Immediate versus delayed insertion of an etonogestrel releasing implant at medical abortion—a randomized controlled equivalence trial

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Submitted on July 19, 2016; resubmitted on August 19, 2016; accepted on August 25, 2016

STUDY QUESTION: Does a progestin releasing subdermal contraceptive implant affect the efficacy of medical abortion if inserted at the same visit as the progesterone receptor modulator, mifepristone, at medical abortion?

SUMMARY ANSWER: A etonogestrel releasing subdermal implant inserted on the day of mifepristone did not impair the efficacy of the medical abortion compared with routine insertion at 2–4 weeks after the abortion.

WHAT IS ALREADY KNOWN: The etonogestrel releasing subdermal implant is one of the most effective long acting reversible contraceptive methods. The effect of timing of placement on the efficacy of mifepristone and impact on prevention of subsequent unintended pregnancy is not known.

STUDY DESIGN, SIZE, DURATION: This multicentre, randomized controlled, equivalence trial with recruitment between 13 October 2013 and 17 October 2015 included a total of 551 women with pregnancies below 64 days gestation opting for the etonogestrel releasing subdermal implant as postabortion contraception. Women were randomized to either insertion at 1 hour after mifepristone intake (immediate) or at follow-up 2–4 weeks later (delayed insertion). An equivalence design was used due to advantages for women such as fewer visits to the clinic with immediate insertion. The primary outcome was the percentage of women with complete abortion not requiring surgical intervention within 1 month. Secondary outcomes included insertion rates, pregnancy and repeat abortion rates during 6 months follow-up. Analysis was per protocol and by intention to treat.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women aged 18 years and older who had requested medical termination of a pregnancy up to 63 days of gestation and opted for an etonogestrel releasing contraceptive implant were recruited in outpatient family planning clinics in six hospitals in Sweden and Scotland.

MAIN RESULTS AND THE ROLE OF CHANCE: Efficacy of medical abortion was 259/275 (94.2%) in the immediate insertion group and 239/249 (96%) in the routine insertion group with a risk difference of 1.8% (95% CI –0.4 to 4.1%), which was within the ±5% margin of
equivalence. The insertion rate was 275/277 (98.9%) in the immediate group compared to 187/261 (71.6%) women in the routine group (P < 0.001). At 6 months of follow-up significantly fewer women in the immediate group had become pregnant again (2/277, 0.8%) compared to the routine group (10/261, 3.8%) P = 0.018.

LIMITATIONS, REASONS FOR CAUTION: For the main outcome loss to follow-up data was minimized through access to patient records. Efforts were made to reduce loss to follow-up also for secondary outcomes. The results of the sensitivity analysis did not differ from the intention to treat or per protocol analysis.

WIDER IMPLICATIONS OF THE FINDINGS: Guidelines on postabortion contraception should be amended to include insertion of the etonogestrel releasing implant at the time of mifepristone intake for medical abortion up to and including a gestation of 63 days.

STUDY FUNDING/COMPETING INTEREST(S): This study was funded by the Swedish Research Council (2012–2844), Stockholm City County and Karolinska Institutet (ALF). The contraceptive implants were provided by Merck and supplied by MSD Sweden. HKK and KGD have received honorariums for giving lectures for MSD/Merck and have participated in the national (HKK and KGD) and international (KGD) medical advisory boards for MSD/Merck. The other authors have nothing to declare.

TRIAL REGISTRATION NUMBER: ClinicalTrials number NCT01920022.

TRIAL REGISTRATION DATE: 06 August 2013.

DATE OF FIRST PATIENT’S ENROLMENT: 13 October 2013.

Key words: abortion / termination of pregnancy / LARC / contraceptive implant / etonogestrel / unintended pregnancy / unwanted pregnancy

Introduction

The introduction of mifepristone for medical abortion has changed abortion practice dramatically in many countries where it is available. Given the choice, the majority of women in the first trimester choose medical rather than surgical abortion (Henshaw et al., 1993, Winikoff, 1995). In Europe and globally a significant proportion of women having an abortion have had one or more previous abortions. Long acting reversible contraception such as intrauterine contraception (IUC) and implants have been shown to be highly effective in preventing unintended pregnancy and repeat abortions (Heikinheimo et al., 2008, Cameron et al., 2012, Rose and Lawton, 2012, Winner et al., 2012). Studies show that most women (83%) ovulate in the first cycle after a medical abortion. In addition, as many as 15% of women have resumed sexual intercourse within 1 week of a medical abortion (Saav et al., 2012). Immediate postabortion start of long acting contraception is therefore desirable and recommended by guidelines (WHO, 2012).

