Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome

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BACKGROUND: Approximately 15–20% of all clinically confirmed pregnancies end in a miscarriage. Intrauterine adhesions (IUAs) are a possible complication after miscarriage, but their prevalence and the contribution of possible risk factors have not been elucidated yet. In addition, the long-term reproductive outcome in relation to IUAs has to be elucidated.

METHODS: We systematically searched the literature for studies that prospectively assessed the prevalence and extent of IUAs in women who suffered a miscarriage. To be included, women diagnosed with a current miscarriage had to be systematically evaluated within 12 months by hysteroscopy after either spontaneous expulsion or medical or surgical treatment. Studies that included women with a history of recurrent miscarriage only or that evaluated the IUAs after elective abortion or beyond 12 months after the last miscarriage were not included. Subsequently, long-term reproductive outcomes after expectant (conservative), medical or surgical management were assessed in women with and without post-miscarriage IUAs.

RESULTS: We included 10 prospective studies reporting on 912 women with hysteroscopic evaluation within 12 months of miscarriage and 8 prospective studies, including 1770 women, reporting long-term reproductive outcome. IUAs were detected in 183 women, resulting in a pooled prevalence of 19.1% [95% confidence interval (CI): 12.8–27.5%]. The extent of IUAs was reported in 124 women (67.8%) and was mild, moderate and severe respectively in 58.1, 28.2 and 13.7% of cases. Relative to women with one miscarriage, women with two or three or more miscarriages showed an increased risk of IUAs by a pooled OR of 1.41 and 2.1, respectively. The number of dilatation and curettage (D&C) procedures seemed to be the main driver behind these associations. A total of 150 congenital and acquired intrauterine abnormalities were encountered in 675 women, resulting in a pooled prevalence of 22.4% (95% CI: 16.3–29.9%). Similar reproductive outcomes were reported subsequent to conservative, medical or surgical management for miscarriage, although the numbers of studies and of included women were limited. No studies reported long-term reproductive outcomes following post-miscarriage IUAs.

CONCLUSIONS: IUAs are frequently encountered, in one in five women after miscarriage. In more than half of these, the severity and extent of the adhesions was mild, with unknown clinical relevance. Recurrent miscarriages and D&C procedures were identified as risk factors for adhesion formation. Congenital and acquired intrauterine abnormalities such as polyps or fibroids were frequently identified. There were no studies reporting on the link between IUAs and long-term reproductive outcome after miscarriage, while similar pregnancy outcomes were reported subsequent to conservative, medical or surgical management. Although this review does not allow strong clinical conclusions on treatment management, it signals an important clinical problem. Treatment strategies are proposed to minimize the number of D&C in an attempt to reduce IUAs.

Key words: adhesions / infertility / miscarriage / reproductive outcome / systematic review

Introduction

The term miscarriage is used to describe a pregnancy that fails to progress before the middle of the second trimester (24 weeks of gestation), resulting in the death, and often expulsion, of the embryo or fetus (Christiansen et al., 2005). Approximately 15–20% of all clinically recognized pregnancies will end in a miscarriage (Ballagh et al., 1998; Hemminki, 1998; Wang et al., 2003). Some women will experience recurrent miscarriage but these are estimated to be a small proportion of all women experiencing a miscarriage.

Miscarriage can be managed expectantly (i.e. conservatively), aiming at spontaneous resolution, or medically or surgically with dilatation and curettage (D&C). D&C has been the cornerstone in the treatment of women with a miscarriage for many years, based on the assumption that retained trophoblastic tissue increases the risk of infection and hemorrhage (Tam et al., 2005). Over the last decade, medical treatment, primarily with mifepristone and misoprostol, has been introduced as a non-surgical alternative for women with early pregnancy failure and has proven to be cost-effective (You and Chung, 2005; Niinimäki et al., 2009). However, even after medical evacuation, 30–50% of women undergo a surgical procedure because of the suspicion of incomplete evacuation (Creinin et al., 2004; Graziosi et al., 2004, Davis et al., 2007).

Post-traumatic intrauterine adhesions (IUAs) were first described by Heinrich Fritsch in 1894 (Fritsch, 1894). In 1948, Joseph Asherman was the first to describe the etiology and frequency of this syndrome, ever since known as the Asherman syndrome (Asherman, 1948a, b). Since then, multiple reports addressing the cause, diagnosis and treatment of IUAs have been published. Although IUAs have been described after spontaneous miscarriage, it is mainly reported as a complication after intrauterine surgery (Schenker and Margalioth, 1982).

