Risk of miscarriage after previously induced abortion

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A Student Thesis (V-2015)

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List of contents:

Abstract 3

Introduction:

- Surgical induced abortion 4
- Medical induced abortion 5
- Miscarriage 6

Methods 9

Results:

- Risk of miscarriage after previous surgical termination 10
- Risk of miscarriage after previous medical termination 13

Discussion 14

Summary and conclusion 16

Reference list 17

Table 1 21
Abstract

**Background:** The risk of miscarriage is approximately 15 % of clinically recognized pregnancies, most of them appearing in first trimester. Miscarriage is known to be a distressing event in a woman’s life. Hence, it would be in the patients’ favor to find any association which reduces the risk of miscarriage. On the other hand, it is estimated that 30 – 50 % of all women undergo at least one induced pregnancy termination in their lifetime, making any link between miscarriage and induced termination important.

**Objectives:** The purpose of this literature review is to investigate if there is any increased risk of miscarriage in women who previously have undergone induced abortion. This thesis will review the impact both prior surgical and medical termination has on subsequent pregnancies in terms of miscarriage.

**Methods:** The searching tools Pubmed, Sciencedirect, McMastersPluus and Cochrane Library have been used. They have been non-systematically searched with the words: prior induced termination, surgical termination, medical termination, spontaneous abortion, miscarriage, pregnancy outcomes, reproductive outcomes and birth outcomes.

**Results:** Fourteen articles were reviewed. Twelve were looking at the association between surgical abortion and miscarriage and two at the association between medical abortion and miscarriage. Three review articles and eleven original studies are included. Two of the review articles conclude with increased risk of miscarriage after surgically induced abortion, while six of the nine primary studies looking at the risk of miscarriage after surgical abortion state increased risk. Of these six studies, two show increased risk of early miscarriage, two show increased risk of late miscarriage and the rest two studies show increased risk of miscarriage at non-specified gestational week. None of the two primary studies which looked at the impact medical abortion has on the risk of miscarriage show any increased risk. In total, eight of the fourteen studies conclude with increased risk of miscarriage after induced abortion.

**Conclusion:** It is suggestive that medically induced termination does not increase the risk of miscarriage in the subsequent pregnancies. However, there is difficult to draw a firm conclusion on the risk of miscarriage in women with prior surgically induced abortion based on the findings in this thesis. The results are conflicting and inconclusive. Further research, methodologically stronger, is needed to assess the risk.
Introduction

The risk of miscarriage is around 15 %, most of them appearing in the first trimester(1). Miscarriage is known to be a distressing event in a woman’s life. (2). Hence it would be in the patients’ favor to find any possible evidence which reduces the risk of miscarriage.

Today up to 42 million abortions are performed each year. It is well known that almost 1/3 to ½ of all women undergo at least one induced abortion during their lifetime (3). Worldwide estimation indicate that 28 of 1000 women per year experience induced abortion; half of these abortions are classified as unsafe, generally referring to terminations caused by illegal procedures (4). The rate and safeness of pregnancy terminations are important health indicators of one community since it is highly influenced by socioeconomically patterns. Africa has the highest rate of unsafe abortions, as much as 97% percent of the terminations is estimated to be unsafe. Western countries have the lowest rate of both safe and unsafe abortions. The rate of complications is determined by the procedures used to induce the abortion and the level of quality of the health care system where the termination is experienced. (4)

This thesis is mainly reviewing the terminations performed in the Western countries where it is generally two types of procedures to induce abortion: surgically induced and medically induced abortions. A brief description of these two methods follows.