Contraceptive implants and IUC are commonly inserted immediately after surgical first-trimester abortion, with well documented effectiveness, compliance and safety (Okusanya et al., 2014). With medical abortion, it has been traditional practice to provide long acting reversible contraception at a follow-up visit several weeks after treatment. This practice may discourage women from using long acting reversible contraception due to the need for several follow-up visits. This particularly applies to settings where women travel significant distances for abortion care or where services are poor or expensive for women. A potential advantage with implants could be that insertion could be done at the same time as administration of the initial abortion medication. The WHO guideline on postabortion contraception recommends immediate implant insertion (WHO, 2012). However, this practise has not been widely implemented due to the theoretical concerns about a potential interaction between mifepristone and the progestin in the contraceptive implant resulting in an adverse effect on the efficacy of the medical abortion.

Mifepristone is a 19-nor steroid that acts a progesterone receptor modulator. It binds with high affinity to the progesterone receptor and thereby prevents the action of progesterone. Theoretically, treatment with a progesterin could affect the binding of mifepristone to the progesterone receptor. An interaction between a progesterone receptor modulator and a progesterin has previously been demonstrated (Gemzell-Danielsson et al., 2002). New evidence shows that the progesterone receptor modulator, ulipristal acetate, interacts with a progesterin-only oral contraceptive pill containing desogestrel (Brache et al., 2015). Desogestrel is the precursor of the progesterin etonogestrel, which is the progesterin in the contraceptive implant used in this study. An interaction between etonogestrel and mifepristone was demonstrated when mifepristone was given to treat breakthrough bleeding in women using the etonogestrel containing implant (Weisberg et al., 2011). However, since the uptake of mifepristone is rapid with maximal serum concentrations at 1 hour after ingestion (according to the summary of products characteristics for mifepristone), insertion of an etonogestrel containing implant 1 hour after administration of mifepristone may not impact upon the efficacy of the medical abortion process. There are few pilot studies reporting on the insertion of the etonogestrel releasing implant at the time of mifepristone in medical abortion (Church et al., 2010, Sonalkar et al., 2013, Barros Pereira et al., 2015). In addition there is one randomized study performed in Mexico and the United States (Raymond et al., 2016). However, the latter study had unclear dating of pregnancies in the Mexican sites. Furthermore, the protocol did not specify at what time point the implant was inserted in either study group. Thus, it is not possible to judge from this trial how soon after mifepristone the implant may be inserted. Robust research to show or exclude a possible interaction and impact on the efficacy of medical abortion following early insertion of an implant is therefore required.
The primary objective of this study was to compare immediate (insertion 1 hour following mifepristone on Day 1), versus delayed insertion (insertion at follow-up at 2–4 weeks after the mifepristone) of an etonogestrel releasing contraceptive subdermal implant on complete abortion rates with medical abortion (without need for surgical evacuation). Secondary objectives were to compare complications, rates of insertion, acceptability of the timing of insertion between the two groups and pregnancy and repeat abortion rates during the first 6 months following insertion.

Materials and methods

Study design and participants

The study was performed as a randomized controlled equivalence trial. The study protocol was designed according to the recommendations in the modified CONSORT statement for equivalence trials in collaboration with a professional medical statistician employed by Karolinska Institutet. An equivalence design was used due to advantages for women such as fewer visits to the clinic with immediate insertion.

