 signed informed consent. Out of these 29 women, nine could not be reached for the interview. The final sample was thus 20 women who completed the study.

Theory-based random purpose sampling was used (110) to include ten study women who had chosen placement of an IUD and ten women who had not chosen placement of an IUD during the elective CS. The study was part of a larger initiative to improve contraceptive counseling prior to childbirth.

4.5.1.1 Data collection instrument

A semi-structured interview guide was developed and created through literature review and discussion within the research group (111).

Two pilot interviews were performed to test the interview questions. The research team decided to make a slight adjustment of the opening question in the guide. Face-to-face interviews were conducted through Microsoft Teams® at places and times chosen by the women. The interviews lasted for 20-55 min (median 37 min). They were digitally recorded, de-identified and transcribed verbatim.

4.5.2 Analyses

The transcripts were analysed using reflexive thematic analysis according to Braun & Clarke (112). Each transcript was thoroughly read through several times by two members in the research group, with following discussion and reflection on interpretation and exploration of important units to reach a deeper understanding of the meaning. Two of the transcripts were coded individually and then compared and discussed within the research group to form a unanimous concept and understanding. Every transcript was coded using inductive thematic theory letting the data drive the final codes and the forming of initial themes (n=16). Then, the researchers who performed the data analysis reflected on the structure and variation of the themes and adjusted the meaning of

each theme using the researchers' interpretations of the text. The key finding themes were discussed in the study group and through iterative reflection we again explored and reflected together over the key findings, to finally summarize three main themes and identify representative quotes corresponding to these themes.

5 RESULTS

5.1 Study I

We included 11,066 women who had given birth during 2013 and 2014 at three Swedish birth centers. Women who had an abortion during the 12-24 month of follow-up were significantly younger, had higher parity and had a higher rate of previous abortion(s) (table I:I). A total of 2080/11,066 (18.8%) women reported at least one previous abortion.

Table I:I Characteristics of women with vaginal deliveries during 2013 and 2014

Characteristics	Abortion (n = 277)	No abortion (n = 10,478)	p-value
Age, years (n = 11,023)			<.001
Median (min–max, IQR)	27.7 (18–43, 24–30.5)	30.3 (15–52, 26–34)	–
Mean (SD)	27.7 (5.2)	30.2 (5.3)	–
BMI, kg/m^2 (n = 10,673)			.38
Median (min–max, IQR)	24.6 (17.2–43.6, 21.6–28.2)	24.1 (15.1–58.7, 21.6–27.6)	–
Mean (SD)	25.5 (5.3)	25.1 (5.2)	–
Parity (n = 10,823)			.005
Median (min–max, IQR)	1.0 (0–6, 0–2)	1.0 (0–11, 0–1)	–
Mean (SD)	1.1 (1.0)	0.9 (1.1)	–
History of miscarriage (n = 10,823)			<.05
Median (min–max, IQR)	0 (0–6, 0–1)	0 (0–8, 0–0)	–
Mean (SD)	0.4 (0.9)	0.3 (0.7)	–
Previous abortion (n = 10,823)			<.001
Median (min–max, IQR)	0 (0–4, 0–1)	0 (0–9, 0–0)	–
Mean (SD)	0.6 (0.9)	0.2 (0.6)	–

IQR: interquartile range, SD: standard deviation

Of the women in the study, 7745/11,066 (70 %) attended the postpartum visit at Maternity Health Care. Among attendants, 2.1 % had an abortion during follow-up. In the group of study women not attending the postpartum visit, 3.6 % had an abortion during follow-up. Of all women, 1945/11,066 (17.6 %) chose a LARC-method. Age was found to be a significant factor for the choice of a LARC-method. Women <25 years chose the implant significantly more often (93/1609 (5.8%) vs. 255/9457 (2.7%); p< .001) compared with women 25 years or older (table I:II).

Table I:II Proportion of women who had at least one abortion during follow-up in relation to the choice of contraceptive method

Contraceptive choice	Number of women (%)	Number of women with abortion (%)
Did not attend follow-up	3321 (30.0)	118 (3.6)
Attended follow-up	7745 (70.0)	159 (2.1)
No choice	1891 (24.4)	42 (2.2)
Implant	348 (4.5)	7 (2.0)
IUCD	1597 (20.6)	18 (1.1)
Pill (COC and POP)	2587 (33.4)	74 (2.9)
Condom	1068 (13.8)	17 (1.6)
Other contraceptive method	254 (3.3)	8 (3.1)
Total	11,066 (100)	277 (2.5)

COC: combined oral contraceptive pill; POP: progestogen-only pill.

Age was also found to be a significant factor for the risk of abortion. Women aged 20–24 years were at highest risk of abortion during study follow-up (76/1492, 5.1%). Furthermore, characteristics such as smoking and having had a previous abortion were associated with a higher risk of abortion. A decision to use LARC postpartum was associated with a lower risk (OR 0.74; 95% CI 0.60, 0.91; p = .005) as was exclusive breastfeeding at the time of the postpartum visit (p < .001). Attendance to the postpartum visit was not solely found to be associated with a lower risk of abortion but a prerequisite to decide upon LARC at that time postpartum (table I:III).

