Prevalence of intrauterine adhesions after termination of pregnancy: a systematic review

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ABSTRACT

Objectives: Termination of pregnancy (TOP) is one of the most performed interventions in women worldwide: approximately one in three women will have at least one TOP in their reproductive life. Intrauterine adhesions (IUAs) have been reported as a possible complication after TOP, but their prevalence has not been established, as women are not routinely evaluated. IUAs are associated with menstrual disturbances, infertility and obstetric complications.

Methods: We searched Ovid MEDLINE, Ovid EMBASE and CENTRAL from inception until November 2015 for studies evaluating women following TOP. We selected studies in which women were evaluated consecutively, independently of symptoms, by hysteroscopy or hysterosalpingography (HSG), for the presence of IUAs.

Results: After an extensive review of the literature, no studies were found that evaluated women after medical TOP and no randomised trials following surgical TOP. Only two prospective cohort studies were identified. In the first, IUAs were detected in 21.2% of women evaluated by hysteroscopy following first trimester surgical TOP; adhesions were moderate to severe in 48%. In the second, IUAs were detected in 16.2% of women evaluated by HSG after second trimester TOP by intra-amniotic prostaglandin induction followed by D&C; a pathologically wide internal cervical os was observed in 12%.

Conclusions: This systematic review suggests a link between TOP and adhesion formation, but, according to the scientific literature and despite new diagnostic facilities, the relationship between the methods of TOP and IUA formation remains unclear. Nevertheless, the reported frequency is in accordance with that found in women following D&C for miscarriage. Further research is required.

Introduction

Every year some 36–53 million pregnancies are terminated worldwide, making termination of pregnancy (TOP) one of the most performed interventions on women of reproductive age [1,2] and a costly public health problem [3].

Approximately 90% of terminations are performed because of unintended or unwanted pregnancy, and only a small proportion because of fetal abnormality or serious illness of the woman [1]. It is estimated that 30–50% of women will undergo at least one TOP during their lifetime [1,4]. Surgical TOP by dilation and sharp, blunt or suction curettage (D&C) has been the standard method of management since the 1960s. D&C is effective and relatively safe, and has a low rate of short-term complications [5–7].

Intrauterine adhesions (IUAs) are abnormal fibrous connections joining tissue surfaces of the uterine cavity [8]. IUAs can be asymptomatic and remain undiscovered, but they are commonly associated with menstrual disorders, infertility and obstetric complications [9]. Over the last decade, medical TOP, primarily with mifepristone and misoprostol, has emerged as a non-surgical option.

In 1927, Bass was the first to report IUAs as a possible long-term complication after surgical TOP [10]. The possibility of adhesion formation following surgical TOP has been reported ever since, but the prevalence has not yet been determined. We conducted this systematic review to determine the prevalence of IUAs after first and second trimester medical and surgical TOP and to identify possible risk factors.

Methods

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Institutional review board approval was not sought, since all data were extracted from previously published data.

Systematic search

A systematic literature search was carried out to identify relevant papers. The following terms were used in the title or abstract, or as MESH terms: “TOP”, “induced abortion”, “abortus provocatus”, “therapeutic abortion”, “pregnancy termination”, “abortion”, “embryotom”, “fetus wastage”, “dilatation and curettage”, “vacuum aspiration”, “curettage”, “evacuation”, “adhesions”, “asherman”, “synechiae”, “misperosol”, “medical management”. 

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Supplemental data for this article can be accessed here.

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The following electronic databases were searched from inception to November 2015: MEDLINE (Ovid), EMBASE (Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms were modified according to database requirements. The reference lists of the studies examined to determine study eligibility were hand-searched for relevant studies.

**Paper selection procedure**

All cohort studies, clinical trials and randomised controlled trials (RCTs) reporting the prevalence of IUAs in women after TOP were considered for inclusion. Original articles had to be published as full papers in peer-reviewed journals; language restrictions were not applied. Abstracts of conference presentations or dissertations, unpublished data, and case reports were also considered for inclusion.

Two authors (A.H. and D.F.) independently selected the studies in a two-stage process. First, eligibility was assessed based on the title and abstract. Second, examination of the full manuscript was performed to determine study eligibility. An attempt was made to contact authors when additional information was needed.

**Eligibility criteria**

Studies reporting the prevalence of IUAs in women after first or second trimester TOP were considered for inclusion. TOP was defined as the intentional termination of a vital pregnancy for therapeutic or elective reasons. Women had to be included consecutively and evaluated for the presence of IUAs, independently of symptoms. Studies evaluating women after other conditions, including spontaneous, incomplete, delayed or recurrent miscarriage, were excluded because of the possibility of difference in adhesion formation.

