Study protocol

Innehåll

Short title: Immediate insertion of intrauterine contraception after medical abortion

EudraCT: 2018-000287-29

Version no: 20180403 version III

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Signature page

Agreement

I have read the protocol and agree to conduct the study according to the protocol, regulations and good clinical practice (GCP).

I will inform the staff involved in the study and ensure that they have the knowledge and competence necessary to carry out the study.

Title **Immediate versus delayed insertion of intrauterine contraception at the time of medical abortion- An open-label, randomized, multicenter study**

Protocol ID nr: **20180403 version III**

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Synopsis

EudraCT:

Title: **Immediate versus delayed insertion of intrauterine contraception at the time of medical abortion- An open-label, randomized, multicenter study**

Aim	To study use, safety and patient acceptability of intrauterine contraception after immediate insertion compared with standard insertion 2-4 weeks post medical abortion at 3, 6 and 12 months post abortion.
Drug:	Mirena® (LNG-IUS 52mg), Kyleena® (LNG-IUS 19.5mg), Jaydess® (LNG-IUS 13.5 mg), NovaT® (Cu-IUD, medical device, but due to use outside indication it is included in this application)
Design:	Open label, randomized, controlled, multicenter study. Phase III (therapeutic confirming).
Primary objective:	To study if immediate insertion of intrauterine contraception is superior to insertion at 2-4 weeks post abortion with regard to number of women using IUC as contraception at 6 months post abortion.
Variable:	The proportion of women in each group (immediate or delayed) using IUC as contraception at 6 months post abortion (use vs non-use).
Secondary objectives:	To study if immediate insertion of intrauterine contraception is non-inferior to delayed insertion with regard to safety and acceptability.

Variables:

Efficacy, acceptability:

- Use of IUC at 3, 6 and 12 months post insertion evaluated by telephone or e-mail follow-up (continued use/voluntary discontinued use, involuntary discontinued use including expulsions etc) reasons for discontinuation will be recorded and subsequent use of other contraceptive methods will be noted)
- Difference in the proportion of women who successfully have the IUC inserted (success versus failure),
- Ease of insertion according to health care provider (judged as very easy, easy, moderately, or very difficult)
- pain at time of insertion (women will indicate the pain before insertion, at placement of tenaculum, sound and IUC by putting a vertical mark on a 10 cm long horizontal line with a Visual Analogue Scale (VAS) from 0, indicating no pain to 10 indicating worst imaginable pain. Result will be noted in millimeters and entered into case report forms).
- Post-abortion bleeding (number of days of fresh bleeding and spotting after the abortion)
- Reasons for non-attempted insertion of IUC (change of mind, heavy bleeding, not coming for insertion, staff being unavailable etc),
- Pregnancies occurring during the 6 and 12 month follow-up (planned and unplanned, wanted and unwanted, pregnancy outcomes- ectopic, miscarriage, abortion, molar, kept pregnancy),
- Acceptability of immediate and delayed insertion of IUC by asking women if they would recommend the procedure to a friend (yes/no, asked at the time of insertion and at the 3 and 6 month follow up),
- Acceptability of IUC as post abortion contraception- evaluated as above,

Safety:

- Expulsion rate during 12 months following insertion in both groups evaluated by telephone follow up at 3, 6 and 12 months post abortion (complete, partial or no expulsion. The exact day of expulsion will be noted to determine the risk of expulsion as a function of time post insertion),
- Complications (adverse events (AE) and serious AE) bleeding requiring any treatment, uterine perforations and cervical tears, infection requiring treatment with antibiotics, hospitalization for any reason, surgical procedures due to heavy bleeding, incomplete abortions, prolonged bleeding or patient request,
- The proportion of surgical procedures in total and for each study site (type of procedure, reasons therefore- infection, retained products of conception, prolonged bleeding etc).

PICO:

Population:
Women with unwanted pregnancy having a medical abortion and fulfilling inclusion and without exclusion criteria and opting for IUC as post abortion contraception. The medical abortion will be carried out according to the Swedish national evidence based guidelines.

Intervention:
Randomized to insertion of IUC within 48 hours after medical abortion.

Control:
Randomized to insertion of IUC at the time of a follow-up visit scheduled 2 to 4 weeks after the abortion according to routine care.

Objectives:
Evaluation of use of IUC, feasibility, safety, compliance, and acceptability of immediate insertion of IUC 0 to 48 hours after medical abortion compared with delayed IUC insertion at 2 to 4 weeks post abortion. The primary outcome measure will be the use of IUC at 6 months in both groups evaluated by telephone calls/emails follow up.

Time plan: Planning: -March 2018

Study start: May 2018

End of recruitment: April 2020

Last patient Last visit April 2021

Analysis: 2022

Report of primary outcome and Safety: 2021

Abbreviations

LARC	Long Acting Reversible contraception
IUC	Intrauterine contraception
Cu-IUD	Copper Intra Uterine Device
LNG-IUS	Levonorgestrel Intra Uterine System (levonorgestrel releasing IUC)
LMV/MPA	Läkemedelsverket/Medical Products Agency
RERB	regional Ethical Review Board

1 Protocol Summary

The overall aim of this study is to increase use of intrauterine contraception (IUC) after medical abortion as IUC post abortion lowers rates of abortions and repeat abortions.(1-4) Our hypothesis is that immediate insertion of IUC after medical abortion results in higher use of IUC at six months post abortion compared to the current routine of delayed IUC insertion at 2-4 weeks post abortion.

Today 90 percent of terminations of pregnancy are medical abortions. Approximately 33 000 medical abortions are performed in Sweden each year and 20-30 percent of these women opt for IUC as post abortion contraception. Thus, the results of this study potentially affect at least 6600-9900 women every year in Sweden alone. A disadvantage with medical abortion compared with surgical abortion is the standard practice of delayed insertion of IUC. It has been shown that 42 percent of women scheduled for delayed insertion after surgical abortion did not return for the follow up and IUC insertion.(5) This problem is common also in medical abortion practice. Immediate insertion could lead to insertion rates close to 100 percent. However, this practice has not been studied for medical abortion.

The background for this trial is the belief that a higher rate of insertion of IUC, perhaps close to 100 percent, within 48 hours after medical abortion, can compensate more than well for a potentially higher rate of expulsion at immediate insertion. A clinically significant difference in IUC use at six months following the medical abortion of at least 20 percent is expected.

This large multicenter, randomized, patient centered clinical trial will investigate the effectiveness, feasibility, continued use, safety and acceptability of immediate insertion of intrauterine contraception within 0-48 hours after a completed medical abortion when compared to delayed IUC insertion at 2-4 weeks post abortion which is current practice.