Table I:III Factors influencing the risk of abortion during follow-up

Factor	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
BMI ≥30 kg/m^2	1.21 (0.89, 1.66)	.23	1.06 (0.77, 1.46)	.719
Smoking	2.56 (2.01, 3.25)	<.001	1.51 (1.07, 2.11)	<.018
Age <25 years	2.51 (1.92, 3.26)	<.001	2.25 (1.72, 2.95)	<.001
Previous abortion	1.82 (1.60, 2.07)	<.001	1.71 (1.50, 1.95)	<.001
Chose LARC	0.64 (0.52, 0.78)	<.001	0.74 (0.60, 0.91)	.005
Breastfeeding[a]	0.36 (0.27, 0.47)	<.001	0.54 (0.39, 0.74)	<.001
Postpartum visit <13 weeks	1.94 (1.53, 2.47)	<.001	1.06 (0.77, 1.47)	.705

[a] Exclusive or partial breastfeeding

5.2 Study II

We included 101 women, either allocated to early placement (52/101) of a hormonal IUD within 48 hours after vaginal delivery or to standard placement (49/101) at 6-8 weeks postpartum.

The study was prematurely stopped due to expulsions exceeding the predefined level of up to 20 % expulsions within the first 28 days of placement in either of the study arms. Instead of including 600 women as calculated, we stopped the inclusion after 101 women. The rate of expulsion was highest, reaching 23 %, during the first 14 days after placement. No expulsion occurred in the standard placement group (table II:I).

Table II:I Expulsions within 28 days of early IUD placement

Expulsion	**Complete**	**Partial**	**Total**
n/N (%)	11/52 (21.1)	12/52 (23.1)	23/52 (44.2)

There were no differences in baseline characteristics of the women in the study (table II:II).

Table II:II Baseline characteristics of women

Placement		**Early n= 52**	**Standard n= 49**	**p-value**
Age (years)	median	30	30	.85
	IQR	28–32	27–32	
	min-max	22-36	20–35	
Parity	median	2	2	.48
	IQR	1.25–3.0	2.0–2.0	
	min-max	1–4	1–4	
Vaginal delivery	median	2	2	.59
	IQR	1–2	1–2	
	min-max	1–4	1–4	
Caesarean section	median	0	0	.76
	IQR	0–0	0–0	
	min-max	0–1	0–1	

IQR, interquartile range.

All IUDs were placed according to the allocated time and no pregnancies occurred during the study follow-up of 1 year after IUD placement.

The IUD continuation rate for the early group was 37/52 (71.2%), compared to 41/49 (83.7%, p = .13) for the standard placement group at study closure. In the early group 10 women had replacement of IUD after expulsion and two IUDs were removed on request. In the standard placement group there were six removals on request and two perforations. One woman in each placement groups chose to have an implant instead of an IUD, and in the standard placement group one woman chose placement of a Cu-IUD instead of the hormonal IUD. The proportion of women using LARC was thus 38/52 (73.1%) in the early placement group and 43/49 (87.8%, p = .064) in the standard group at study closure.

The average postpartum bleeding period was significantly shorter for women allocated to early placement (21 vs 30 days of bleeding, p < .01). We found no significant difference in pain measured by the visual analog scale (VAS) at IUD placement. The mean pain level measured on a VAS was 20/100 in the early placement group and 24.5/100 in the standard group, p = .77. We found high grades of satisfaction with the IUD method in both groups. All women would choose placement of a hormonal IUD again when asked directly after placement, and more than 90 % of women in both groups would choose the hormonal IUD method again when asked at the 6-month follow-up with no difference between early placement 37/41 (90.2 %) vs standard placement 42/45 (93.3 %), p = .70.

The proportion of women who preferred the allocated time of IUD placement in the early placement group were 31/41 (75.6%) and in the standard placement group 30/45 (66.7%; p= .48). We found no significant difference regarding breastfeeding between the two groups, neither for exclusive breastfeeding nor the length of breastfeeding. Furthermore, there were no differences in infant growth in terms of weight, length, or head circumference at the age of 12 months. Finally, we did not find adverse events to differ between the two placement groups, beside the two perforations in the standard placement group. Besides the perforations, there were no serious adverse event connected to the IUD method.

5.3 Study III

We included 240 women who had early medical abortion at up to 63 days' gestation and opted for IUD postabortion. From January 2019 to February 2021, women were allocated to the intervention group with IUD placement within 48 hours (n=120) after assumed complete abortion, or to the control group with IUD placement 2 to 4 weeks after abortion (n=120). Baseline characteristics of women are shown in table III:I.

Table III:I Baseline characteristics of women having medical abortion at up to 63 days´ gestation and opting for IUD as postabortion contraception

Characteristics	Intervention (n=120)	Control (n=120)
Demographic characteristics		
Age, years		
Median	31	30
IQR	26-35	26-35.75
min-max	18-48	18-48
Missing	1	
Number of school years, n (%)		
≤ 9	3 (2.5)	6 (5)
10-12	60 (50.4)	58 (48.3)
> 12	56 (47.1)	56 (46.7)
Missing	1	
Other baseline characteristics		
Gestational age at mifepristone intake		
Median	43	42
IQR	40-51.25	38-49.75
Min-max	28-68	28-63
Missing	2	
Parous women, n (%)	88 (73.3)	84 (70)
Previous abortion, n (%)	72 (60.5)	72 (60)
Missing	1	
Misoprostol taken at home, n (%)	104 (87.4)	101 (84.2)
Missing	1	
Type of IUD placed, n (%)		
Mirena®	59 (54.6)	45 (44.1)
Kyleena®	39 (36.1)	49 (48)
Jaydess®	3 (2.8)	1 (1.0)
Copper IUD Nova T™	7 (6.5)	7 (6.9)
IUD not placed	12	18

IQR, interquartile range; IUD, intrauterine device.