Women with pregnancies below 64 days gestation (based on ultrasound) and opting for the etonogestrel releasing subdermal implant (Nexplanon®, Merck Sharp and Dohme Sweden, Gavlegatan 22, PO Box 45192, 113 30 Stockholm, Sweden) as postabortion contraception, were asked to participate. Study recruitment started 13 October 2013 and ended 17 October 2015. Recruitment took place in outpatient family planning clinics of Danderyd Hospital (Stockholm, Sweden), Karolinska University Hospital (Stockholm, Sweden), National Health Service Lothian (Edinburgh, Scotland, Great Britain), Stockholm South General Hospital (Stockholm, Sweden), Örebro University Hospital (Örebro, Sweden) and Sahlgrenska University Hospital/Ostra (Gothenburg, Sweden). The researcher at each site obtained informed consent after written and oral information had been provided and the woman had had the opportunity to ask questions according to the Declaration of Helsinki. If the woman agreed to participation she signed informed consent in the presence of the researcher. Women were randomized to either immediate insertion of the implant 1 hour after ingesting mifepristone (Mifegyne Exelgyn, 254 Boulevard Saint Germain 75007 Paris, France, or Mifepristone Linepharma, CampusPharma AB, Karl Gustavsgatan 1A, 411 25 Göteborg, Sweden or in Scotland Linepharma France, 55 Rue de Turbigo, 75003 Paris, France) or to insertion at the follow-up visit.

Randomization and masking

The randomization procedure was a third party concealed 1:1 randomization with computer-generated blocks of 10. A study nurse, not directly involved in the study, created opaque numbered envelopes containing the randomization allocation for each participant which were opened in consecutive order after written informed consent was obtained. All centres had separate randomization series. The study was unblinded for ethical and practical reasons.

Procedures

Inclusion criteria were age of 18 years or above, opting for medical abortion and postabortion contraception with the etonogestrel releasing implant, good understanding of Swedish or English language (as appropriate), gestational age <64 days, willing to participate and give written informed consent. Exclusion criteria were declining participation, and having contraindications to the implant (according to the summary of products characteristics, MSD/Merck) or any of the medical abortion drugs. Women with miscarriage or molar pregnancies were excluded from the study. Demographic characteristics such as age, gravidity, parity, previous abortions, height and weight were recorded. All women had an ultrasound to assess gestational age and all were screened for Chlamydia trachomatis infection. In Sweden women were also screened for bacterial vaginosis (BV). At the Swedish sites, only women with BV received treatment with antibiotics according to national guidelines. In Scotland, no BV screening was performed, but all women received prophylactic antibiotics (generic single dose metronidazole 800 mg orally).

All women received mifepristone 200 mg in the clinic. Women allocated to immediate insertion received the implant using local anaesthesia 1 hour after mifepristone had been ingested. All women received treatment with vaginal misoprostol (Cytotec, Pfizer, Vetenskapsvägen 10, 191 90 Sollefteå, Sweden or Pfizer Limited, Walto Oaks, Tadworth, Surrey, KT20 7NS, United Kingdom) 800 mcg 24–48 hours after the initial treatment with mifepristone. Women in Sweden had a choice of administering misoprostol at home or receiving it in the clinic. In Scotland, all women had misoprostol administered at the clinic (legal requirement) but returned home after misoprostol administration to expel the pregnancy. In Sweden women received a second dose of 400 mcg of misoprostol if there was no bleeding by 3 hours after the initial dose of misoprostol (Ashok et al., 2002).

Follow-up was either in the clinic with a low sensitivity urinary hCG test (CheckTop, Exelgyn, Paris, France) or via telephone using a self performed low sensitivity urinary hCG-test (Baby Duo, Quadratech diagnostics, UK) 2–3 weeks after mifepristone treatment (Cameron et al., 2015, Oppegaard et al., 2015), according to the local clinic protocol. Women allocated to delayed insertion had the implant inserted by a nurse-midwife using local anaesthesia at the follow-up visit. At the same follow-up visit women completed an interviewer administered questionnaire with questions regarding duration and quantity of bleeding, the worst pain they had experienced during the abortion (using a visual analogue scale of 0–10), if they had had unscheduled visits to the abortion service, if they had received any extra treatment for a complication related to the abortion, and if they would prefer immediate or delayed implant insertion if they were ever to have a medical abortion again. All centres in the study had access to patient records for the entire region in which the abortion took place.