The presence of IUAs had to be studied as a primary or secondary outcome parameter. Evaluation of the uterine cavity by hysteroscopy or hysterosalpingography (HSG) for the presence of IUAs following TOP was obligatory. Because of differences in diagnostic accuracy between the diagnostic modalities, women were divided by the method of evaluation used. Women were also divided into a first or second trimester group and, depending on the treatment received, into a medical or surgical group.

**Outcome measures**

The primary outcome measure was the presence of IUAs and, if available, the extent and degree of the reported IUAs. There is no internationally accepted and validated classification system: different systems are currently used. In order to allow eventual meta-analyses, we re-categorised the degree and severity of IUAs into three clinical categories based on data extracted of the different classification systems.[11] The categories were defined as mild, moderate or severe depending on the scale of the different classification systems.

**Data extraction and assessment of methodological quality**

The following information was extracted from the included studies: publication year, study design, inclusion and exclusion criteria, patient characteristics, first or second trimester gestation, treatment received, duration of follow-up, time between treatment and evaluation, method of evaluation (hysteroscopy or HSG), and IUAs occurrence rate. If available, the degree and extent of IUAs were also extracted. Potential prognostic factors were analysed if registered.

The methodological quality of the selected papers was evaluated independently by two reviewers (A.H. and D.F.) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist.[12] The checklist consists of key elements that should be transparently addressed and reported concerning objectives, study design, patient selection, verification, statistical method, outcome data and main results, limitation and generalisability. During evaluation, items are rated “1” if the content is transparently and adequately described, “0” if items were inadequately or insufficiently reported, and “NA” if not applicable. The final score is the number of items scored “1”, with a maximum of 34.

**Data analysis**

All data were entered and analysed using SPSS, version 16.0 (SPSS, Chicago, IL). Data are presented as proportions with standard deviations, frequencies and/or percentages for dichotomous variables. The prevalence of IUAs was calculated for each study separately and, if justified, pooled, with 95% confidence intervals.

**Results**

Using the limitation “human only”, the search strategy yielded 1547 citations, including 372 duplicates. The flow diagram illustrating the selection procedure is shown in Figure 1. Of the 1175 remaining articles, 1113 were excluded after title and abstract selection, as they did not study the presence of IUAs following TOP. Seven articles were not available for full manuscript review.[13–19]

After reviewing the full manuscripts of the remaining 55 articles, 11 (clinical) reviews were excluded, as they did not report the presence of IUAs following TOP.[20–30] Twenty-five articles reported solely on women with symptoms and/or IUAs.[8,31–54] Twelve articles reported the prevalence of IUAs after different gynaecological conditions and were therefore excluded.[55–66] Three articles reported on women following TOP but were excluded as not all participants were evaluated for the presence of IUAs.[43,67,68] Furthermore, three case reports were excluded.[69–71] One remaining article [72] and one additional article retrieved from the reference list [73] reported on IUAs following TOP.

**Characteristics of included studies**

Only two prospective studies fulfilled the inclusion and exclusion criteria.[72,73] No studies were found that reported the prevalence of IUAs following medical TOP. The characteristics of the two included studies are shown in Table 1.

The article of Salat-Baroux et al. [73] analysed the frequency of complications in 118 women after first trimester
surgical TOP. Women before 10 weeks of gestation were treated by aspiration (n = 55), curettage (n = 2) or both (n = 61). All women received norethindrone for two menstrual cycles and underwent a diagnostic hysteroscopy 15 days after the surgical procedure. Thereafter, hysteroscopic evaluation was performed weekly until a normal uterine cavity was seen; in some cases sonography or hysterography with biopsies was also performed. The methodological quality was assessed using the STROBE checklist (Table S1). The study had a score of 11 out of a maximum of 34.

In the second study, a prospective cohort study by Kajanoja and Aantaa,[72] 395 nulliparous women following second trimester TOP were invited for evaluation. TOP was performed between 13 and 20 weeks of gestation by intra-amniotic prostaglandin induction. All women underwent a D&C irrespective of completeness, even after expulsion of the fetus. An HSG for detection of changes in the cervical canal was performed in 173 women (43.8%) between the 5th and 12th day of the menstrual cycle, 5–8 months after the surgical procedure. The study had a score of 14 using the STROBE checklist (Table S1).

As the time and method of evaluation, the study population and the accuracy of the diagnostic methods applied differed completely, it was not justified to pool the results. The results of the included studies are therefore presented separately.