The proportions of IUD users at 6 months after the abortion are shown in table III:II.

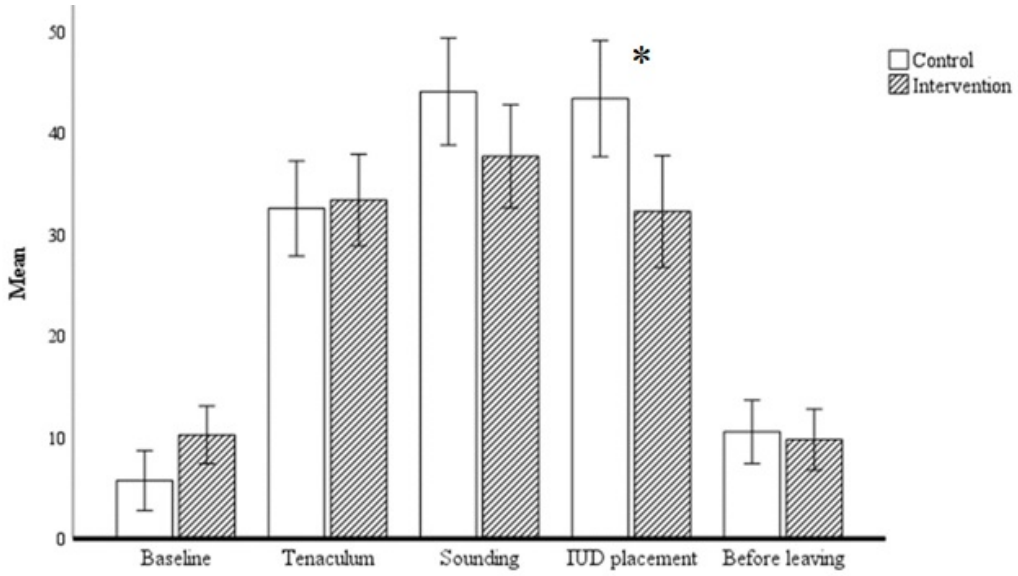
Table III:II Proportion of women using an intrauterine device at 6 months

IUD users	Intention-to-treat			Per-protocol		
	Intervention n=111	Control n=112	p-value	Intervention n=97	Control n=89	p-value
At 6 mo, n (%)	91 (82)	87 (77.7)	.51	84 (86.6)	79 (88.8)	.82

Intervention=placement of an intrauterine device within 48 hours after early medical abortion; control=placement of an intrauterine device at 2 to 4 weeks after early medical abortion. IUD, intrauterine device.

In the intervention group 103/120 (85.8 %) and in the control group 92/120 (76.7 %) received the IUD as allocated. Ultrasound was used significantly more often during IUD placement in the intervention group 43/108 (39.8 %) compared to the control group 15/101 (14.9 %, P<.001). No retained gestational products were found with ultrasound in the intervention group. In the control group ultrasound detected one woman with a retained gestational sac. Pain scores at IUD placement were significantly lower in the intervention group compared with the control group, P= .002. Pain scores at different points of IUD placement are shown in figure III:I.

Figure III:I Mean pain score during placement of intrauterine devices



Error bars represent±2 standard errors. Asterisk indicates significant difference. IUD, intrauterine device.

The women preferred the allocated time of IUD placement significantly more often in the intervention group (83/111, 74.8%) than in the control group (70/114, 61.4%; P= .03).

We did not find any difference in IUD expulsion between the groups in the mITT or in the per-protocol analysis, table III:III.

Table III:III Expulsions of intrauterine devices within 6 months following medical abortion

Time postabortion	**Intervention**			**Control**			**p-value, overall expulsions**
Expulsion	Complete	Partial	Overall	Complete	Partial	Overall	
	n	n	N	n	n	N	
	(%)	(%)	(%)	(%)	(%)	(%)	
Within 3 months							
mITT	4/112	4/112	8/112	2/114	1/114	3/114	.13
	(3.6)	(3.6)	(7.1)	(1.8)	(0.9)	(2.6)	
Per-protocol	4/97	3/97	7/97	2/89	1/89	3/89	.33
	(4.1)	(3.1)	(7.2)	(2.2)	(1.1)	(3.4)	
Between 3-6 months							
mITT	2/111	0	2/111	1/112	0	1/112	.62
	(1.8)		(1.8)	(0.9)		(0.9)	
Per-protocol	2/97	0	2/97	1/89	0	1/89	1.00
	(2.1)		(2.1)	(1.1)		(1.1)	
Within 6 months							
mITT	6/111	4/111	10/111	3/112	1/112	4/112	.11
	(5.4)	(3.6)	(9.0)	(2.7)	(0.9)	(3.6)	
Per-protocol	6/97	3/97	9/97	3/89	1/89	4/89	.25
	(6.2)	(3.1)	(9.3)	(3.4)	(1.1)	(4.5)	

mITT, modified intention-to-treat

We did not find any infections requiring antibiotic treatment or any IUD perforations in any of the groups.

5.4 Study IV

We identified three themes; *Receptivity to contraceptive counseling during pregnancy; Communication and decision-making of postpartum contraception during pregnancy and Needs to navigate in the Maternal Health Care System to receive contraceptive services before and after caesarean section (CS).*

5.4.1 Receptivity to contraceptive counseling during pregnancy

We found the awareness of contraception overall limited and that participants often had continued with the same method they once started without adapting method to the contraceptive needs of the period in life.