Outcomes

The primary aim was to show equivalence between the two groups for successful completion of abortion without the need for surgical evacuation. Assuming 97% success in both groups (based on Kopp Kalner et al., 2015), and a two-sided margin of equivalence (−5% to 5%) 252 patients per group would be required to establish equivalence with an alpha of 0.05 and a power of 90%. In order to compensate for loss to follow-up 560 women were expected to be recruited. The primary outcome was assessed at follow-up at 2–4 weeks, and/or by patient records. An equivalence design was used due to advantages for women such as fewer visits to the clinic with immediate insertion.

Secondary outcomes were serious adverse events and adverse events of special interest, rates of insertion of the implant, preferred allocated allocation time of insertion as determined by responses to a questionnaire completed at the outpatient visit or telephone review following the abortion. Satisfaction with the implant, continued implant use and pregnancies and repeat abortions where reported by the patients at telephone follow-up 3 and 6 months after the abortion.

Statistical analysis

The primary outcome was analysed with a generalized estimating equation model using a binomial distribution and an identity link and
presented as a risk difference with a 95% CI. Treatment centre was included as a random factor using an exchangeable correlation structure in the model. The intention to treat population was defined as all women randomized except women who withdrew consent before abortion or before insertion of the contraceptive implant. The per protocol population was defined as all women in the intention to treat analysis except those who changed their mind about method of contraception before insertion of the implant or had implant insertion at the wrong delayed timing. The primary analysis was performed on the per protocol population corroborated by the intention to treat population. In addition a sensitivity analysis was performed excluding all women in the per protocol population who did not come for follow-up. All other analyses were presented for the intention to treat population. Fisher’s exact test was used to evaluate the differences between the groups regarding categorical data. Continuous variables are presented as medians and range and compared between groups using Mann–Whitney U-test. Results were considered statistically significant if the two-sided P-value was <0.05. The analyses for the primary endpoint were performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). For all other analyses the IBM Statistical Package for Social Sciences version 22 (1 New Orchard Road, Armonk, New York 10504-1722, USA) was used.

The study was approved by the Swedish Medical Products Agency which issues permits for clinicaltrials in the European Union. The trial received EudraCT number 2013-001945-15. The institutional review board of Karolinska Institutet granted permit for all Swedish sites (permit no 2013/907-31/4). The ethical committee approval number for the Edinburgh site was IRAS 141042 ref 14/SS/011. The trial was registered at Clinicaltrials.gov with number NCT01920022 prior to recruitment of women.

Results

Study participants

A total of 551 women were enrolled between October 2013 and October 2015. A total of 13 women were not included in the study due to: miscarriage before the mifepristone visit (n = 1), decision to continue the pregnancy (n = 2), to have a surgical abortion (n = 2) or withdrawal of consent (n = 8). Of the remaining 538 women (the intention to treat population), 261 were allocated to delayed insertion and 277 to immediate insertion. The flow of patients is described in Fig. 1. There were no significant differences in demographic or baseline characteristics between the treatment groups including the gestational age of pregnancies (Table I).

In the immediate insertion group 3/277 (1.1%) women did not receive the implant as allocated, as they changed their mind regarding this contraceptive method. In the delayed group 12/261 (4.6%) did not have an implant inserted due to change of mind of contraceptive method (n = 10) and two women received the implant at the time of misoprostol instead of at the follow-up visit (P = 0.017, Fisher’s exact test). These women are included in the intention to treat analysis but not in the per protocol analysis.

**Figure 1** Trial flow chart.
Outcomes
In the per protocol population 16/275 (5.8%) of women in the immediate insertion group and 10/249 (4%) in the delayed insertion group had a surgical intervention resulting in a risk difference of 1.8% (95% CI –0.4% to 4.1%) which was within the pre-specified margin of equivalence of ±5%. Therefore, equivalence between the two groups could be established. The results were similar for the intention to treat population with a risk difference of 1.3% (95% CI 0.9% to 4.1%). Of the 16 women in the immediate group who underwent surgical evacuation, five were performed after the scheduled follow-up visit at 2–4 weeks compared to 3/10 women in the delayed group.