IUAs are thought to develop following the 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 (Schenker and Margalioth, 1982; Schenker, 1996). IUAs formation is multifactorial with multiple predisposing and causal factors; the specific role of factors like intrauterine trauma,
particularly in women with post-miscarriage IUAs. The category of possible fertility symptoms in patients with IUAs includes secondary infertility and recurrent miscarriages (Schenker and Margalioth, 1982). Other reported complications in patients with IUAs are miscarriage, ectopic pregnancy, abnormal placentation, fetal growth restriction, fetal anomalies, premature delivery and post-partum hemorrhage (Schenker and Margalioth, 1982; Valle and Sciarra, 1988; Capella-Allouc et al., 1999).

Because of the possible implications of IUAs, some investigators have advocated to perform a hysteroscopy after every miscarriage (Salzani et al., 2007). Early IUAs detection is claimed to be important because early treatment can prevent further complications (Valle and Sciarra, 1988; Goldenberg et al., 1995; Katz et al., 1996). Treatment aims to restore the normal size and shape of the uterine cavity, normal endometrium function and to increase the chance of becoming pregnant (Protopapas et al., 1998). However, the effect of treatment of IUAs on improvements in reproductive outcome has not been established.

Hysteroscopy is considered to be the most reliable technique for IUAs detection; direct vision of the uterine cavity enables accurate identification of their presence, localization and extent (Goldenberg et al., 1997; Cohen et al., 2001). Although heavy bleeding might impaire the visualization and therefore limit this utility shortly after the miscarriage or in the case of symptomatic pregnancy remnants, hysteroscopy generally has the advantage of enabling immediate treatment following the diagnostic procedure. Furthermore, both congenital and acquired intrauterine abnormalities can be detected.

The reported prevalence of post-miscarriage IUAs varies considerably, depending on different parameters including the population studied, the diagnostic method applied and the classification system used (Shaffer, 1986). Subsequently, the effect of number of miscarriages and D&C procedures on the rate of IUAs has not been established. We present a systematic review of the literature to evaluate adhesion formation after miscarriage and to identify potential risk factors. We also assessed long-term reproductive outcome following a miscarriage, particularly in women with post-miscarriage IUAs.

Methods

This systematic review and meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Institutional review board approval was not sought since all data were extracted from previously published data.

Systematic searches

We searched the literature for published papers reporting on women who were systematically evaluated by hysteroscopy after miscarriage. The following terms were used in title or abstract searches or as MESH terms: ‘abortion’, ‘miscarriage’, ‘curettage’, ‘intrauterine adhesions’, ‘uterine adhesions’, ‘Asherman syndrome’, ‘traumatic amenorrhea’, ‘endometrial sclerosis’, ‘adhesive endometrosis’, ‘post-traumatic intrauterine synechiae’, ‘uterine synechiae’ and ‘uterine atresia’. The latter terms have been used in the past for intrauterine adhesions and were therefore included in the search.

To be able to compare the long-term reproductive outcomes, a second search was performed for published papers in which key reproductive indicators (conception rate, pregnancy rate and miscarriage rate) in women following a miscarriage, in particular women with post-miscarriage IUAs, were reported. The following terms were used in title or abstract searches or as MESH terms: ‘abortion’, ‘miscarriage’, ‘curettage’, ‘fertility’, ‘infertility’, ‘pregnancy rate’, ‘human’ and ‘reproductive outcome’.

The following electronic databases were searched: MEDLINE (1966 to January 2013), EMBASE (1974 to January 2013), Cochrane Central Register of Controlled Trials (CENTRAL). The search terms were modified according to database requirements. The reference lists of the included studies were also hand-searched for additional relevant studies.

Paper selection procedure

All prospective cohort, cross-sectional studies or randomized controlled trials (RCTs) reporting on prevalence, risk factors and/or symptoms of IUAs in women diagnosed with a current miscarriage (first search) and key reproductive indicators following a miscarriage (second search) were considered for inclusion. Original articles had to be published as full papers in peer-reviewed journals while language restrictions were not applied. Case reports and small case series with < 30 patients were not included.