Surgically induced abortion

Background Abortions induced through surgical methods are more invasive than medical terminations. The different surgical techniques available are dilatation and curettage, vacuum aspiration and hysterotomy. The following will describe each of the techniques. (3)

Surgical methods:

Dilatation and curettage: Cervix is dilated either with medical intervention or placing laminaria (thin seaweed sticks which expand in the presence of body moisture) through the vagina before inserting forceps or curette to remove the content in the uterus. Patient is in general anesthesia. (3)
Dilatation and electric vacuum aspiration: After cervix dilatation one cannula is inserted into the uterus. Connected to an electronic vacuum aspirator the cannula will be able to suck out the contents in the uterus. Patient is in general anesthesia. (3)

Manual vacuum aspiration: A hand-held vacuum syringe will evacuate the contents of the uterus into the syringe by suction. Local anesthesia is commonly used. (3)

Hysterotomy: This is a method similar to caesarian section where an abdominal opening is made to get straight into the uterus. The contents are directly removed from the uterus without going through the vagina. Rarely used. (3)

Complications:

Surgical termination is shown to be safe, effective and with minimal complications when done in the first trimester. It seems to be a link between the complication rate and the gestational length, the longer the gestation, the more increase in complications we see. The complications we may see are cervical laceration, uterine perforation, infection, hemorrhage and incomplete removal of the fetus and placenta. (3)

Medically induced abortion

Background: Medical terminations get increasingly available throughout the world. This is a non-surgical method of inducing abortion with the use of prostaglandins, anti-progestagens and/or methotrexate. This method is mostly used in first trimester terminations. Medical termination with the use of prostaglandins was developed in the 1970s, later in the 80s anti-progestagens became readily available and in 1993 methotrexate was introduced for the same purpose. (5) In Sweden the method got available from the 90s, while Norway, Denmark and Finland started using it after 2000. Nowadays there are several drugs in the market to induce termination; they may be used alone or in combination.

Pathophysiology of the drugs:

Prostaglandins: Prostaglandins are inflammatory mediators and are known to soften the cervix and cause uterine contractions. It can be used both orally and vaginally. The most known type is called misoprostol. Misoprostol has a success rate of 61% for single dose and 93% for repeat doses at inducing complete abortions. (5)
Anti-progestagens: Mifepristone, an anti-progestagen, acts by increasing the sensitivity to prostaglandins in uterus and inhibiting the progesterone and glucocorticoid receptors in uterus leading to breakdown of the maternal capillaries in the desidua, increased prostaglandin synthesis and inhibition of prostaglandin dehydrogenase. Mifepristone is shown to give higher abortion rate when given in combination with prostaglandins, more than 95% efficiency at up to 63 days of amenorrhea. (5)

Methotrexate: Methotrexate is a folic acid antagonist which is cytotoxic to the trophoblasts. Used in combination with misoprostol it is highly effective, leading to a 98% complete abortion rate if misoprostol is administered 7 days after methotrexate.(5)

Sideeffects and complications:
Side effects of medical method are heavy bleeding, nausea, pain, vomiting and diarrhea. Medical termination is found to give longer duration of post termination bleeding compared to surgical procedures.

The most important, but rare complication of medically induced termination is failed abortion where the fetus continues growing. (5)

Miscarriage

Definitions, symptoms and signs:
Miscarriage is defined as inevitable spontaneous fetal loss caused by natural causes before the 20th – 22th gestational week. Spontaneous abortion is a synonym to miscarriage. ICD10 classifies spontaneous abortion into three groups:

- Complete spontaneous abortion
- Incomplete spontaneous abortion
- Missed spontaneous abortion

In the complete spontaneous abortion the products of conception are expelled completely out of the uterus without any remaining. If the patient has retained tissue in the uterus after pregnancy loss the diagnosis of incomplete spontaneous abortion is to be applied. In the
newest ICD10 missed spontaneous abortion is described as a condition of retention of an abortus which has been dead for at least 4 weeks. (6)

A pregnancy loss can proceed clinically unnoticed the first weeks of gestation if the pregnancy is not detected by an hCG test before the onset of the miscarriage. Signs of a miscarriage can include vaginal spotting or bleeding, abdominal pain or cramping, and fluid or tissue passing from the vagina, though a missed miscarriage can lack any signs and symptoms. (6)