2 Scientific background

Sweden has the highest abortion rate in Western Europe. In Sweden approximately 33 000 medical abortions are performed every year (www.sos.se) and 40 percent of all abortions are repeat abortions. Approximately 20-30 percent of women opt for intrauterine contraception

(IUC) post abortion. Results from several large retrospective and prospective studies from Finland, Scotland, USA and New Zealand show that use of long acting reversible contraceptive methods (LARC) such as implants and IUC lower the rate of abortions and repeat abortions.(1-4) IUC has the highest rate of user satisfaction and compliance among all contraceptive methods(3) and thus increased use benefits women as well as society.

Ovulation may return within one week of an abortion regardless whether it is medical or surgical. Therefore, immediate post abortion initiation of contraception is encouraged. In surgical abortion IUC is placed at the time of the surgery. Expulsion of an IUC inserted immediately following surgical abortion is rare (<6%).(6) There is no clear difference in the risk of expulsion, bleeding pattern, risk of infection or pain if the IUC is inserted at the time of the surgical abortion or if insertion is performed after 3 to 4 weeks. (5-7)

A disadvantage with medical abortion compared with surgical abortion is the delayed insertion of IUC, which is done at the follow up visit 2-4 weeks after the abortion treatment. It has been shown that 42 percent of women scheduled for delayed insertion after surgical abortion did not return for the follow up and IUC insertion. Among those who did return for a delayed IUC insertion a large proportion had already been exposed to risk of pregnancy. Studies show that a significantly higher proportion of women come for insertion of IUC post medical abortion if the insertion is performed at one week post abortion compared to insertion at the follow up visit scheduled at 2-4 weeks.(8) Provision of implants at the time of the medical abortion results in higher rate of use at 6 months following the treatment and a significantly lower risk of a subsequent unplanned pregnancy and abortion compared with insertion at 2 to 4 weeks post abortion.(9)

Post partum is also a sensitive period for unplanned and unwanted pregnancy. Insertion of IUC immediately after placental expulsion in childbirth results in lower rates of expulsion compared to insertion after 48 hours. Expulsion at immediate insertion post partum has been estimated at 15 percent.(10) The expulsion rate of IUC at delayed insertion has been shown to be 5 percent.(6) The approach of immediate IUC insertion post medical abortion has not been explored. There have been concerns that immediate post medical abortion IUC insertion may increase IUC expulsions due to bleeding and contractions or increase the risk of infection.

Our previous studies on the development of medical abortion, reduction of the number of visits for abortion and increased access to safe abortion through simplified medical abortion have had great impact on implementation and guidelines in Sweden and worldwide (11-13). However, there is an urgent need to update guidelines on post medical abortion IUC insertion where evidence based recommendations are lacking(14).

The rationale for this study is the hypothesis that a greater proportion of women undergoing medical abortion – close to 100 percent - will receive their intended post abortion IUC if it is inserted within 0-48 hours of the expulsion of the placenta compared with routine insertion at a scheduled follow up visit 2-4 weeks later. This could more than well compensate for a possible slightly higher rate of IUC expulsion and will reflect in a higher usage rate at 6 months following the abortion. If shown to be successful immediate IUC insertion will help women avoid subsequent unplanned and unwanted pregnancy following the abortion.

3 Risk-benefit and ethical considerations

3.1 Early insertion of IUC

Risk: The LNG-IUS 52mg is recommended for immediate insertion only after a surgical abortion in the first trimester according to the manufacturer Bayer. However, the LNG-IUS 19.5mg and 13.5mg are recommended for insertion immediately after any first trimester abortion- the abortion method is not specified. There is no mention of any recommendation for insertion after abortion in the second trimester. The manufacturers recommendation for insertion post partum of all LNG-IUS is after the uterus has reached normal size- earliest at 6 weeks post partum. The recommendation is likely based on the assumption that the uterus might be more sensitive to device perforation, infection or device expulsion immediately after an abortion. However, this is not the case according to current evidence base.

For the copper-IUD the manufacturer recommends insertion “after a first trimester abortion”. The exact timing is not specified nor is the method for abortion. The WHO recommendation are based on research on surgical abortion. There are no studies on insertion of IUC within 48 hours of medical abortion.

The risk with immediate insertion is foremost early expulsion due to contractions in the uterus following the abortion and an open cervix. Expulsions have been shown to be more common after immediate insertion following normal delivery (15) and after immediate insertion in surgical abortion(6).

The has been concern that there may be an increased risk of perforation of the intrauterine device at immediate insertion. However, no such risks have been shown within immediate post partum insertion (15) or immediate post surgical abortion insertion (6). The uterus may quite contrary be thicker and less susceptible to perforation. If the women experiences abnormal pain at insertion a confirmatory ultrasound will be performed according to clinical practice.

There has also been concern that women may be at increased risk for infection due to residual material and decidua being left in the uterus. This has not been found after immediate post partum insertion where there may be considerable more blood and decidua in the uterus ppst delivery compared to post abortion(15).

Benefit: LNG-IUS is an established method with a well-known pharmacological profile including side effects also when used post abortion. Intrauterine contraception (IUC) is the contraceptive method with the highest user satisfaction in all age groups (29). LNG-IUS is one of the most effective contraceptive methods (30). Early insertion might reduce the risk of unintended pregnancy post-abortion due of immediate uptake of IUC. Women may also have one less visit to the hospital if the abortion is performed in the hospital and women have the IUC inserted before they leave the premises. It may also decrease the menstrual blood flow and ease menstrual pain in case of LNG-IUS being inserted (31,32). Immediate uptake of LNG-IUS may decrease the amount of bleeding post abortion(8). Insertion within 48 hours post abortion could be less painful because of the dilated cervix.

There is ample evidence on the use of copper IUDs within 48 hours of childbirth which may be considered more similar to a second trimester abortion. Thus, risks and benefits have more studies for copper IUDs. Risk have been considered very small and the benefits of immediate insertion outweigh the risks in the post partum period. We therefore believe that benefits will outweigh risks also for second trimester abortion.

INTRAUTERINE DEVICES (IUDs)

IUDs do not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe, but are not used as widely by national programmes as male condoms.