There were no serious adverse events or adverse events related to the implant insertion. Reasons for removal of implants are shown in Table II. In the immediate group 28/277 (10.1%) women made a total of 38 unscheduled visits for a problem related to the abortion procedure compared to 17/261 women (6.5%, 35 visits, P = 0.16) in the delayed group. The most common reason for making an unscheduled visit was troublesome bleeding and/or pain. A total of 19/277 (6.5%) women in the immediate group received an extra dose of mifepristone compared to 9/261 (3.4%, P = 0.083) in the delayed group. Of these women, six women in the immediate group and three women in the delayed group had surgery for incomplete abortion. One woman in the immediate group received treatment with antibiotics for presumed pelvic infection.

In the immediate group 88/277 (31.7%) women did not attend the scheduled follow-up at 2–4 weeks after the abortion compared to 64/261 (24.5%, P = 0.21) women in the delayed group. In the delayed group 74/261 (28.4%) women did not receive the implant for postabortion contraception. Of these 74 women, 10/261 (3.8%) changed their mind about having the implant and received other postabortion contraception and 64/261 (24.5%) women did not attend for insertion. In the immediate group 3/277 (0.1%) women changed their mind about the implant and received other postabortion contraception. Thus, the insertion rate was 275/277 (99.2%) in the immediate group and 187/261 (71.6%) in the delayed group (P < 0.001).

In the immediate insertion group 180/277 (64.9%) stated that if given the choice they would prefer immediate insertion whereas 12/277 (4.3%) women stated a preference for delayed insertion (85/277, 30.7% missing answers). In the delayed insertion group 102/261 (39%) women stated that they would prefer immediate insertion whereas 51/261 (19.5%) women indicated a preference for delayed insertion (108/261, 41.3% missing answers). Acceptability was defined as ‘preferring the allocated time of insertion’. Thus, acceptability was 64.9% in the immediate group and 19.5% in the delayed group (P < 0.001, Fisher’s exact test).

At the 3-month follow-up 224/277 women (80.9%, 37 women missing) had continued use of the implant compared to 179/261 (68.6%, 43 women missing) in the delayed group (P = 0.001). In the immediate group 14/277 (6.5%) had a verified removal of the implant compared to 17/262 (5.1%) women in the delayed group (P = 0.58).

At the 6-month follow-up 199/277 women (71.8%, 40 women missing) in the immediate group had verified continued use of the implant compared to 151/261 (57.9%, 52 women missing) in the delayed group (P < 0.001).

In the immediate group 23/277 (8.3%) had a verified removal of the implant between the 3- and 6-month follow-up compared to 23/261 (8.8%) women in the delayed group (P = 0.88). The cumulative removal rate of the implant in women who received the implant was significantly lower (37/274, 13.5%) for women in the immediate group compared to the delayed group (40/187, 21.4%, P = 0.03). Reasons for removal at 3 and 6 months are shown in Table II. Satisfaction with the implant was significantly higher in the immediate group at 3 months (P = 0.015, Chi-Square test) but not different at 6 months (P = 0.66) (Table III).

At the 3-month follow-up there were no pregnancies in the immediate group compared to four pregnancies in the delayed group. All four pregnancies occurred in women who never came for insertion of the implant and never received any contraceptive method. Between the 3- and 6-month follow-up there were two pregnancies in the immediate group in women who had discontinued the implant and had not wanted any new contraceptive method. Both of these pregnancies ended in abortion. There were six pregnancies in the delayed group. One of which was in a woman who had the implant removed and did not initiate any other method. This pregnancy ended in miscarriage. The remainder occurred in women who never received the implant or any other contraceptive method. All these pregnancies ended in abortion. Thus, at the 6-month follow-up significantly fewer women in the immediate group (2/277) had become pregnant compared to the delayed group (10/261, P = 0.018).