Studies were selected independently in a two-stage process by two researchers; the first search was by A.B.H. and J.A.F.H. and the second search was by A.B.H. and M.L. First, eligibility was assessed based on the title and abstract. Full manuscripts were obtained for all studies that were selected. In the second step, examination of the full manuscript was carried out to study the eligibility of the study. Additional information was sought from authors if papers contained insufficient information.

Eligibility criteria

Studies reporting the prevalence of post-miscarriage IUAs had to include women with a previous miscarriage, in whom within 12 months after spontaneous expulsion or medical or surgical treatment a hysteroscopy was performed to study the presence of IUAs.

Studies reporting on women after elective abortion were excluded; elective abortion is considered a different clinical condition, implicating the possibility of a difference in adhesion formation. Studies mainly evaluating women because of a history of recurrent miscarriage, without a recent miscarriage within 12 months, were also excluded. These articles evaluated a selective group, women with a history of recurrent miscarriage who did not achieve a new pregnancy, to elucidate possible causal factors. We excluded these studies since we consider them to evaluate a group with a potentially higher prevalence of intrauterine abnormalities, causing the risk of overestimation of IUAs due to selection bias.

The presence of IUAs had to be studied as a primary or secondary outcome parameter. A hysteroscopic evaluation of the uterine cavity after miscarriage for the presence of adhesions was obligatory; studies in which other diagnostic methods were used for evaluation were not included.

In the second search, studies had to report time to conception, conception rate, pregnancy rates and/or miscarriage rates by natural conception in women with post-miscarriage IUAs and/or women following conservative, medical or surgical management of miscarriage. Studies reporting reproductive outcomes of subfertile couples or after assisted reproductive treatment (ART) were excluded. Papers describing obstetric complications, apart from miscarriage, in the pregnancy subsequent to miscarriage were also excluded.
Women with a history of recurrent miscarriage were excluded. The prevalence of other factors affecting long-term reproductive outcome, such as subsequent miscarriage, is expected to be increased in this selected population. By including this group, the relationship between adhesions and subsequent pregnancy outcome is affected and cannot be interpreted because of selection bias.

Overall, women had to be included consecutively and independent of their symptoms.

### Nomenclature

The nomenclature used to describe clinical events in early pregnancy in this paper was according to the revised terminology by the ESHRE Special Interest Group for Early Pregnancy (SIGEP) (Farquharson et al., 2005). A miscarriage was defined as the spontaneous expulsion of products of conception or the disappearance of fetal heart activity on ultrasound or a gestational sac that did not grow in consecutive ultrasound examinations during the first 20 weeks of gestation. A delayed miscarriage, previously named missed abortion, was defined as an anembryonic pregnancy without blood loss or expulsion of products of conception. Women were divided into conservative, medical or surgical treatment groups depending on the treatment received.

### Outcome measures

The primary outcome measure was the presence and degree of the reported IUAs. Secondary meta-analyses were performed to estimate the associations between prevalence of IUAs and type of miscarriage, number of miscarriages or number of curettage procedures. Furthermore, the frequencies of both congenital and acquired abnormalities, such as polyps and fibroids, were assessed if reported.

Subsequently, in the second analysis, conception, live birth and miscarriage rates and time to conception in women diagnosed with IUAs following a miscarriage were assessed and compared for women after conservative, medical or surgical management of a miscarriage.

### Extent and degree of intrauterine adhesions

To enable evaluation of the extent and degree of IUAs and outline prognosis and results of treatment, a classification system is essential. Over time a variety of updated classifications systems have been used, based on different diagnostic tools, clinical presentation and past reproductive performance. Unfortunately the classification systems are not uniformly used and none have been validated by clinical studies (Yu et al., 2008). The most used IUAs classification systems are the classification of March et al., the American Fertility Society (AFS) classification, the European Society of Hysteroscopy (ESH) classification and the European Society of Gynecological Endoscopy (ESGE) classification.

In the classification system of March et al. (1978), the adhesions are categorized in minimal, moderate and severe groups based on a combination of the type of adhesions and cavity involvement. The American Fertility Society (AFS) classification of IUAs is based on the extent of cavity involvement, type of adhesions and menstrual pattern. Cumulative scores determine the severity ranging from stage I to III. The ESGE emerged from the ESH; both classifications are based on a combination of the type of adhesions, site and extent of cavity involvement and the presence of amenorrhea or pronounced hypomenorrhea (Wamsteker, 1990; Wamsteker and de Blok, 1995). The severity of the adhesion is classified in seven grades.