Medial and social attitudes along with information from friends sometimes had a deeper impact on the choice and expectations of contraceptive methods than information from expertise. Women generally desired more information about contraception. Furthermore, skepticism was sometimes expressed regarding contraception containing hormones and referred to as "not being natural". Additionally, some women had experienced side-effects from methods containing hormones.

Women generally expressed low receptivity to discuss contraception during the first months of pregnancy. From around mid-term of pregnancy women experienced rising receptivity and interest to talk and discuss postpartum use of contraception (Q 1). Communication about contraception a few times during the second part of pregnancy would be appreciated, to have the time to reflect and decide upon postpartum use.

(Q 1) *"…the optimal time to discuss contraception during pregnancy…from about mid-term to the end of pregnancy, I think. When the delivery is getting closer… because then you start to focus on the delivery, and then it is also easier to imagine the time period after that (delivery)"* (Interview code 12)

5.4.2 Communication and decision-making of postpartum contraception during pregnancy

The women generally preferred to communicate with their midwife in Maternity Health Care about postpartum contraception. A trustful relationship with the caregiver was considered important when discussing contraception.

Most women had received sparse information about postpartum contraception during pregnancy. Despite that, many women would have appreciated a rich information about contraceptive methods. They suggested written and audio-visual information as additional forms to receive information.

Being informed and involved in the decision of contraception was central for all interviewed in the study. They expressed that too sparse information could lead to not

feeling involved enough or informed enough to decide on contraception. Women who had decided on, and had an IUD placed during the CS, were usually satisfied with the decision.

We found that many women expressed interest in decision-making about postpartum contraception during pregnancy, and to have an IUD placed during CS was usually considered as convenient (Q 2).

(Q 2) *"…to have an IUD placed during the CS would have been excellent, because when the baby is born there is so much else to do, and now I must arrange for that (placement of IUD) myself after six weeks."* (interview code 7).

5.4.3 Needs to navigate in the Maternity Health Care System to receive contraceptive services before and after CS

The women expressed a need for a reliable system for communication and coordination of contrceptive services for postpartum contraception use. Women often reported a necessity to navigate in the Health Care contraceptive services by themselves, without a supportive and predictable system to rely on. Some women expressed a need to struggle and find their own way to receive individualised counseling and support for postpartum contraception.

The insufficient structure of contraceptive services in the context of CS seemed to adversely affect women's use of effective contraception. They expressed suboptimal structures, for example, some women had received diverging information from different units of health care. Some women had been seeking information and advice about contraceptive methods from the internet, podcasts, and friends in lack of professional health care support (Q 3).

(Q 3) *"..(IUD placement during CS).. but then I asked, for me, is a hormonal-IUD the right choice to lower the risk for the myoma to come back? And she (midwife) said, I cannot answer that, you need to find that out yourself. And I felt that I had so many other things on my mind at that point, so I thought I'd rather wait."* (interview code 24)

6 DISCUSSION

6.1 Methodological considerations

6.1.1 Internal validity – systematic errors

Internal validity describes to what extent a study reflects a true and trustworthy causal relationship of what is observed, and that the cause-effect relationship cannot be explained by other factors. Systematic errors are non-random and occur because of flaws in design, conduct, analyses, and reporting, leading to underestimation or overestimation of the true intervention effect (bias). Internal validity may also be describe as to what extent a study is free from bias (113, 114).

6.1.1.1 Selection bias

In **study I** abortion was measured as a surrogate for unintended pregnancy. There is a risk that the surrogate variable missed unintended pregnancies, because women might have continued with a pregnancy even if the pregnancy was not intended. Furthermore, women might have had an unintended pregnancy but had a miscarriage or an extrauterine pregnancy, which we did not look for in the study. Finally, we might have missed some women with unintended pregnancy who had an abortion outside the catchment area. In summary, the measurement of abortion as a surrogate variable for unintended pregnancy probably led to an underestimation of the number of pregnancies that were unintended. We were aware of this dilemma but found no more precise way to measure this variable.

Data regarding choice of contraception use postpartum, breastfeeding at the time of postpartum visit and demographics, were extracted from the obstetric electronic medical record for every woman. The data had been manually registered by the midwife or doctor at Maternity Health Care into the medical record. Some data was missing for the 11,066 women, and we assumed that it was missing at random, but we cannot be completely sure of that. The missing data could theoretically have influenced the result. However, the cohort was very large and missing data sparse, and all results were based on observed outcomes without imputation of missing data. The 30 % of women who did not attend the postpartum visit, might have made an informed choice, and even initiated contraception, outside the postpartum visit at Maternity Health care. We have no possibility of finding that out but cannot exclude that some women might have had a prescription of contraceptives outside maternity care.

Data regarding subfertility was not known. In the light of primary outcome of abortion in relation to the choice of contraceptive choice, data of subfertility would have been of interest. There may have been a substantial number of women with infertility or subfertility among attendees at the postpartum visit, who did not make an active choice

about contraceptive method. This may explain the low rate of abortion in this group. A prospective trial design would have been a well-suited design to take subfertility into account but it would have been difficult to achieve the current sample size.