**Epidemiology:**

A study done on the incidence of spontaneous abortion with a high sensitivity hCG test among women who tried to conceive detected a miscarriage rate of 22% before the pregnancy was clinically detectable. The total incidence of miscarriage, including the clinically detected ones were estimated to be 31% of the total of 198 identified pregnancies. (7)

**Etiology:**

There is ongoing research on a large scale of any risk factors associated with miscarriage. Some of the possible risk factors mentioned in the literature are caffeine, obesity, alcohol, maternal age, tobacco, autoimmune sykdom (coliaki blir for snevert-selv om det sikkert er riktig; diabetes, SLE ….er også risikofaktorer), fetal abnormalities, uterine anomalies, infertility and earlier induced termination.

A large population based study from Denmark consisting of more than 600 000 women concluded that there is high level of fetal loss in women in their late 30s or older. (8) On a similar note a population based cohort study from 2005 found miscarriage to be moderately increased in women with celiac disease ( Rate ratio 1,31 ; 95% CI (1,06 to 1,61) ). (9)

A meta-analysis from 2006 found significantly higher odds of miscarriage among the women with BMI ≥ 25 compared to normal weight women and concluded that there may be an association between high body mass index and miscarriage risk. (10) A systematic review from 2011 concludes that obesity ( BMI ≥ 28) is associated with increased miscarriage rate in women compared to non-obese women (OR: 1,31; 95% CI (1,18 to 1,46) ). Since the results are considered preliminary the same review is asking for larger studies on this association to verify the results. (11)
When searching for fetal abnormalities / chromosome defects linked to miscarriage, most of the recent studies which came up were done on recurrent miscarriages. This is believed to be the case because the recurrence risk in sporadically occurring miscarriage is low (12) and there are already many well established studies from the 80s and 90s which have shown the link between miscarriage and fetal abnormalities. One such study from 1980 showed that 493 of 1000 spontaneous abortions were having abnormal chromosome constitution (13). Fetal abnormality is one of the most well established risk factors of miscarriage. Another well-known risk factor is uncorrected uterine anomalies. The increased risk of miscarriage in this patient population is estimated to be 36 % in one study from 1991 (14). This study and a literature review from 2004 found septate uteri to be the uterine anomaly with the highest abortion rate (15).

Smoking is yet another risk factor associated with miscarriage. A systematic review and meta-analysis conducted in 2013 found that both maternal smoking and secondhand smoking during pregnancy increased the risk of miscarriage significantly (16).

Besides maternal BMI, maternal age, fetal chromosomal defects, uterine abnormalities and smoking previous miscarriage and subfertility are well known risk factors for having miscarriage. A study from 2000 found that subfertility defined as a delay of 1 year or more before recognizable conception gave a significantly higher miscarriage risk compared to fertile women. (17) A literature review from 2002 which has reviewed the present literature assessing risk factors of miscarriage suggests that there is a higher risk of miscarriage among the women who have experienced miscarriage before and that the risk increases with the number of previous cases. (18) A large population based study from 2007 concluded the same finding that the increase doubled after one previous miscarriage. The same study also found that the increase in risk doubled for those who had taken more than a year to conceive compared to those who took less than 3 months. (19)

The link between miscarriage and alcohol and caffeine remains inconclusive in systematic reviews and needs further investigative methodically strong studies. (20, 21)
Methods

MacMasters Plus, Pubmed, Science Direct and Cochrane were searched with these words: prior induced termination, surgical termination, medical termination, spontaneous abortion, miscarriage, pregnancy outcomes, reproductive outcomes and birth outcomes. Most of the studies that assessed the association between induced abortion and spontaneous abortion were included in this literature review. There were no exclusion criteria, both old and new studies with different methodological approach, different surgical techniques and different gestational age at termination have been included. In total 14 studies are reviewed.
**Results**