In order to allow eventual meta-analyses, we re-categorized the severity of adhesions in three categories, based on data extracted from the reported classification system. The categories were defined as mild, moderate or severe depending on the scale of the different classification systems (Table I).

### Classification of intrauterine abnormalities

Intrauterine malformations found by hysteroscopy can be divided into congenital and acquired abnormalities. Congenital uterine abnormalities may arise from malformation at any step of the Mullerian developmental process and are classified in different groups, some with further division in subtypes (Grimbizis et al., 2013). Acquired intrauterine abnormalities include uterine polyps, leiomyoma, retained products of conception and endometriosis. The prevalence of intrauterine abnormalities was calculated for the entire group and furthermore, according to the number of miscarriages.

### Data extraction and assessment of methodological quality

The following information was extracted from the included studies: publication year, study design, inclusion and exclusion criteria, patients’ characteristics, treatment received, duration of follow-up, evaluation after miscarriage, congenital and acquired intrauterine abnormalities, evaluation of adhesions and IUAs occurrence rate. If available, the degree and extent of IUAs were also extracted. Potential prognostic factors such as infection or inflammation contributing to adhesion formation were analyzed if systematically registered in the paper. Data on the long-term reproductive outcomes (cumulative conception, live birth, miscarriage rates and time to conception) in women following miscarriage, in particular women with post-miscarriage IUAs, were assessed.

The methodological quality of the selected papers was evaluated independently by two reviewers (A.B.H. and J.A.F.H.) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement-Checklist (von Elm et al., 2007). 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 generalizability. During evaluation, items are ‘rated ’1’ if the content is transparently and adequately described, ’0’ if items are inadequately or insufficiently reported and ’NA’ if items are not reported.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Stage I</td>
<td>Stage I</td>
<td>Stage I</td>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
<td>Stage II</td>
<td>Stage II, IIa or III</td>
<td>Stage II, IIa or III</td>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
<td>Stage III</td>
<td>Stage IIIa, IIIb or IV</td>
<td>Stage IV, Va or Vb</td>
<td>Severe</td>
</tr>
</tbody>
</table>

*The European Society of Hysteroscopy (ESH) was adopted by the European Society of Gynecological Endoscopy (ESGE) in 1995.
if not applicable. The final score is the number of items scored ‘1’, with a maximum of 34. Discordant ratings of the two researchers were adjusted through consultation with a third author (H.A.M.B.).

Data analysis

Statistical analyses were conducted using the Review Manager (RevMan version 5.0 software (Cochrane Collaboration) and SAS 9.3 (SAS Institute, Cary, NC, USA). For each study separately, the odds ratio (OR) with 95% confidence interval (CI) was calculated for dichotomous variables. The presence of statistical heterogeneity was determined using the $I^2$ statistics. Heterogeneity was considered substantial when $I^2 > 50$% (Higgins and Thompson, 2002; Higgins et al., 2003).

In order to compare the overall prevalence of IUAs in women following miscarriage and in women with versus more than one miscarriage, incomplete versus delayed miscarriage or one D&C versus more than one D&C, pooled ORs and 95% confidence intervals (CI) were calculated. Differences in the incidence of IUAs in women with one, two, three or more miscarriages were tested using meta-regression.

Depending on the presence of statistical heterogeneity, the data of studies were pooled on the basis of a fixed effects model or a random effects model. Cumulative conception, live birth and miscarriage rates were calculated for women with IUAs after miscarriage and compared for women after conservative, medical or surgical management of the miscarriage. For all tests performed, statistical significance was determined at $P < 0.05$.