### Table I Patient characteristics. Data are Median (Minimum–Maximum).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Immediate N = 277</th>
<th>Delayed N = 261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>25 (18–42)</td>
<td>25 (18–43)</td>
</tr>
<tr>
<td>BMI Kg/m²</td>
<td>23.1 (14.7–38.9)</td>
<td>23.1 (16.8–45.2)</td>
</tr>
<tr>
<td>Parity</td>
<td>0 (0–5)</td>
<td>0 (0–6)</td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
</tr>
<tr>
<td>Previous ectopic</td>
<td>0 (0–1)</td>
<td>0 (0–8)</td>
</tr>
<tr>
<td>Previous abortion</td>
<td>1 (0–4)</td>
<td>0 (0–8)</td>
</tr>
<tr>
<td>Gestational age at mifepristone intake (days)</td>
<td>46 (30–63)</td>
<td>46 (28–63)</td>
</tr>
</tbody>
</table>

### Table II Reason for removal of implant in each group at 3 and 6 months postabortion. Data are n (%)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Immediate n = 275</th>
<th>Delayed n = 187</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>6 (2.2)</td>
<td>12 (4.3)</td>
<td>18 (4.6)</td>
</tr>
<tr>
<td>Mood change</td>
<td>3 (1.1)</td>
<td>2 (0.7)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Wish for pregnancy</td>
<td>1 (0.4)</td>
<td>3 (1.1)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Other reason</td>
<td>2 (0.7)</td>
<td>3 (1.1)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing information</td>
<td>1 (0.4)</td>
<td>2 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>14 (5)</td>
<td>23 (8.4)</td>
<td>37 (13.2)</td>
</tr>
</tbody>
</table>
Table III  Satisfaction with the implant at 3 and 6 months in women with verified implant in place at the time of follow-up. Data are n (%).

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th></th>
<th>Delayed</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months</td>
<td></td>
<td></td>
<td></td>
<td>Chi-Square test</td>
</tr>
<tr>
<td></td>
<td>N = 224</td>
<td>3</td>
<td>N = 199</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Very satisfied/ fairly satisfied</td>
<td>173 (77.2)</td>
<td>147 (73.9)</td>
<td>115 (64.2)</td>
<td>105 (69.5)</td>
<td>0.015</td>
</tr>
<tr>
<td>Neither/nor</td>
<td>24 (10.7)</td>
<td>19 (9.5)</td>
<td>33 (18.4)</td>
<td>17 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Fairly dissatisfied/ very dissatisfied</td>
<td>27 (12.1)</td>
<td>33 (16.6)</td>
<td>31 (17.3)</td>
<td>29 (19.2)</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

In this study, we could establish equivalence for the impact of immediate insertion of an etonogestrel releasing subdermal implant 1 hour after mifepristone intake compared to delayed insertion at 2–4 weeks postabortion on the efficacy of medical abortion. There were no significant differences in complications rates between groups. However, the insertion rates were significantly higher in the immediate insertion group. In addition, immediate insertion of the implant was significantly more acceptable to women and resulted in significantly lower risk of unintended pregnancy and abortion at 6 months follow-up compared to delayed insertion.

Immediate insertion of contraceptive implants has several advantages for women and justifies the equivalence study design. It enables a ‘one stop’ visit for medical abortion with contraceptive counselling and provision of long acting reversible contraception, home use of misoprostol and home self-assessment of the outcome of treatment using a low sensitivity urinary hCG test. In previous studies it has been shown that women prefer as few visits as possible in connection to an abortion (Winikoff, 1995, Cameron et al., 2012). Uptake of long acting reversible contraception at the time of abortion has been shown to decrease the risk of a subsequent abortion for women in several studies (Heikinheimo et al., 2008, Cameron et al., 2012, Rose and Lawton 2012). Previously, a potential disadvantage with implants and IUC after a medical abortion has been that insertion was scheduled at the follow-up visit with resulting lower rates of implant uptake. In this study, we could show that immediate insertion of the etonogestrel releasing implant results in a higher rate of implants being inserted and, reduces the risk of subsequent unintended pregnancy and abortion in the subsequent 6 months.

The stringent protocol with dating of pregnancy according to ultrasound and insertion of the implant at 1 hour after mifepristone adds to the robustness of this trial and assures reproducibility. The size and multicentre design of the study provide reassurance that the results are independent of treatment centre. The finding that the insertion rate is influenced by the timing of the scheduled insertion is important since it demonstrates that many women do not receive this method or any contraceptive method at all if insertion is delayed.