Fourteen studies were reviewed. Nine primary studies and three review articles which also included some of the primary studies assessed the association between surgically induced abortion and miscarriage. Two primary studies looked at the impact medically induced abortion has on miscarriage. Of the three reviews one shows increased risk of 1.trimester miscarriage after a prior induced abortion with vacuum aspiration, while one shows increased risk of 2.trimester miscarriage after dilatation and curettage. One of the reviews states no increased risk. As for the primary studies none show any increased risk of miscarriage after medical abortion, two conclude with increased risk of 1.trimester miscarriage after surgical abortion, two state increased risk of late miscarriage after surgical abortion and one shows that there is increased risk of both early and late miscarriage in women with multiple prior surgical abortion. There is one primary study which doesn’t specify the gestational week of the miscarriage, but has shown that there is increased risk when the interpregnancy interval is less than 3 months. In total six of the nine primary studies looking at surgical abortions state increased risk of miscarriage, none of the two primary studies looking at medical abortions show increased risk and two of the three review articles conclude with increased risk of miscarriage after surgical abortion. These results are shown in table 1. I will hereby briefly review the results of each study included in this thesis.

**Risk of miscarriage after previous surgical induced abortion**

A prospective study from the US published in 1979 (Harlap. S), observing 31 197 pregnant women has evaluated the impact induced abortion has on miscarriage. They found no increased incidence of miscarriage among women who opted for induced termination in their second pregnancy having one livebirth in their first pregnancy, but the risk of midtrimester miscarriage was increased in nulliparous women who underwent induced abortion. The risk increased with the number of induced abortions after adjusting for age, social and demographic factors. However the relative risk became statistically insignificant for those who underwent induced abortion after 1973 with gentler techniques (Before 1973:RR 3,27. CI (1,72 – 6,23), after 1973: RR 1,42, CI (0,72 – 2,65). Almost all the terminations were done in the first trimester and the technique of choice after 1973 was suction curettage with laminaria dilatation which replaced instrumental dilatation used before 1973. This study thus
concluded that there is no increased risk if the induced abortion is done with gentle procedures. (22)

One retrospective case-controll study, also from the US (Levin. A) published the year after challenged the previous results and concluded that a history of multiple induced abortions is a risk factor for subsequent pregnancy loss up to 28 weeks gestation. A total of 1312 women were included in this study. (23)

A pregnancy cohort study from 2003 done in China has evaluated if there is any increased risk of miscarriage after a first trimester surgical termination. This study was conducted during a 5 years period, from 1993 to 1998, with 2891 pregnant women. The pregnant women were enrolled in a cohort group consisting of pregnant women with prior induced termination through vacuum aspiration and a reference group consisting of primigravida. The odds ratio of miscarriage between these two groups was calculated to be 1.55 (95% CI 1.08 – 2.23) after controlling for the confounding factors. This study article concluded that having first trimester termination through vacuum aspiration increased the risk of first trimester miscarriage in the subsequent pregnancy, but not of second trimester miscarriage (24). This is contradicting to the WHO report from 1979 which suggested that second trimester miscarriage was more common in women who had a history of induced abortion compared to primigravida. (25)

A Danish cohort study from 2000 consisting of 61753 women who were primigravidas in the years 1980 to 1982, with 12-14 years follow up time studied the risk of having miscarriage after induced abortion as a function of the interpregnancy interval (time between the induced abortion and the subsequent pregnancy). Their study showed that the risk of miscarriage after prior first trimester termination is increased when the interpregnancy period is less than 3 months independent of the surgical method of use (OR=4.0, 95% C.I.=1.98± 8.31)). The number of induced abortions and the gestational age when the termination was conducted was found not to affect the risk. (26)

An American retrospective study published in 2002 has assessed the impact of second trimester dilatation and evacuation on subsequent pregnancy outcomes, miscarriage being one of those. Ninety-six subsequent pregnancies in 81 women following prior second trimester dilatation and evacuation were identified and assessed. This study concludes that there is no
increased risk of second trimester miscarriage after a previous second trimester dilatation and evacuation. (27)