The actual use of contraceptive methods including the use of LARCs postpartum were the primary objective, but as this information was not available due to the study design, we used the registration of intended use or choice of contraceptive method noted in the postpartum medical chart. Sometimes initiation of LARC required an additional visit after the postpartum visit, and we cannot be sure that the women attended the additional visit to initiate LARC, despite the decision to use LARC postpartum. Data from the National Prescribed Drug Register could have provided additional information of dispensed contraceptives including IUDs at pharmacies in Sweden. Register data could have added valuable information, even if use of dispensed contraceptives still would have been unknown. Another methodology than a retrospective cohort study would have been needed to clarify the contraceptive methods that were initiated and used. A prospective trial would have been excellent to clarify contraceptive use during follow-up. However, even if use of contraceptives was unknown, the results clearly showed that the choice of contraceptive method had a significant impact on the risk of abortion, regardless of data on future use.

Study II and III were designed as randomised, controlled, prospective studies with randomization to placement of an intrauterine device within 48 hours after vaginal delivery (**study II**) or after medical abortion (**study III**) in the "early placement arm" of the studies. The control/standard- groups were intended to represent the placement of IUD under circumstances compatible to standard clinical practice.

The risk of unknown systematic differences between the baseline characteristics of the compared groups in **study II and III** seems reasonably low. In **study II** the number of women was small because of the premature stopping of inclusion, which per se gave small differences in potential background distribution of prognostic factors in the allocated groups a greater impact. However, the cohort of women was homogenous, and the demographic analysis did not show any differences between intervention- and control/standard group in **study II or III**.

In **study II and III** the randomization envelopes were prepared centrally and the randomisation process was thereby considered sufficiently concealed for the involved staff not to know allocation sequence and risk being influenced by knowing allocation to the treatment groups.

The results in RCTs may be influenced by adherence to assigned treatment of allocated groups. The overall risk of beneficial versus harmful effect of treatment influencing the adherence to allocated treatment is not applicable in **study II and III** because of a single intervention, i.e IUD placement, soon after allocation. Adherence to follow-up might be

influenced by the outcome, for example, participants experiencing IUD expulsion in study II might have less motivation to continue through follow-up. However, the rate of follow-up was very high in both **study II and III**.

Study IV was a qualitative study including 20 women who had to understand and speak Swedish and had to be > 18 years. Furthermore, demographics showed that women were >28 years old, had a high education, and were cohabitant or married. The exclusion criteria and the selection of women visualised by demographic characteristics, might have limited the understanding of the outcome for younger women at a lower educational level and with more challenging social conditions. Thus, there might be a selection bias and the experiences from socially vulnerable groups may not have been fully explored.

In **study IV,** theory-based random purpose sampling was used. A purposeful choice of a small sample of women relevant to the study, and the use of an inductive approach, were some techniques to enhance the validity (115) The sample size was considered as valid (112). A purposeful sampling also enhanced the transferability of the results (115).

6.1.1.2 Performance bias

Study II was prematurely stopped as expulsion rate exceeded 20 % within 28 days after placement for the early placement group. The medical staff performing the IUD placements were all experienced with IUD placement but not specifically with placement within 48 hours after vaginal delivery. There might have been a risk that the IUDs were not located correctly in the fundus of the uterus related to staff inexperienced with the method. Moreover, the multicenter setting of the study might have added impact to eventual performance bias.

6.1.1.3 Detection bias

Systematic differences between allocated groups in how outcomes are determined may result in detection bias. For women in **study I**, who gave birth early during the index year of 2013 or 2014, the time of follow-up was almost twice as long compared to the time of follow-up for women who gave birth at the end of 2013 or 2014. The length of follow-up thus differed between 12 to 24 months, which might have influenced the outcome. A subgroup analysis might have clarified any difference in the incidence of abortion related to length of follow-up. In **study III** we relied on self-reported expulsions and continuation.

6.1.1.4 Reporting bias

In **study I**, three centers reported data which probably lowered the risk for eventual reporting bias from one of the centers, for example if registration would differ between the birth centers. In **study II and III** the reporting of findings followed a specific

predetermined statistical analysis plan with high compliance of reporting according to this plan.

6.1.1.5 Response bias

In study **II and III** blinding was not feasible.

In both studies the women were asked to rate pain during the procedure of IUD placement using the Visual Analogic Scale (VAS). There might have been a risk that the women consciously or unconsciously tended to report lower pain scores because the same personnel who placed the IUD also asked for the pain score. Pain scores such as VAS, are preferably used for repeated measurement for the same participant, which is a strength in these trials. The women were asked to rate secondary outcomes such as satisfaction with the IUD method and with the allocated time of placement, bleeding patterns, perceived side-effects and eventual pain related to the IUD. These questions were repeatedly asked during follow-up. There might have been a risk that the women tended to answer more favorable due to the establishment of a relationship with the personnel involved over time, or due to any subconscious expectations to answer in a specific way. In **study III,** women were asked to answer questions by an electronic form to minimize this risk, but if the electronic form was not completed, the personnel called the women. Overall, there might have been a response bias that could have influenced the outcome in both studies.

In **study II** every IUD was placed according to allocation in both groups. In **study III**, a high grade of women received the allocated intervention in both groups. The number of women attending the placement visits were notably high and higher than expected under circumstances outside a study setting.