CONDITION	CATEGORY I = initiation, C = continuation		CLARIFICATIONS/EVIDENCE
	Cu-IUD	LNG-IUD	
† recommendations reviewed for the MEC 5th edition, further details after this table * additional comments after this table	Cu-IUD = copper-bearing IUD LNG-IUD = levonorgestrel-releasing IUD (20 µg/24 hours)		
POST-ABORTION*			
a) First trimester	1	1	**Clarification:** IUDs can be inserted immediately after first-trimester, spontaneous or induced abortion. **Evidence:** There was no difference in risk of complications for immediate vs delayed insertion of an IUD after abortion. Expulsion was greater when an IUD was inserted following a second-trimester abortion vs a first-trimester abortion. There were no differences in safety or expulsions for post-abortion insertion of an LNG-IUD compared with a Cu-IUD *(36–48)*.
b) Second trimester	2	2	

IUDs

Table 1. WHO Medical Eligibility Criteria for contraceptive use 2015 Recommended timing of insertion of a LNG-IUS and Cu-IUD

3.2 Delayed insertion of IUC

Risk: There is a risk for unintended pregnancy possibly followed by an abortion due to a period of several weeks post-abortion without contraception. Women need an additional visit for insertion of an IUC. This need of another appointment to a midwife or doctor might lead to women not attending and as a consequence missing the opportunity to start up with IUC.
Benefit: The uterus might be less susceptible to device perforation compared with immediate insertion in the time span 48 hours-2 weeks post abortion but most likely not to insertion within 48 hours post-abortion. The risk of device expulsion may or may not be increased compared to immediate insertion.

3.3 Ethical considerations

There is strong evidence that an unintended pregnancy is a potential risk for poor fetal outcome, poor quality relationship between the mother and the child, and adverse effects on mental health (16, 17). A repeat abortion may entail small health risks.

If the results of the study can show that early insertion is superior to standard procedure

concerning use, patient satisfaction and safety, we will have a possibility to offer a highly effective long acting contraceptive method immediately after medical abortion and thereby avoid the risk of unintended pregnancy because of non-attendance for the delayed insertion.

The women will be informed regarding the study at the first visit to the family planning unit. Women can easily decline participation. The free choice to enter and also drop out of the study without having to motivate the decision will be stressed. All women will receive contraceptive counseling and information irrespective of participation in the study or not.

It is important that the individual woman does not feel forced to enter the study. If she chooses another, less effective method she will be offered counselling according to her wishes outside the study. Also, if she is not prepared to make any decision regarding further use of contraceptives this will be respected.

The women will be assured that we do not know the difference in outcome of the study in advance, so that they do not get disappointed when allotted to delayed insertion. Furthermore, it is important not to increase fear of pain related to the insertion, which may make women refrain from showing up at delayed insertion. The hypothesis that immediate insertion is less painful than delayed insertion must not turn to the belief that delayed insertion is more painful than ordinary insertion of an intrauterine device at any other time. It is therefore important that this is correctly described in the information to study subjects.

The main outcome of use of IUC at 6 months post abortion is a surrogate for unintended pregnancy. As IUC is such a highly effective method compared to other methods it is assumed that a higher use of IUC will lead to fewer unintended pregnancies compared to all other methods except sterilization and the implant. This will be stressed at the follow ups but also by scrutinizing the patient records. The participating subjects will be informed both orally and in written before they give informed consent. Abortion could be a very personal question and there might be a risk that the woman can feel that her integrity is affected. The subjects will however be informed before the study starts and before they give their consent. Moreover, all data will be coded and at the time of analysis there will be no possibility to link the information to a specific woman.

4 Aim

This large multicenter, randomized, patient centered clinical trial will investigate the use, safety and acceptability of immediate insertion of intrauterine contraception within 0-48 hours after a completed medical abortion when compared to delayed IUC insertion at 2-4 weeks post abortion which is current practice.

4.1 Primary objective

The primary outcome measure will be the use of intrauterine contraception at 6 months post abortion in both groups evaluated through follow up by telephone/email.

4.2 Variable

The proportion of women using IUC as contraception at 6 months post abortion (use vs non-use).

4.3 Secondary objectives

The secondary objectives are to study if immediate insertion of IUC postpartum is non-inferior to golden standard (insertion 2-4 weeks postpartum) with regard to efficacy, safety and acceptability.

4.4 Variables

4.4.1 Efficacy, acceptability:

- Difference in the proportion of women who successfully have the IUC inserted (success versus failure),
- Continued use of IUC at 3 and 12 months post insertion evaluated by telephone/email follow-up (continued use/voluntary discontinued use, involuntary discontinued use including expulsions etc) reasons for discontinuation will be recorded and subsequent use of other contraceptive methods will be noted)
- Ease of insertion according to health care provider (judged as very easy, easy, moderately, or very difficult)
- pain at time of insertion (women will indicate the pain before insertion, at placement of tenaculum, sound and IUC by putting a vertical mark on a 10 cm long horizontal line with

a Visual Analogue Scale (VAS) from 0, indicating no pain to 10 indicating worst imaginable pain. Result will be noted in millimeters and entered into case report forms).