One similar American retrospective study published in 2007 and reviewing 114 subsequent singleton pregnancies after prior dilatation and curettage found no difference in the incidence of miscarriage compared to overall expected incidence found in the literature. (28)

A population based study consisting of 2364 pregnancies among women with one induced abortion has been conducted in Finland over a period of 12 years (1989 to 2001). This study, published in 2006, has investigated if prior induced abortion is an independent risk factor for different pregnancy outcomes, miscarriage being one of those. They found a miscarriage rate of 40.2% in the obstetric history of women who had a previous induced abortion. (29)

A study from 2005 done in the US has aimed at describing the obstetric outcomes in patients with prior surgical abortion at ≥ 20 weeks gestation. The surgical method of choice was dilatation and evacuation. 121 pregnancies in 89 women were included in this study and first trimester miscarriages occurred in 13 of these patients which is 10.3% of the patient group. There were no cases of fetal loss in the second trimester. (30)

An UK population based case-control study from 2007 looking at the risk factors for first trimester miscarriage shows that women who underwent one prior induced termination had increased risk (OR 1.72 (1.27–2.31)), this increase in OR disappeared in women who had undergone two or more prior terminations. 603 cases and 6116 controls were included in this study. The method of induced termination is not specified. (19)

An American review from 1982, reviewing 10 different studies, evaluating the impact of vacuum aspiration termination on future child bearing concludes that there is no increased risk of having second trimester spontaneous abortion after a prior first trimester termination through vacuum aspiration. (31)

An article from 1990 reviewing the effect of induced abortion on future reproduction writes that most studies have concluded that vacuum aspiration carries no increased risk of spontaneous abortion, while dilatation and evacuation, which as opposed to vacuum aspiration more commonly is done in second and not first trimester, is associated with significantly increased risk of spontaneous abortion (32)
The latest review article included in this literature review, an article from 2010 assessing 3 systematic reviews and 2 primary studies on the association between induced abortion and miscarriage writes that no clear cut conclusions can be made from the reviewed papers as the literature is conflicting. (33)

**Risk of miscarriage after previous medical induced termination**

A population based study from 2007 done in Denmark consisting of 11,814 pregnancies has obtained information about the subsequent pregnancies in women who have undergone first trimester medical termination. Risk of miscarriage is one of the outcomes which have been analyzed. The risk is compared to women who have undergone surgical termination and not women without any past history of termination. After adjusting for confounding variables the risk of having spontaneous abortion was not found to be significantly increased. The total percentage of miscarriage in the group of women with prior medical termination was estimated to be 12.2%. As previously mentioned in this literature review, the rate of miscarriage in healthy women is ranged to be between 11-22%. The percentage found in the population study therefore doesn’t raise any concern. The authors’ conclusion is that there was no evidence that first trimester medical termination increases the risk of miscarriage. (34)

A French prospective case-control study published in 2009 has examined whether induced abortion with misoprostol either in the first or second trimester is a risk factor for late abortion in the following pregnancies. 245 cases consisting of women with singleton deliveries between week 16 – 18 of gestation because of late miscarriage, preterm delivery or preterm premature membrane rupture were compared to 490 controls consisting of women with singleton deliveries after 37 weeks of gestation. 16, 3% of the cases and 11, 5% of the controls had a past history of induced termination with misoprostol, either alone, with mifepristone or for cervical ripening before dilatation and curettage. This study concludes that their study can give some reassurance that there is no increased risk of subsequent miscarriage after prior induced abortion with misoprostol. (35)
Discussion