Prevalence, extent and degree of adhesions

Details of the included studies are shown in Table 1. In the study of Salat-Baroux et al.,[73] IUAs were detected by hysteroscopy in 25 of 118 women (21.2%) following first trimester surgical TOP. The hysteroscopic findings of 26 women (22%) were not reported, and were therefore considered normal. No difference in IUAs was detected in the aspiration group compared with the curettage and combined groups in this study, although the groups were small. The extent and degree of IUAs were classified based on intrauterine involvement: adhesions with only one wall involvement were reported in 13 women (52%), and as bridge-like formations in 12 women (48%).[73]

Thirty women (25.4%) received a second hysteroscopic examination, 17 (14.4%) a third and 7 (5.9%) a fourth; intra-uterine abnormalities were reported in, respectively, 81.8%, 52.9% and 0% of women. All women had a normal uterine cavity after their first menstrual period. Other uterine abnormalities besides IUAs were reported on women with symptoms and/or IUAs (n = 25). Reported on women with IUAs after different conditions (n = 12). Not all women following TOP were evaluated (n = 3). Case report (n = 3).

In the study of Kajanoja and Aantaa,[72] IUAs were detected in 28 of 173 women (16.2%) evaluated by HSG after second trimester TOP by intra-amniotic prostaglandin

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Figure 1. Flow diagram showing the selection procedure of articles reporting on IUAs after TOP.
induction followed by D&C. In 21 of 173 women (12.1%), a pathologically wide internal cervical os was observed.

Discussion

Findings and interpretation

No studies were identified that reported the prevalence of IUAs following medical TOP. Only two prospective studies were included. The prevalence reported in the two studies is in accordance with the prevalence of IUAs following D&C for miscarriage.

The prevalence of IUAs in women following first trimester surgical TOP evaluated by hysteroscopy was 21.2%. This prevalence is an underestimation: in 22% of women the hysteroscopic findings were not reported, and were therefore considered normal. The extent of the IUAs was mild in 52% and moderate to severe in 48%. Residual tissue and blood clots were encountered in 40.7%. Residual tissue and villous elements are considered possible risk factors for adhesion formation by promoting fibroblastic activity and collagen formation.[9] It was not possible to investigate other potential risk factors. A significant percentage of women (25.4%) underwent more than one hysteroscopic evaluation.

The prevalence of IUAs in women following second trimester TOP by intra-amniotic prostaglandin induction followed by D&C was 16.2%. A pathologically wide internal cervical os was observed in 12% during HSG, but the clinical significance is unknown, as a pathologically wide os is not pathognomonic of cervical incompetence. D&C can have a negative impact on cervical competence: an increased risk of subsequent preterm birth was reported in a systematic review and meta-analysis following D&C for miscarriage and TOP.[74]

Strengths and weaknesses of the study

To the best of our knowledge, this is the first published systematic review reporting the prevalence of IUAs following TOP. We performed an extensive search of the literature to determine the prevalence of IUAs after surgical and medical TOP. The methodology and quality of the included studies were analysed. All participants were included prospectively and analysed independently of symptoms. Studies including only symptomatic women were excluded to minimise selection bias. Although there are differences in diagnostic accuracy between hysteroscopy and HSG, both are validated methods for IUA ascertainment and were included in the review.

This review has several limitations. Unfortunately, no studies were found in which women were reviewed after medical TOP for the presence of IUAs. Only two prospective cohort studies, evaluating a total of 291 women and published in the 1980s, were identified. No RCTs are available on this topic; cohort studies are less reliable to determine treatment-linked factors. The methodological quality of the included studies was poor, with a score of 11 and 14 out of a maximum of 34. It was not possible to evaluate the risk and prognostic factors. Despite an extensive search of the literature, it is possible there are unpublished or undetected studies on this subject.

In the study of Salat-Baroux et al.[73] all women underwent first trimester surgical TOP, but women were treated...
by aspiration, curettage or both, which could have influenced the reported results. Furthermore, women received norethindrone following surgical treatment. The hysteroscopic findings were not reported in 22% of cases (Table 1), and were therefore considered normal. Residual tissue and blood clots could have contributed to adhesion formation and influenced the reported prevalence of IUAs. Because of (suspected) intrauterine abnormalities, a significant percentage of women received additional interventions: hysteroscopy, sonography or hystegraphy with biopsies. All women had a normal uterine cavity after their first menstrual period. Interpretation of these results is difficult because the impact of the performed investigations on adhesion removal is unknown. IUAs are thought to develop directly within the first 5–7 days after surgery or trauma to the endometrium, with development of the adhesion commencing during surgery itself. Probably, IUAs were removed (un)intentionally by the hysteroscopic procedure. It is unlikely that the adhesion would have disappeared.