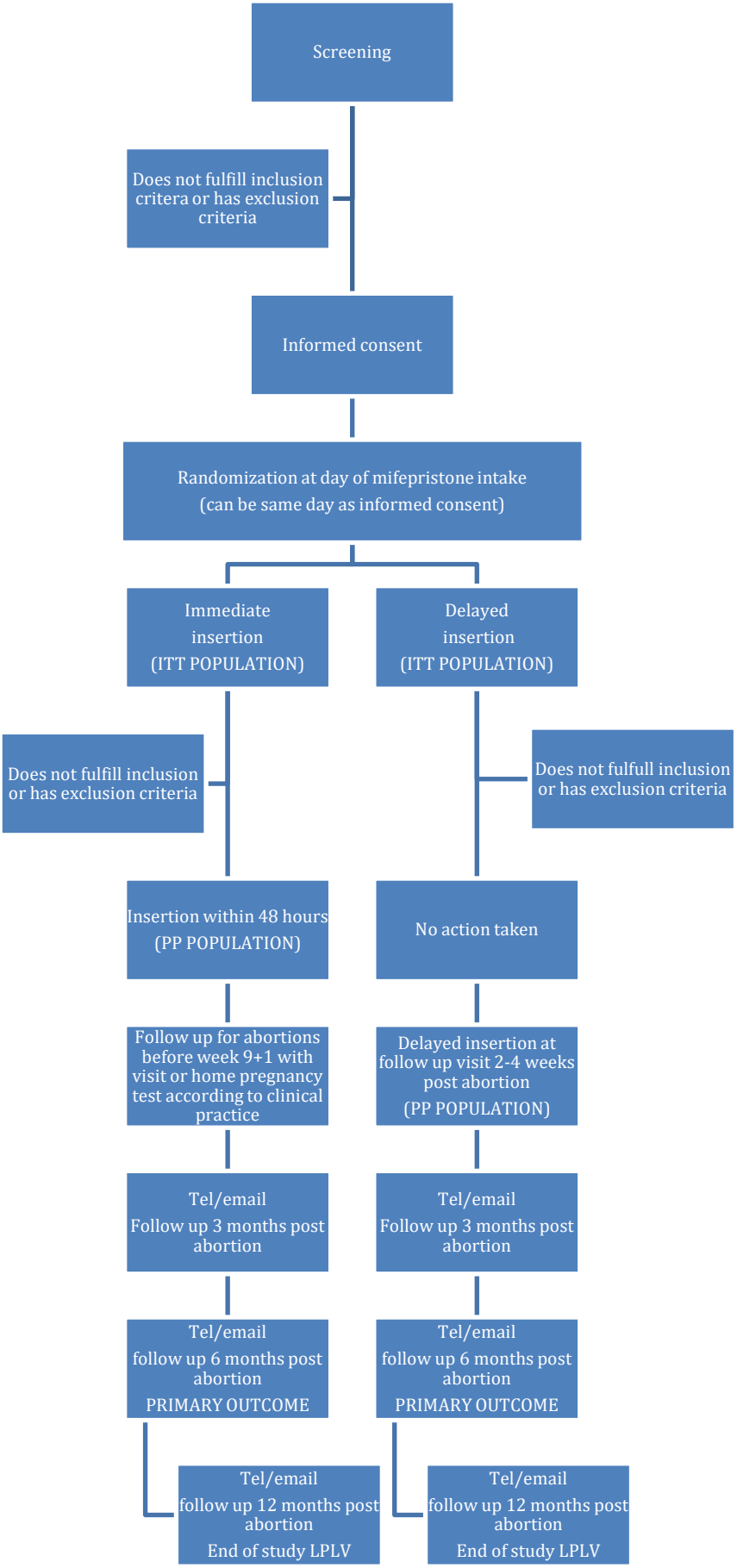
- Post-abortion bleeding (number of days of fresh bleeding and spotting after the abortion)
- Reasons for non-attempted insertion of IUC (change of mind, heavy bleeding, not coming for insertion, staff being unavailable etc),
- Pregnancies occurring during the 12 month follow-up (planned and unplanned, wanted and unwanted, pregnancy outcomes- ectopic, miscarriage, abortion, molar, kept pregnancy),
- Acceptability of immediate and delayed insertion of IUC by asking women if they would recommend the procedure to a friend (yes/no, asked at the time of insertion and at the 3, 6 and 12 month follow up),
- Acceptability of IUC as post abortion contraception- evaluated as above,

4.4.2 Safety:

- Expulsion rate during 12 months following insertion in both groups evaluated by telephone follow up at 3, 6 and 12 months post abortion (complete, partial or no expulsion. The exact day of expulsion will be noted to determine the risk of expulsion as a function of time post insertion),
- Complications (adverse events (AE) and serious AE) bleeding requiring any treatment, uterine perforations and cervical tears, infection requiring treatment with antibiotics, hospitalization for any reason, surgical procedures due to heavy bleeding, incomplete abortions, prolonged bleeding or patient request,
- The proportion of surgical procedures in total and for each study site (type of procedure, reasons therefore- infection, retained products of conception, prolonged bleeding etc).

5 Design

The study protocol is designed as a superiority trial according to the recommendations in the CONSORT statement for randomized superiority trials (www.consort-statement.org). It is defined as a Phase III trial (therapeutic confirming).
The flow of patients is presented in this flowchart.


Screening
Does not fulfill inclusion critera or has exclusion criteria
Informed consent
Randomization at day of mifepristone intake
(can be same day as informed consent)
Immediate insertion
(ITT POPULATION)
Delayed insertion
(ITT POPULATION)
Does not fulfill inclusion or has exclusion criteria
Does not fulfull inclusion or has exclusion criteria
Insertion within 48 hours
(PP POPULATION)
No action taken
Follow up for abortions before week 9+1 with visit or home pregnancy test according to clinical practice
Delayed insertion at follow up visit 2-4 weeks post abortion
(PP POPULATION)
Tel/email
Follow up 3 months post abortion
Tel/email
Follow up 3 months post abortion
Tel/email
follow up 6 months post abortion
PRIMARY OUTCOME
Tel/email
follow up 6 months post abortion
PRIMARY OUTCOME
Tel/email
follow up 12 months post abortion
End of study LPLV
Tel/email
follow up 12 months post abortion
End of study LPLV

Research questions:

- Does immediate post placental insertion of IUC result in higher use of IUC at 6 months post medical abortion compared to delayed insertion at 2-4 weeks post abortion?
- Can immediate insertion be performed with maintained safety and acceptability of IUC insertion?
- Which factors determine use of IUC after medical abortion?

This multicenter trial will investigate IUC use, safety and acceptability of immediate insertion of IUC within 0-48 hours after a completed medical abortion compared with delayed (routine) insertion at 2-4 weeks post abortion, which is current practice in women having medical abortion at a pregnancy length up to and including 21+6 days (as this is the current practice for judging healthy fetuses as viable outside the uterus) and opting for IUC for post abortion contraception. We will stratify the women in three gestational age categories (≤9 weeks+0 days, 9weeks +1 day ≤12 weeks+0 days, and >12 weeks) to make study data more internationally applicable as medical abortion in some countries is only used for early (<9 weeks gestation) or second trimester abortions.

Sample size and calculated power

Justification of power calculation

A total of 720 women will be recruited. In order to be able to show a difference of 80 percent in IUC usage in the immediate insertion group at 6 months post insertion compared to 60 percent use in the delayed group with a power of 90 percent and an alpha of 0.05 we would need to randomize 109 women in each group.

If close to 100 percent of women receive the IUC in the immediate group and there is an expulsion rate of maximum 15 percent (immediate post placental insertion after delivery has expulsion rates of 15 percent) and some women have the IUC removed a use of approximately 80 percent could be expected in the immediate group. In the delayed group fewer women are estimated to come for insertion and the expulsion rate is estimated at 5 percent.

We will stratify women in three gestational age categories (≤9 weeks+0 days, 9weeks +1 day ≤12 weeks+0 days, and >12 weeks) to make study data more internationally applicable. We will compensate for surgical procedures due to incomplete abortions and prolonged bleeding which is estimated to be needed in approximately 3-5 percent (13). We will also compensate for a 15 percent loss to follow up which is commonly seen in studies in abortion. Thus, we will randomize 240 women in each gestational strata (total 720 women). Analysis will be presented as intention to treat for all randomized women as well as per protocol for women completing the 6 month follow up (see analysis plan). Follow up at 3, 6 and 12 months will be performed by telephone/email. In women who do not attend FU electronic patient records will be searched for main and secondary outcomes (safety, pregnancy, abortion).