Loss to follow-up is a problem in studies on abortion. Many women do not wish to come for extra visits if they feel well and are certain of complete abortion. All centres in the study had access to patient records for the entire region (including maternity records) in which the abortion took place and the patient records were scrutinized for any surgical or medical intervention. The likelihood of missing on ongoing pregnancy, surgical interventions or extra visits is low although this cannot be completely excluded. Furthermore, the proportion of women who did not complete follow-up did not differ between groups and the results of the sensitivity analysis did not differ from the intention to treat or per protocol analysis.

Until the initiation and completion of this study there had been only small observational pilot studies and one randomized study of insertion of an etonogestrel releasing implant at the time of mifepristone administration for medical abortion (Church et al., 2010, Barros Pereira et al., 2015, Raymond et al., 2016). In accordance with our study these studies suggested that immediate insertion did not seem to impair efficacy of the medical abortion while resulting in higher insertion rates compared with delayed insertion in women with gestations up to 9 weeks. A small study including women up to 13 gestational weeks found that a significantly higher proportion of women with immediate insertion of an implants (n = 39) required repeat doses of misoprostol compared with delayed start of contraception (n = 39) (Church et al., 2010). However, in view of the small sample size it is not possible to determine if this observed difference was due to higher gestational age, the different medical abortion regimen used or simply a chance finding. It is also possible that the treatment allocation to immediate insertion may have influenced the physician to administer additional treatment. The same may be true for our study. While there was no significant differences between the groups in the proportion of women requiring extra doses of misoprostol for incomplete abortion, more women in the immediate group received extra treatment with misoprostol after the initial treatment day. However, there was no difference in unscheduled visits between study groups.

The only previously published randomized study included treatment with buccal misoprostol for medical abortion and was performed in Mexico and the United States (Raymond et al., 2016). In contrast to that study, we conducted ultrasound dating of all pregnancies and women with a gestational age beyond 64 days were excluded. Furthermore, the time for insertion of implants in tour study in the immediate group was 1 hour after ingestion of mifepristone, but time of insertion was not standardized in the study by Raymond et al., (2016). Thus, it is not possible to judge from the previous trial how soon after mifepristone the implant may be inserted. In our study there was a significantly lower rate of unintended pregnancy at 6 months follow-up in the immediate insertion group. This was not observed in the study by Raymond et al., and
the authors partly attribute this to the compensation that women received for participation and follow-up.

This study provides evidence for provision of contraceptive implants on the same day as administration of mifepristone for early medical abortion. Although this study was carried out in high resource settings the results of this study will have an important impact in all countries were medical abortions are performed and has the potential to increase both satisfaction for women and also increase the number of women who receive the most effective methods of contraception at the time of abortion. Ultimately, this should prevent more subsequent unintended pregnancies and abortions for women.

Acknowledgements

The authors would like to acknowledge the outstanding assistance of the study nurses and study nurse midwives and gynaecologists who have helped with recruitment, reminders for patients and data entry and Merck/MSD for supplying the implants used in this study.

Authors’ roles

K.G.D. was the principal investigator, developed the protocol and study design, directed implementation of the study, study funding and the data analyses. H.K.K. took part in the study design, was responsible for data analysis, and manuscript writing. H.K.K., H.H., C.N., S.C. and R.H. participated in the implementation of the study, and in data collection, and analysis. L.B. was the statistician and coordinated the data management, and participated in analysis. H.K.K., H.H., C.N., S.C., A.A. and I.J. were investigators, and were responsible for the supervision of the trial and their sites. All authors had access to the data, commented on the manuscript drafts, and approved the final version submitted.

Funding

This study was funded by the Swedish Research Council (2012–2014), Stockholm City County and Karolinska Institutet (ALF). The contraceptive implants were provided by Merck and supplied by MSD Sweden.

Conflict of Interest

H.K.K. and K.G.D. have received honorariums for giving lectures to MSD/Merck and have participated in the national (H.K.K. and K.G.D.) and international (K.G.D.) medical advisory boards for MSD/Merck. The contraceptive implants used in this study were funded by MSD/Merck and have participated in the national (H.K.K. and K.G.D.) medical advisory boards for MSD/Merck. H.K.K. and K.G.D. have received honorariums for giving lectures for their sites. All authors had access to the data, commented on the manuscript drafts, and approved the final version submitted.

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