6.1.1.6 Researcher bias

In the qualitative **study IV**, the researcher subjectivity was the primary tool for reflexive thematic analysis (112). We designed a transparent and consistent setting using established qualitative interview techniques, document- and record analysis, and reflective processing in several steps according to the method. We defined the audit trail in the method of the study and presented quotes to illustrate the relation between the transcripts and the findings, to strengthen the trustworthiness (116). A qualitative study like **study IV** can contribute to thoughts and ideas and form a base and direction for further studies and research in the area, but it is generally difficult to draw any major conclusions from the outcome. The results from the study could inspire to a guideline of the concept antenatal contraceptive counselling in a Swedish setting, but more explorative research is needed. 6.1.2

6.1.2 External validity and generalizability

In **study I**, data was extracted from medical birth records of women who delivered during two years at three birth centers in Sweden. The study setting was advantageous because it included all women of the cohort, and was thus comparable to a register-based study setting. The setting made it necessary to exclude women without a personal identification number to compare medical birth records for the primary outcome variable for every included woman. The need to exclude new immigrants without a personal identification number, might have led to a study cohort not completely representative for women living in Sweden.

Study II and III were randomised controlled trials (RCT) where women had to be >18 years and understand and speak Swedish. There might have been a selection bias based upon several factors. First, exclusion of adolescents in both the RCTs unabled evaluation of effects of early IUD placement for the youngest women, who might have had the greatest benefit of long-acting reversible contraception because of common compliance difficulties with short acting contraception. In both **study II and III**, women might have been a cohort of highly educated, high performance persons with a structured lifestyle and a high social support, which is common in RCTs. Furthermore, women who signed-up for participation in the trials might have been a cohort of women highly motivated to use IUD which could affect acceptability and continued use. This kind of involuntary selection of study population is a common phenomenon in RCTs. The high attendance rate and high compliance in **study II and III** support this kind of selection of women. Furthermore, the Swedish regulations of study settings state that the IUDs must be at no cost for participants. Thus, the IUDs were free of charge, corresponding to a cost of approximately 100 Euro, which may have affected the attendance rate for placement and participation rate for women who could otherwise not have afforded a hormonal IUD.

An additional aspect regarding the high attendance rate and compliance in **study III**, was the comforting setting of personnel being in contact with the women and reminding non-attendants up to three times of the IUD placement. Moreover, the personnel were adjusting timepoints for IUD placements to be suitable for the women. All these aspects, may influence the external validity of the two RCTs.

Ultrasound confirmation of IUD position after placement was not part of the study protocol in study **II or III**. The method of IUD placement without needing an ultrasound control increases the generalisability of the method also to low-income parts of the world. Furthermore, vaginal ultrasound is mostly performed by gynecologist, and because midwives perform most of IUD placements in Sweden, not needing an ultrasound examination forms a base for a higher generalisability of the method.

6.2 The results in a clinical context

6.2.1. Risk of abortion within 1–2 years after childbirth in relation to contraceptive choice: a retrospective cohort study (**Study I**)

In Sweden, the health care system of postpartum contraceptive care has been the same for decades. Contraceptive counseling is generally not available during pregnancy and prescription and initiation of contraception is not a defined task for the staff at the delivery wards or maternity wards. Instead, communication about contraception is an assignment for the midwife or doctor at Maternity Health Care. Considering that up to 30 percent of women do not attend the follow-up visit, as shown in **study I**, there is reason to believe that there is an unmet need of contraception postpartum also in Sweden.

In **study I** women who had a registered choice to use IUD as postpartum contraception had the lowest risk of abortion(s), which is in accordance with earlier findings (65, 117). A decision to use IUD as postpartum contraception ahead of the postpartum visit would reasonably optimise the chance of IUD placement at that visit. When the hormonal IUD is prescribed at the postpartum visit one more visit is often needed for placement of the device. Studies of postabortion care have shown that the need of additional visits lowers the chance of attendance, and thus initiation of contraception (54). In the absence of standards or routines in Sweden for immediate IUD placement after delivery, reducing the need from two to one postpartum should be considered as minimum requirement to comply with highest level of evidence.

Unintended pregnancy is associated with lower socio-economic status, stress, and less social support (118). Women with the highest need of effective contraception after delivery might be at high risk of not attending additional visits and thus miss the opportunity to initiate contraception. Until the health care system is reorganised to provide efficient contraception for postpartum women who wish to use contraception, the availability of the postpartum care can be modified to match modern needs. One improvement could be the possibility to attend the postpartum visit while having the partner still at home. In Sweden, the father has the benefit of staying at home 10 days with economical compensation by the Swedish Social Insurance Agency within the first weeks of parenthood. If follow-up at Maternity Health Care could be provided within these 10 days, or in evenings, a higher number of women would probably attend the follow-up visit postpartum. Another improvement would be postpartum contraceptive counseling at the delivery ward before discharge from hospital.

In **study I,** attendance to the follow-up visit about 8 weeks postpartum was a prerequisite for initiation of LARC. The positive association between attendance to the postpartum visit and the use of LARC has previously been shown (119) but we must ask ourselves if waiting to address contraception to the postpartum visit is what modern

women expect and need. In the light of resumption of fertility and sexual activity already a few weeks postpartum, the ideal situation for women who wish to use contraception might instead be the chance to initiate immediate postpartum contraception. A health care system that includes contraceptive counseling in good time ahead of delivery is a prerequisite for deciding and initiate immediate use of contraception postpartum.