In my review I have looked at the impact surgical and medical abortion have on both early and late miscarriage. There were two primary studies and one review article that showed increased risk of 1.trimester miscarriage, two primary studies and one review article which stated increased risk of 2.trimester miscarriage, while I didn’t find any increased risk of miscarriage after medical abortion. The three review articles included did have some of the primary studies I have looked at. Since medical abortion is a relatively new method there was not many studies on that and I couldn’t find any review articles on that area, however both the primary studies included have the advantage of being done in the later years, thus making them reliable. Coming to the studies of surgical abortion my findings are sort of in agreement with the review articles included in this thesis as my thesis also finds eight of the twelve studies showing increased risk of miscarriage. Nevertheless, I find it difficult to state a firm conclusion of increased risk after prior surgical abortion based on my findings since there are many conflicting results and my included studies don’t consist of homogenous study groups in terms of trimester of induced abortion, trimester of miscarriage and the methods used to induce abortions. It seems clear that medical abortion is safe on future pregnancies, maybe because all are done in the 1.trimester.

Reviewing the association between induced abortion and miscarriage is challenging since the women who undergoes induced abortion is thought to naturally have a greater fertility compared to those who experience miscarriage. On the other side both fecundity and early miscarriage is methodologically difficult to measure that can lead to an underestimation of the fertility among the women with higher rate of miscarriage. A conflicting situation in these studies is that for some women who have induced abortion their pregnancy would have ended in a spontaneous abortion anyways. Since prior miscarriage is believed to be an independent risk factor for future miscarriage and since women with induced abortion and women with miscarriage is believed to be different groups in terms on fertility it makes it important yet complicated to differentiate these two groups of women. It is hard to adjust for these factors which in most cases remains unknown. There is also a possibility that many women with mid-trimester miscarriages could be missed out if they opt for early induced abortion.

Another problem that arises in this type of studies is the decision of when to include the women in the study so that we don’t miss clinically undetectable miscarriages. In prospective...
studies which start in the first prenatal visit which normally happens to be in the second trimester the women who had early miscarriage are already eliminated. (37)

There are also challenges in how to stratify the case and control groups included in studies assessing the association between induced abortion and miscarriage. How to determine the most comparable groups for getting the most unbiased results still remains undiscussed in most of the literature described in this article. Most of the studies have compared nulliparous women with one or more induced abortions to primigravida women, some have compared the groups accordingly to their gravity. None of the groups would be completely comparable in terms of fertility and risk factors, since a woman with one induced abortion is different to both a primigravida, a nulliparous with prior miscarriage and a multigravida with one childbirth.

Confirmation of induced abortion through interviews in the old studies and in the new studies in countries without accurate registrations through medical chords makes the studies rely fully on the information from the patients, which could give biased findings.
Summary and conclusion

Fourteen articles were reviewed. Five prospective studies, six retrospective studies and three review articles are evaluated. Twelve were looking at the association between surgical abortion and miscarriage and two at the association between medical abortion and miscarriage. Three review articles and eleven original studies are included. Two of the review articles conclude with increased risk of miscarriage after surgically induced abortion, while six of the nine primary studies looking at the risk of miscarriage after surgical abortion state increased risk. Of these six studies, two show increased risk of early miscarriage, two studies show increased risk of late miscarriage and two studies shows increased risk miscarriage with non-specified gestational week. None of the two primary studies which looked at the impact medical abortion has on the risk of miscarriage show any increased risk. In total, eight of the fourteen studies conclude with increased risk after prior termination.

On the basis of the findings from these studies the conclusion of this literature review article would hence be that having medical abortion is highly suggestive of no increased risk of miscarriage in the subsequent pregnancies. The patients should be advised to wait minimum 3 months until the next pregnancy after a prior termination since short interpregnancy interval is associated with increased risk of miscarriage. There seems to be a correlation between the method used to terminate and the risk of subsequent miscarriage, the gentle and safe surgical procedures used in the developed countries in the first trimester today seems not to affect the miscarriage risk. More methodologically strong large-scale studies looking at the risk of having miscarriage are desirable. No conclusion can safely be made of the impact surgical termination has on the risk of having miscarriage in the subsequent pregnancies from the studies included in this article.
Reference list