Women will be recruited at several sites in Sweden. Recruitment (numbers) is not expected to be equal at each site but this will be considered in the statistical analysis.

Statistical advice from statistician Johan Bring (adjunct professor and professional medical statistician) has been sought for study design, power calculation, and analysis plan.

Randomization:

The randomization ratio between intervention and control group will be 1:1 in permuted blocks of 4-8 in three strata and per site.

Randomization will be performed by the midwife in the family planning/ abortion clinic at the time of intake of mifepristone after the patient has been judged eligible for participation and has signed informed consent in the presence of the attending physician. Allocation to intervention or control will performed via opening of opaque sealed envelopes in consecutive order. Each site will have a separate randomization sequence. All women will be identified through a patient log with name and Swedish personal identification number and the randomization number. The randomization number will be used on all paper and eCRFs. The study will for practical and ethical reasons not be blinded. The medical abortion will be performed according to the Swedish national guidelines.

Choice of study design:

The project will be performed as a randomized, controlled, multicenter superiority trial. It is known that sociodemographic factors such as parity and age may influence the choice of contraception and the rate of continued use. The rate of expulsion may be influenced by parity and gestational length. To eliminate these confounders the randomized design is superior. Many of the factors studied such as the primary outcome are objective and should not be affected by the non-blinded design. It is not deemed feasible to do a single blinded study where the health care provider would be blinded to the insertion time as the women with immediate insertion will likely be bleeding more than the women with delayed insertion. The women with immediate insertion will also have an open outer cervical os. Therefore, the health care provider would likely be affected by these findings at the IUC insertion.

Primary outcome will be the use of IUC at 6 months follow up. A difference of 20 percent between the study groups (immediate versus delayed insertion) will be considered as clinically significant (please see justification for power calculation).

Secondary outcomes include the rate of IUC inserted, rate of expulsion, pain at insertion, bleeding, reasons for non-insertion of IUC, IUC use, complications, acceptability, pregnancies and abortions evaluated at 3 and 6 months follow up and annually up to five years.

Variables and measures

Primary outcome measure:

- Use of IUC at 6 months post insertion evaluated by telephone follow-up and through patient records. This will be evaluated as the proportion of women in each gestational strata (use of IUC versus no use of IUC).

Secondary outcome measures:

- Difference in the proportion of women who successfully have the IUC inserted (success versus failure),
- Expulsion rate during 12 months following insertion in both groups evaluated by telephone/email follow up at 3, 6 and 12 months post abortion (complete, partial or no expulsion. The exact day of expulsion will be noted to determine the risk of expulsion as a function of time post insertion),

- Continued use of IUC at 3, 6 and 12 months post insertion evaluated by telephone follow-up (continued use/voluntary discontinued use, involuntary discontinued use including expulsions etc) reasons for discontinuation will be recorded and subsequent use of other contraceptive methods will be noted)
- Ease of insertion according to health care provider (judged as very easy, moderately-, or very difficult)
- pain at time of insertion (women will indicate the pain before insertion, at placement of tenaculum, sound and IUC by putting a vertical mark on a 10 cm long horizontal line with a Visual Analogue Scale (VAS) from 0, indicating no pain to 10 indicating worst imaginable pain. Result will be noted in millimeters and entered into case report forms).
- Post-abortion bleeding (number of days of fresh bleeding and spotting after the abortion)
- Reasons for non-attempted insertion of IUC (change of mind, heavy bleeding, not coming for insertion, staff being unavailable etc),
- Complications (adverse events (AE) and serious AE) bleeding requiring any treatment, uterine perforations and cervical tears, infection requiring treatment with antibiotics, hospitalization for any reason, surgical procedures due to heavy bleeding, incomplete abortions, prolonged bleeding or patient request,
- Pregnancies occurring during the 12 month follow-up (planned and unplanned, wanted and unwanted, pregnancy outcomes- ectopic, miscarriage, abortion, molar, kept pregnancy),
- Acceptability of immediate and delayed insertion of IUC by asking women if they would recommend the procedure to a friend (yes/no, asked at the time of insertion and at the 3, 6 and 12 month follow up),
- Acceptability of IUC as post abortion contraception- evaluated as above,
- The proportion of surgical procedures in total and for each study site (type of procedure, reasons therefore- infection, retained products of conception, prolonged bleeding etc).

Follow up for all women will be by telephone (call) and/or email (by special invitation to a link) with a structured questionnaire wth multiple choice questions at 3, 6 and 12 months post abortion when primary and secondary objectives will be reported as described above. Women will answer questions regarding: post abortion bleeding and current bleeding pattern, continued use of IUC/other use of contraception, reasons for non-use of IUC (expulsion, never inserted-reasons, extracted- reason for this), complications (expulsion, infection, surgical intervention

etc), satisfaction with their current contraceptive method and experience of unintended/intended pregnancy and the results of these pregnancies. In addition, patient records in both groups will be reviewed after 6 months in order to extract information concerning possible extra visits related to the abortion or IUC related complications.

Data will be recorded on individual printed case report forms (CRFs), after which they will be entered via a digital case report form (eCRF) using a centre-specific module. Data quality will be assured by both computer-generated verification of consistency and by manual review at monitoring visits. E-CRFs from all sites can only be accessed by the PI and will be transferred into a database. The database will contain information on demographic variables, type of IUC inserted and sound measurement in addition to the variables above.

The end of study is defined as completion of the last visit of the last subject. The sponsor and the investigators reserve the rights to discontinue the study at any time for safety reasons or other reasons jeopardizing the justifications of the study.

An interim analysis of results will be performed when 50 percent of women have been recruited in any gestational strata. If expulsion rates exceed 20 percent or if acceptability rates are below 50 percent by the 3 month follow up the study will be stopped. If the study is prematurely terminated or suspended, the investigator should promptly inform the participants and assure appropriate therapy and follow-up.

6 Study population

Women with unwanted pregnancy having a medical abortion and fulfilling inclusion and without exclusion criteria and opting for IUC as post abortion contraception. The medical abortion will be carried out according to the Swedish national evidence based guidelines.

6.1 Inclusion criteria

- Above 18 years old,
- eligible for medical abortion,

- opting for post abortion IUC,
- able and willing to comply with planned follow up.