In the study of Kajanoja and Aantaa,[72] only 43.8% of the cohort was evaluated following second trimester TOP by intra-amniotic prostaglandin induction followed by D&C; a significant percentage of eligible women were not evaluated. It remains unclear why only this group was evaluated and whether the group is a representative selection of the cohort. The reported prevalence, as an indication of the real prevalence, should be interpreted with caution. Although all included women underwent TOP, there was insufficient information regarding demographic characteristics and potential influencing factors including age, parity, inflammation and infection, number of previous TOPs or miscarriages, and applied surgical technique. No distinction could be made between women with and without previous D&C and women requiring a second procedure, and these are known risk factors for adhesion formation.[11]

The studies were conducted and published in the 1980s. There are important differences in diagnostic methods used today. Hysteroscopy was conducted at a time before continuous flow hysteroscopy was available, making the visibility and interpretation of the images during the procedure more difficult. HSG is now considered a less suitable diagnostic tool for this indication. Furthermore, the accuracy of the diagnostic tools has significantly improved over time, making interpretation of the reported results extremely difficult. These and other unknown risk factors might have significantly biased the results in an unknown way; therefore, solid conclusions cannot be drawn. On the basis of all these points, the results should be interpreted with caution, since they may not be completely reliable.

Differences in results and conclusions

The aetiology of IUAs or Asherman’s syndrome is multifactorial and has multiple predisposing and causative factors.[9,75,76] Any event that causes damage to the endometrium may lead to development of IUAs through destruction of the basal layer of the endometrium. In the healing process, opposing walls of the uterus adhere together causing minimal, marginal or complete obliteration of the uterine cavity.[9,76,77] Pregnancy is the major predisposing factor, reported in up to 91% of cases.[9] Gestational changes result in softening of the uterus; the traumatising effect of (surgical) treatment is more intense. Furthermore, low estrogen status at the time of intervention or immediately afterwards increases vulnerability, as the endometrium depends on estrogen for regeneration.[78]

Surgical TOP is reported as the predisposing factor in 15–30% of women diagnosed with IUAs, suggesting that it is an important aetiological cause.[40,78–82] The prevalence of IUAs following TOP is difficult to determine, as only symptomatic women are generally evaluated. Theoretically, D&C for miscarriage is considered a different clinical condition, although the surgical intervention is identical. The prevalence of IUAs following D&C for miscarriage is 19%; the extent of IUAs was mild in 58% and moderate to severe in 42%.[11] The prevalence and extent of IUAs after surgical TOP reported in this article are similar.

Relevance of the findings: implications for clinicians and policy-makers

It is surprising that there is such little information on long-term complications following TOP, one of the most performed interventions worldwide. Surgical TOP is considered a safe procedure. However, the scope of complications is large, both numerically and economically. The most reported factors influencing immediate complications are gestational age at the time of the procedure, technique, age and parity.[20,83] Medical TOP, with mifepristone and misoprostol, has proven to be safe and efficient, with low short-term complications.[84] Theoretically, the chance of IUAs formation seems lower after medical management, but this requires confirmation. Long-term complications develop over many years before an effect is seen. Studies to detect any late complications must be rigorously designed and have structured follow-up.

IUAs can be a source of major concern because of their potential consequences on the well-being of women.[8] After treatment, reproductive performance correlates with the severity of IUAs. The clinical relevance, significance and impact of IUAs on further reproductive performance still need to be determined.

Women undergoing TOP tend to be young and in their early reproductive life, meaning that safety, well-being and possible long-term complications are important health care concerns. The incidence of TOP is inversely associated with the level of contraceptive use.[85] Approximately half of unintended pregnancies are the result of contraceptive failure.[86] TOP can be reduced by providing educational support and promoting effective contraceptive methods.

Unanswered questions and future research

The possibility of IUAs following TOP presents additional research on the topic. The prevalence of IUAs following surgical or medical TOP remains undetermined. Large RCTs with structured follow-up are needed to identify risk and prognostic factors.

Conclusion

TOP is one of the most performed interventions worldwide. There is a link between surgical TOP and adhesion...
formation, but, according to the scientific literature and despite new diagnostic facilities, the relationship between IUAs and the different methods of TOP remains unclear. Nevertheless, the reported prevalence is in accordance with the prevalence of IUAs in women following D&C for miscarriage. Medical TOP, theoretically a less invasive option, should be considered a real alternative, while further research using modern diagnostic facilities is urgently needed.

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