Studies have shown that antenatal counseling for postpartum use of contraception is feasible and acceptable to women in modern medical settings (79, 120). Easily available and individually adapted antenatal contraceptive counseling is therefore preferrable for everyone interested in using postpartum contraception. Antenatal counseling is also a prerequisite for placement of an intrauterine device during an elective caesarian section or immediately after vaginal delivery. In the light of equal and fair medical care in Sweden and in an international perspective, a new medical era of immediate postpartum LARC provision also influences Sweden. During the latest years, international guidelines and best practice bulletins have been revised (7, 87), making it necessary and fare to reorganize systems for modern care and standards for the Maternity Health Care organization and birth clinics in Sweden. We need to take responsibility to initiate a plan for provision of immediate and early LARC placement after delivery, also in Sweden.

6.2.2. Effectiveness, safety and overall satisfaction of early postpartum placement of hormonal IUD compared with standard procedure: An open-label, randomised, multicenter study (**Study II**)

The expulsion rates in **Study II** were high. High expulsion rates of almost every second device for immediate and early placed IUDs after vaginal delivery have been shown in comparable trials, but with great variations between studies (88). In our study, the one-year period of follow-up was comparatively long. In accordance with an RCT by Marangoni et al (121), most expulsions occurred within the first weeks of placement, but a few expulsions occurred after three months and up to one-year after placement. To be able to adequately compare expulsion rates, the study settings must be somewhat comparable regarding for example rate- and time of follow-up. The reported rate of expulsions after immediate and early placement after vaginal delivery differ widely and the non-comparable time periods of follow-up might be one part of the explanation (81).

The dilemma of postpartum IUD expulsion has shifted interest to focus on continuation of the IUD-method per se. Re-insertion of IUD on request is reasonable to provide. In our study, use of the IUD method one year after the index placement reached 71 % in the early placement group mainly due to requested replacement of devices. Our results is similar to the finding of Marangoni et al, who found a 73% 1-year cumulative continuation rate after post-placental IUD placement of hormonal IUD (121). Another recent study found similar continuation rates of up to 80 % one year after the index placement despite expulsion of the primary device. It that setting, Cooper et al provided

replacement of an expelled IUD as part of the protocol (122), which was not provided in **study II.** In the light of high expulsion rates, settings where replacement of expelled IUDs is available, patient populations with low rates of attendance to postpartum visits, are most likely to benefit from provision of post-placental IUD placement (123).

Participants in **study II** reported significantly fewer bleeding days postpartum after having received early placement of the hormonal IUD, compared to having received the device 6-8 weeks after delivery. The effect of hormonal-IUD on the bleeding period postpartum might have affected satisfaction with the method, thus making this important. Similar findings of a shorter bleeding period have been reported also after early placed hormonal IUD after induced abortion (54), and may therefore be a consistent finding after pregnancy in general.

Study II showed no safety concerns or risks with early IUD placement beside the high expulsion rate. Several studies have reported advantages with early IUD placement, and based on the superior convenience, the method is recommended when routine follow-up and IUD replacement can be provided (7, 81, 82). The price of IUDs differs between countries, also in Europe. In Sweden, the cost of a hormonal IUD is approximately 100 Euro and is paid by the patient. There is no insurance covering the costs in the event of an expulsion. In the light of high expulsion rates for immediately and early placed IUDs after vaginal birth, the question arises whether the method is justified to be advocated after vaginal birth in our current Swedish Health Care system. On the other hand, there may be circumstances when early placement in the best choice. In settings with low rates of attendance for interval postpartum intrauterine contraception insertion, PPIUCD could be a useful intervention to prevent unintended and closely spaced pregnancies. Follow up to detect expulsion after PPIUCD and provision of IUD replacement or prescription of other contraceptives must be available. Finally, the dilemma highlights the need of keeping several options available and to specifically individualise postpartum contraceptive care. Implementation of subsidised or free contraception throughout the reproductive years could increase the proportion of women choosing to have an IUD placed postpartum despite high expulsion rates.

6.2.3. Placement of an intrauterine device within 48 hours after early medical abortion—a randomised controlled trial (**Study III**)

There was a high attendance rate for the placement visit not only in the intervention group but also in the control group. Similar findings have been seen in corresponding abortion studies in high-resource settings (54, 124). In contrast, retrospective data on post abortion follow-up attendance behaviour has showed an attendance rate of 57 % (64) which is more in line with expectations and experiences in Sweden. No difference was found regarding expulsion rates between the groups in our study. Expulsion rates in

the intervention group were slightly lower compared with earlier studies (124), whereas results in the control group corresponded well to earlier findings (54, 125, 126).

The pain scores at IUD placement were significant lower in the intervention group. This finding, as well as the convenience of immediate placement, may explain why women in the intervention group significantly more often preferred the allocated time for IUD placement. Ultrasound was used in 40 % of IUD placements in the intervention group, without finding retained gestational products. Based on this result, there is no support for mandatory ultrasound and thus easier to implement the method on a broad basis. The overall interpretation of the outcomes is that the procedure of early IUD placement after complete induced medical abortion can be implemented. The attendance rate for placement within 48 hours in clinical practice remains to be evaluated.

6.2.4 Women's experiences of contraceptive counseling and provision services when elective caesarean section is the method of birth- a qualitative study (**Study IV**)

Women in **study IV** did not see contraceptive counseling as an integrated part of the antenatal care. Most women expressed that they had not communicated or reflected upon contraceptive methods during pregnancy. Furthermore, most women had not been involved enough to decide about IUD placement during CS. Contraceptive care was insufficient according to several women who requested an informative counseling to take place during the second half of pregnancy.