6.2 Exclusion criteria

- Contraindication for medical abortion or
- Contraindication for IUC (contraindications may be present for LNG-IUSs but the woman may still choose a Cu-IUD and thereby enter the study),
- inability to give informed consent.
- Septic abortion
- Known hypersensiblity/allergy to levonorgestrel or any of the substances added to the LNG-IUS
- Known abnormal uterine cavity
- Chorioamnionitis
- Abortion associated bleeding > 1000ml
- Uterine atony postabortion
- Placental retention
- Therapeutic antibiotic treatment during abortion, (antibiotics used only as prophylaxis is accepted)
- History of breast cancer
- If any of the following conditions are present an individual evaluation and decision must be done before inclusion**:** pelvic or genital infection, cervicitis, immunocompromised women, untreated cervical dysplasia, neoplasia in cervix or uterus, acute liver disease or hepatic neoplasia, migraine or other very severe headache, icterus, high uncontrolled blood pressure, serious arterial disease i.e. stroke or myocardial infarction, acute venous thrombosis

6.3 Withdrawal criteria

Patients may be discontinued from the study at any time. Specific reasons for discontinuation can be;

- Every subject is free to drop-out of the study at any time. These subjects will receive contraceptive counseling and treatment according to local routines and will suffer no negative consequences
- Serious adverse events
- Post abortion infection between randomization and planned insertion

Women who discontinue due to side effects or adverse events will be asked permission for follow up for a total of 12 months post abortion.

7 Time plan

Planning: -March 2018

Study start: May 2018

End of recruitment: April 2020

Analysis: 2021

Report of primary outcome and Safety: 2021

8 Methods

8.1 Recruitment

Women will receive written and oral information about the study from the attending physician according to the principles of the Helsinki Declaration at the first visit to the family planning clinic. They will have an opportunity to ask questions. If the woman agrees to participate and is deemed eligible she will sign informed consent in the presence of the attending physician at that consultation. This procedure will not differ between study sites. The Swedish national guidelines on medical abortion will be followed by all sites (www.sfog.se).

All centers will have a specific, GCP-certified study nurse-midwife. Participating women will receive a specific appointment for insertion of the IUC according to the wishes of the woman and the pre-defined allocation window.

9 Study medication

All women will receive the assigned treatment from the study staff at each site at the time of insertion.

9.1 Study Medication, dosage and administration

The following study drugs will be used in the study;

Mirena® (LNG-IUS 52mg),

Kyleena® (LNG-IUS 19.5mg),

Jaydess® (LNG-IUS 13.5 mg),

NovaT 380® (Cu-IUD, medical device, not a drug but due to use outside indication it is included in this application, a separate application for medical device trial has been submitted)

9.2 Supply, labelling, handling and storage

The study drugs are commercially available and will be handled by Apoteket AB (Mirena®, Kyleena®, Jaydess®) and normal clinical practice (NovaT®, Cu-IUD) who will then distribute to site or local pharmacy. It will be stored and kept according to the instructions of the manufacturer. Ordered but yet not distributed study drugs will be stored at each center in a locked cabinet and only personal authorized by the investigator will have access.
The study drug will be labelled with information according to the local regulatory requirements (see the attached supplement). For each patient the batch-number and expiration date will be noted in a drug accountability list at each site.

9.3 Compliance

Complicance is part of the secondary outcomes in this trial and will be evaluated at 3, 6 and 12 months post abortion.

The IUCs can be kept or removed at the end of the study according to the wish of the enrolled woman. If the woman decides to keep the IUC after the end of study, she will be responsible

for removing it at appropriate time. In case of drop-out of the study the woman will have free access to the general health care system regarding contraceptive care. In case of expulsion or if the device has to be removed before the end of study, the woman will receive contraceptive advice and prescription by the study staff.

10 Concurrent/concomitant medication

There are no restrictions for use of other medications. All concomitant medication will be recorded in the CRF.

11 Registration of efficacy and satisfaction

- Difference in the proportion of women who successfully have the IUC inserted (success versus failure),
- Continued use of IUC at 3,6 and 12 months post insertion evaluated by telephone follow-up (continued use/voluntary discontinued use, involuntary discontinued use including expulsions etc) reasons for discontinuation will be recorded and subsequent use of other contraceptive methods will be noted)
- Ease of insertion according to health care provider (judged as very easy, easy, moderately, or very difficult)
- pain at time of insertion (women will indicate the pain before insertion, at placement of tenaculum, sound and IUC by putting a vertical mark on a 10 cm long horizontal line with a Visual Analogue Scale (VAS) from 0, indicating no pain to 10 indicating worst imaginable pain. Result will be noted in millimeters and entered into case report forms).
- Post-abortion bleeding (number of days of fresh bleeding and spotting after the abortion)
- Reasons for non-attempted insertion of IUC (change of mind, heavy bleeding, not coming for insertion, staff being unavailable etc),
- Pregnancies occurring during the 12 month follow-up (planned and unplanned, wanted and unwanted, pregnancy outcomes- ectopic, miscarriage, abortion, molar, kept pregnancy),
- Acceptability of immediate and delayed insertion of IUC by asking women if they would recommend the procedure to a friend (yes/no, asked at the time of insertion and at the 3, 6 and 12 month follow up),
- Acceptability of IUC as post abortion contraception- evaluated as above,

12 Safety registration

- Expulsion rate during 12 months following insertion in both groups evaluated by telephone/email follow up at 3, 6 and 12 months post abortion (complete, partial or no expulsion. The exact day of expulsion will be noted to determine the risk of expulsion as a function of time post insertion),
- Complications (adverse events (AE) and serious AE) bleeding requiring any treatment, uterine perforations and cervical tears, infection requiring treatment with antibiotics, hospitalization for any reason, surgical procedures due to heavy bleeding, incomplete abortions, prolonged bleeding or patient request,
- The proportion of surgical procedures in total and for each study site (type of procedure, reasons therefore- infection, retained products of conception, prolonged bleeding etc).

12.1 Adverse events

All adverse events occurring during the study period, i.e. from informed consent to the final telephone call, irrespective of a relation with the study drug/device/procedure of IUC insertion.

Concurrent diseases that are reported at the time of inclusion will not be considered as adverse events, however any changes in symptoms or severity will be reported as an adverse event.

Definitions

12.1.1 Adverse Events

Any untoward medical occurrence in a study participant administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of an investigational, medicinal product whether or not considered related to the investigational medicinal product.

Adverse Device Event
This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment or insertion of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

12.1.2 Serious Adverse Events (SAE)
An untoward medical occurrence or effect that results in:

- Death
- Life threatening condition
- Requires hospital stay or lead to a prolonged hospital stay
- Results in permanent or serious disability
- Fetal malformation
- Any other serious medical event according to the investigators judgement

12.1.2 Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

12.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)
A suspected unexpected serious adverse reaction of a study drug resulting in any condition mentioned above (12.1.1).

12.2 Assessment of Adverse Event

12.2.1 Assessment of severity
An adverse event will be graded as:

- Mild = the subject is aware of the event but the event is easily tolerated
- Moderate = the subject experiences sufficient discomfort and the symptoms affect daily activities
- Severe = the subject experience significant impairment of functioning and the symptoms substantially affect daily activities

Note: a distinction should be drawn between serious and severe AEs. The term severe is used to describe the intensity of the event and the event does not necessarily need to be considered defining regulatory reporting obligations.

12.2.2 Assessment of causality

The following definitions will be used to estimate the relation with adverse event and the study drug:

- Probable = clinically/biologically highly plausible and there is a plausible time sequence between the onset of the AE and the administration of the study drug. There is sufficient documentation to suspect a casual relationship
- Possible = clinically/biologically plausible and the relation cannot be rejected
- Unlikely = a causal relation is improbable and other explanation is more likely
- Not possible to evaluate = any relationship cannot be ruled out
- For medical device reporting two additional levels: “not related” (causal relationship can definitely be ruled out) and “causal relationship established” (when causal relationship can be established beyond reasonable doubt) will be used.
- The sponsor and the investigators will for medical devices distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

12.3 Reporting of AE, SAE and SUSARs

- All patients will be asked for adverse events at every visit/contact with the investigator or study nurse/midwife with the exception for what is mentioned under 13.1
- Adverse events will be reported irrespective if the event has any relation with the study drug or not
- All Adverse events must be recorded in the CRF, defining the relationship to study medication, severity and seriousness. Adverse Events should also be recorded in the patient records if applicable
- If a reported SAE is present when the patient completes the study the event must be followed for up to three months past the final visit or followed until final outcome is known or the condition is stable

- AE/SAE will be registered until the end of the study

12.3.1 Reporting of SAE, SADE and USADE

- any SAE and any Device Deficiency that might have led to a SAE if: a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate and in addition new findings/updates in relation to already reported events must be reported to the sponsor on a separate SAE report form within 24 hours of the initial notification of the event- for device deficiencies regulatory requirement is within 3 days- however, a 24 hour period will be maintained for all serious adverse events in this trial.
- The initial notification to the sponsor can be made on a SAE-report form, by e-mail or telephone
- At the time of initial reporting the investigator must provide a minimum requirement, the patient number, birth date, description of the SAE and a preliminary assessment of causality
- Supplemental information shall be reported by the investigator to the sponsor as soon as possible. If the SAE is fatal or life-threatening the investigator is responsible to report follow-up information to the sponsor within 5 days after the initial report
- Reportable medical device events must be reported by the sponsor at the same time to all the National Competent Authorities where the clinical investigation has commenced. This includes
  - for all reportable events as described above which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
  - any other reportable events as described above or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

12.3.2 Reporting SUSAR

Sponsor is obliged to report:

- Any suspected serious unexpected reaction of the study drug (SUSAR) which is life threatening or fatal to the Medical Products Agency MPA (”Läkemedelsverket, LMV”) as soon as possible and not later than 7 days after the responsible investigator has been aware of the event. The report should be sent to MPA and the Regional Ethical Review Board (RERB). Relevant follow-up information of the report should be sent within additional 8 days (maximum of 15 days from initial report)
- A suspected serious unexpected reaction of the study drug/device (SUSAR) that is **not** life threatening or fatal should be reported as soon as possible but within a maximum of 15 days to the MPA and the RERB
- All SUSARs should be reported to the MPA on a CIOMS-form and with assistance of the MPA also reported into the Eudra Vigilance Clinical Trial Module

  During the study, the sponsor should report all SAEs with a suspected relation to the study drug, and SUSAR, to the MPA and RERB once a year. Moreover, a safety report concerning the patients included in the study should be supplied together with a summary on a risk/benefit evaluation for the patients participating in the study. The sponsor is obliged to inform all investigators about occurring SUSARs during the study period.

12.4 Serious breaches and urgent safety actions

A serious breach means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the study protocol.

In case of serious breaches;

The sponsor should immediate notify the MPA and RERB about a serious breach of this protocol. An initial report can be done by telephone but must be followed by a written report

- The sponsor and the investigators will when necessary immediately take action to protect the patients from immediate danger
- All patients will be taken care of in the health care system
- The use of the investigational drug will be immediately stopped
- The sponsor may consider stopping the trial temporarily or institute complementary supervision
- In case of a serious event that may cause urgent safety actions the sponsor should be

informed as soon as possible. Moreover, the MPA and the RERB should be informed by the sponsor as soon as possible and the safety actions taken should be specified. The initial report may be oral or written but shall be followed by a written report concerning the new circumstances and taken and planned actions

- The report to the MPA should be done using the EU-common form for substantial amendments

12.5 Safety analysis

An interim analysis of results will be performed when 50 percent of women have been recruited in any gestational strata. If expulsion rates exceed 20 percent or if acceptability rates are below 50 percent by the 3 month follow up the study will be stopped. If the study is prematurely interrupted or stopped due to any reason this will be reported to the Medical Products Agency. When the study is completed according to plan this will also be reported to the Medical Products Agency

13 Data collection and data handling

Every participant will be given an individual, study specific number (i.e study identifying code) at the time of inclusion. A code key with each individual personal data connected to the identifying code will be created (i.e patient identification log) and stored at each center in a way that only authorized persons have access.

All data will be collected in an electronic CRF with the identifying code. The data CRF will thus be transferred in original to the sponsor and stored electronically according to the data protection act. Each study site will hold a printed paper copy of the CRF which will be kept in a locked facility.

Statistical analyses will be performed using SPSS statistical software. All reports will be on group level and none of the study subjects will be identifiable.

15 Procedure for informed consent

Women will receive written and oral information about the study at the first visit at the family

planning unit from the attending physician according to the principles of the Helsinki Declaration. They will have an opportunity to ask questions. If the woman chooses IUC as post abortion contraception, agrees to participate and is deemed eligible she will sign informed consent in the presence of the attending physician at that consultation or at any time prior to the abortion. This procedure will not differ between study sites. Informed consent and participation in the study will be noted in the electronic patient records along with the individual study subject number and the allocation (immediate or delayed insertion). The Swedish national guidelines on medical abortion will be followed by all sites (www.sfog.se).

All centers will have a specific, GCP-certified study nurse-midwife who will act as the study coordinator and collect the individual informed consent forms which will be kept in a locked facility. Participating women will receive a specific appointment for insertion of the IUC according to the wishes of the woman and the pre-defined allocation window. At the time of insertion participation will be re-confirmed by the inserter.

16 Regulatory requirements

The study will be conducted in adherence to the approved study protocol and the latest version of the Declaration of Helsinki, ICH-GCP E6 addendum and all relevant laws and regulations.