Findings in **study IV**, are supported by earlier studies (79, 120) that found antenatal contraceptive counseling feasible and acceptable in modern settings. Integrated contraceptive counseling into the Swedish antenatal program would improve the quality of contraceptive care for women interested in using postpartum contraception. Furthermore, antenatal communication of IUD placement during CS, is a prerequisite to facilitate the method for women who wish to use an IUD postpartum. The insufficient contraceptive service program leads to a risk for unequal medical care. An integration of antenatal contraceptive counseling as part of the Maternal Health Care program in Sweden, would be an improvement for equal and modern contraceptive services, also for women not attending the postpartum visit. Studies on improving antenatal contraception counseling service in Sweden are ongoing. The results of these studies can contribute to updated guidelines that are much needed.

7 CONCLUSIONS

The conclusions of the studies included in the thesis are

- The choice of using a long-acting reversible method postpartum was associated with a reduced risk of induced abortion compared with the choice of other contraceptive methods or no method of all, over a period of 24 months postpartum.
- Exclusive breastfeeding at the time of the postpartum visit significantly decreased the risk of abortion whereas smoking, being younger than 25 years and having had a previous abortion significantly increased the risk of abortion within 24 months postpartum.
- Due to high expulsion rates after early IUD placement after vaginal delivery and stopping of inclusion in our trial, we did not have enough power to conclude if there is possible relation to risk of abortion within 1 year after delivery.
- Placement of a hormonal IUD (Mirena ®) within 48 hours of vaginal delivery is convenient, safe, with high patient acceptability, but associated with high expulsion rates compared to standard placement 6-12 weeks postpartum.
- Placement of an IUD within 48 hours after medical abortion ≤ 63 days' gestation did not lead to higher user rates 6 months after abortion compared with IUD placement at 2 to 4 weeks after abortion when the IUD is provided free of charge.
- Placement within 48 hours after abortion was convenient, safe, preferred by women, associated with lower pain scores, and could be performed without ultrasound examination.
- Antenatal contraceptive counseling was rare but considered relevant and meaningful by the interviewed women. To be informed and involved in planning of the contraceptive method to use postpartum was important.

8 POINTS OF PERSPECTIVE

The concept of "when and how" to communicate about contraception before and after pregnancy is central to provide a high quality contraceptive care that meets the individual needs of women, and in a wider perspective, society of today. Antenatal communication and decision about contraception may be seen as a prerequisite for women to decide about immediately placed IUDs after vaginal delivery and IUD placement during CS. Evidence supports that women find antenatal counseling helpful (79), and in **study IV**, women were generally positive and receptive to antenatal counseling from about 25 gestational weeks, including discussing IUD placement during caesarean section. Evidence of how to communicate about contraception before, during and after pregnancy, is sparse. Effective counseling strategies for informed decision-making on contraception have been investigated but not specifically associated to pregnancy. A study from Sweden supports structured contraceptive counseling including an educational video, information about effectiveness for methods in typical use, a demonstration box with contraceptive models and some key questions to support informed decision-making (127). Corresponding exploring research focusing on counseling for contraception before, during and after pregnancy is needed. Patient autonomy must be respected at every moment of counseling for choice of contraceptive method, including the choice to not use contraception, or to use a less effective method. Choice of method should be made by the women herself and based on adequate information about methods and the consequences for the woman in case of unplanned pregnancy. Every woman´s personal beliefs, preferences, culture, and ability to afford and use the chosen method must be respected. No woman should feel forced to choose LARC, and the counseling needs to include a range of methods and be careful not to restrict the options (128, 129). In Sweden, we have easy access to contraception and to abortion care. In countries with harder restrictions of abortion, the perception of coercion by avoiding unwanted pregnancy by LARC or other contraceptives might be less pronounced although reproductive freedom is in fact limited in such countries.

Evidence supports safety and user satisfaction of PPIUCD after vaginal delivery, but high expulsion rates complicate the use of the method. Acceptability and consequences for the woman of IUD expulsion differ depending on her societal-, economical-, and cultural context. In low-resource/poverty settings, PPIUCD might be a better option than no IUD placement at all in settings where the women might not be able to access placement after leaving the hospital. In high-resource countries where IUDs are subsidized and at low- or no cost for the patient, the high risk of expulsion might still be acceptable. In Sweden the hormonal IUD cost approximately 100 Euro for the woman, which for many people is costly, especially if the IUD is expelled soon after placement. If the cost of IUDs were covered by an insurance system, including free IUD replacements, then expulsion

would be inconvenient for the woman, but still affordable. In our study on post abortion placement we could not show a difference in expulsion between early or standard placement of IUD. However, women in our study were in early pregnancy at the time of abortion. We are continuing to investigate early placement at higher gestational ages. Results may be different with a larger uterus and more dilated cervix. International studies support cost-effectiveness of PPIUCD (130) but further investigations are needed to explore the cost effectiveness in a Swedish service setting and also in an abortion setting. The current standard of contraceptive services during pregnancy in Sweden and many other countries, is not yet adapted to individualized counseling and not prepared to facilitate PPIUCD nor placement of IUD post abortion. Further research is needed to explore the challenges and solutions of contraceptive counseling before, during and after pregnancy and childbirth in order to prepare and facilitate informed choice of contraception and provision of early/immediate LARC after abortion and childbirth to meet individual needs of women.

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