16.1 Applications, and substantial amendments

The study has received RERB approval at Karolinska Institutet with number 2016/1685-31/1. However, due to ongoing applications and lack of funding the study has not been able to start until now when sufficient funding has been ensured. A current modification of the exact immediate timing of insertion in conjunction with this application has been approved with number 2018-48/32.

If substantial changes in the protocol or patient information or consent will be undertaken, an applications will be sent to the MPA using the ”Substantial amendment notification form” as well as the RERB. The study will not start until all approvals by the MPA and RERB are in order.

Changes in the protocol that might affect the safety, physical or psychological integrity, change the scientific value of the study or may be considered as important of any other reason

should be considered as substantial changes. If the study has been temporarily stopped and then re-started, this should also be considered as a substantial change. The study will be performed according to the protocol. All protocol deviations will be noted and kept in a protocol deviation log describing the deviation and actions undertaken. All protocol deviations will be monitored by the PI and the appointed monitor and classified as minor, major or severe. All severe protocol deviations will be reported to the RERB and the MPA.

17 Statistical considerations - Sample size

17.1 Justification of power calculation

A total of 720 women will be recruited. In order to be able to show a difference of 80 percent in IUC usage in the immediate insertion group at 6 months post insertion compared to 60 percent use in the delayed group with a power of 90 percent and an alpha of 0.05 we would need to randomize 109 women in each group. If close to 100 percent of women receive the IUC in the immediate group and there is an expulsion rate of maximum 15 percent (immediate post placental insertion after delivery has expulsion rates of 15 percent) and some women have the IUC removed a use of approximately 80 percent could be expected in the immediate group. In the delayed group fewer women are estimated to come for insertion and the expulsion rate is estimated at 5 percent.

We will stratify women in three gestational age categories (≤9 weeks+0 days, 9weeks +1 day ≤12 weeks+0 days, and >12 weeks) to make study data more internationally applicable. We will compensate for surgical procedures due to incomplete abortions and prolonged bleeding which is estimated to be needed in approximately 3-5 percent (13). We will also compensate for a 15 percent loss to follow up which is commonly seen in studies in abortion. Thus, we will randomize 240 women in each gestational strata (total 720 women). Analysis will be presented as intention to treat for all randomized women as well as per protocol for women completing the 6 month follow up (see analysis plan). Follow up at 3, 6 and 12 months will be performed by telephone/email. In women who does not attend FU electronic patient records will be searched for main and secondary outcomes (safety, pregnancy, abortion).

- Primary outcome:

The primary outcome is the difference in women with IUC use at 6 months between the two groups (immediate and delayed insertion). The results will be analyzed by Fisher's exact test. A sensitivity analysis will be performed using logistic regression taking center, parity and age into account.

- Analysis populations

The main analysis population for primary outcome will be a modified intention to treat (mITT). This population is all randomized women, with medical abortion, and follow up for main outcome recorded at 6 months. Hence, also women with no insertion and women experiencing expulsion are included in this mITT.

A sensitivity analysis will be performed on a strict ITT-population consisting of all randomized women having had medical abortion. In this analysis it is required to impute the outcome for women lost to follow up.

- Secondary efficacy outcomes:
  1. Abortion rate as difference in proportion of individuals in each group at 3, 6 and 12 months,

     Since both the primary outcome and this outcome involve data from different time-points several tests can be performed. In order to reduce the risk for type-I error each research question will be addressed with a global test including all available time-points first, before studying individual time-points. The data has a repeated-measure structure with a dichotomous outcome and most likely more observations available for early time-point compared to later time-points. To properly handle this data-structure we will use a multivariate permutation test based on a Fisher's combination function of individual *p*-vales from time-specific tests (Fisher's exact test). If this global test is non-significant no individual time-points will be considered significant

  2. Difference in the proportion of women who successfully have the IUC inserted (success versus failure),

  Analyzed by Fisher´s exact test.

- Secondary safety outcomes

1. rate of complications such as expulsions, perforations, infections. (Fisher's exact test)
2. Length of post abortion bleeding (difference in mean number of days in groups and per IUC use (hormonal/copper). Analyzed by T-test or Mann-Whitney U-test depending on the observed distribution (normal or skewed).
3. Pain at insertion on a VAS. Analyzed by Student´s t-test

These secondary analyses concern safety where it is not sensible to adjust for multiple testing. The adjustments (with e.g. Bonferroni) increases the risk for type-II errors. As safety issues are very important we do not wish to increase the risk for type-II errors. Moreover, the analyses are listed under secondary endpoints so this implies that the results should be interpreted with more caution compared to the primary result.

- Secondary acceptability outcomes
  1. preferred method: immediate or delayed and if they would recommend their timing of insertion to a friend (yes/no). Analyzed by multivariate logistic regression with group, demographic variables and type of IUC (hormonal/copper) as explanatory variables.

Secondary analyses will be performed on all women with available data.

- Interim analysis:

In the interim analysis no analyses of efficacy will be performed. Hence there is no need to adjust any statistical test due to the interim analysis.

All test will be performed at the 5% significance level. The analysis plan has been developed by the principal investigator and Johan Bring, adjunct professor in medical statistics, Statisticon AB.

Missing data

Missing data on the primary outcome variable will cause the patient to be classified as a "drop-out".

18 Insurance

The participants will be insured through the pharmacological insurance (”Läkemedelsförsäkringen”) and the Swedish patient injury act (” Patientskadelagen”).

19 Monitoring

The study will continuously be monitored by an independent monitor from Danderyd Hospital´s department of General Surgery. A minimum of three monitoring visits (study start, after first 5 recruited subjects and at study completion) will take place at each site. The monitor will check study specific procedures, including safety assessment, handling of study medication, data recording and source data verification. To assure the accuracy and completeness of the data recorded in the study the monitor will compare CRFs with medical records and any other relevant documentation during the on-site monitoring visits.

A source data list will be written for each site defining source data for this study.

Monitor and permitted staff from relevant authorities will be guaranteed access to print outs of patient records by the patients’ agreement at the time of inclusion, and this will be documented in the informed consent form. Random checks will ensure that all relevant copies of records are printed.

20 Archive

All study related documents will be kept in archive for at least 10 years after study completion according to national law.

21 Report and publishing

- Within 90 days of completion of the study as a whole, the sponsor will report to the MPA and the RERB that the study is completed as stated in the protocol
- If the study will be ended and closed prematurely, the sponsor will report to the MPA and the RERB within 15 days. The reasons for the decision shall be reported
- The EU-common form ”end of trial” shall be used and sent electronically to the MPA
- The sponsor will also send a summarizing report to the EudraCT database within 12 months after the study has been closed

- The results will be published as a scientific article in an international, peer-reviewed scientific journal

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