Results

Prevalence of post-miscarriage intrauterine adhesions

Using the limitations ‘human only’ and ‘clinical trial’, the first search strategy yielded 804 citations including 201 duplicates. The funnel flow diagram illustrating the selection procedure is shown in Fig. 1. Of the 603 remaining articles, 503 were excluded after title and abstract selection as they did not study IUAs in relation to miscarriages. One potential eligible article was not available for full manuscript reviewing even after contacting the author and publisher (Santangelo, 1996). After reviewing full manuscripts of the remaining 99 articles, 63 papers were excluded; the reason for exclusion was lack of uterine evaluation after miscarriage. Five articles that used hysterosalpingography for uterine evaluation (Adoni et al., 1982; Harger et al., 1983; Stray-Pedersen and Stray-Pedersen, 1984; Stephenson, 1996; Tsapanos et al., 2002) were also excluded. Additionally, 19 papers were excluded from analysis; 17 articles reported on women evaluated because of recurrent miscarriages in their reproductive history, without a recent miscarriage within 12 months (Shiozuka et al., 1980; Feng et al., 1989; Wang et al., 1992; Tulpala et al., 1993; Raziel et al., 1994; Fedele et al., 1996; Ebrashi et al., 1998; Valli et al., 2001; Badawy et al., 2002; Ballester et al., 2004; Ventolini et al., 2004; Weiss et al., 2005; Guimarães Filho et al., 2006; Dendrinos et al., 2008; Bohlmann et al., 2010; Jaslow et al., 2010; Souza et al., 2011), one reported on infertile women with a history of curettage (Taylor et al., 1981) and one reported on women after elective induced abortion (Salat-Baroux et al., 1984). Two case series with respectively 3 and 10 women were also excluded (Westendorp et al., 1998; Dalton et al., 2006).

Description and quality of included studies assessing post-miscarriage intrauterine adhesions

One RCT (Yasar et al., 2004), eight prospective cohort studies (Golan et al., 1992; Friedler et al., 1993; Römer, 1994; Römer et al., 1996; Tam et al., 2002; Congendre et al., 2011; Kuzel et al., 2011; Wang et al., 2011) and one prospective cross-sectional study (Salzani et al., 2007) met the inclusions criteria. The characteristics of the included studies are presented in Table II. In the only RCT (Yasar et al., 2004), women with a miscarriage were randomized to receive prophylactic doxycycline, prophylactic doxycycline plus conjugated equine estrogen or no treatment for prevention of IUAs following D&C. The prospective cohort study of Tam et al. (2002) was a follow-up study of women enrolled in a previous RCT. In the initial study (Chung et al., 1999), women diagnosed with a complete spontaneous miscarriage were managed conservatively; otherwise women were randomly allocated to either D&C or treatment with misoprostol. In one study, women after IVF-embryo transfer with early pregnancy failure were analyzed, but the method of treatment was not stated (Wang et al., 2011). In the remaining seven studies (Table II), six prospective cohort studies and one cross-sectional study, women diagnosed with a current miscarriage were subjected to D&C and evaluated after surgery for the presence of IUAs.

A total of 912 women evaluated by post-miscarriage hysteroscopy were included in the studies, ranging from 53 to 151 women per study, with a mean of 91. The hysteroscopy was performed between 1 and 12 months following the miscarriage. The majority of the 781 patients (86%) were treated by curettage whereas only 22 patients (2.4%) had been treated medically while 25 (2.7%) were evaluated after a spontaneous miscarriage without any intervention. For the remaining 84 women (9.2%), the treatment method was not stated.

In three studies (Römer et al., 1996; Tam et al., 2002; Salzani et al., 2007), >30% of women were lost to follow-up, as shown in Table II. Given the substantial proportion of women not revised, inducing some kind of verification bias, a separate analysis was performed excluding these studies.

The results of the assessment of the methodological quality of the included studies using the STROBE checklist are reported in Supplementary data, Table SI. The included studies had a mean item score of 17.5 (from 31 relevant items), ranging between 14 and 25.

Intrauterine adhesions

Overall, IUAs were detected in 183 of the 912 women, resulting in a pooled prevalence of 19.1% (95% CI: 12.8–27.5%), $I^2 = 86.9$, $P < 0.001$. When the studies with significant numbers lost to follow-up were excluded, the result did not change significantly; the pooled prevalence was 19.7% (95% CI: 12.0–29.7%).

In one study, some of the women were treated by expectant management ($n = 25$) or medically ($n = 22$), and no IUAs were reported in these women. In nine studies women were treated by D&C, and IUAs were identified in 151 of the 781 patients, with a pooled prevalence of 18.5% (95% CI: 12.6–26.4%), $I^2 = 82.5$, $P < 0.001$, while the pooled prevalence did not change significantly when studies with significant numbers lost to follow-up were excluded; 16.3% (95% CI: 11.2–23.1%). In the 10th study (Wang et al., 2011),
the treatment method was not mentioned and IUAs were detected in 32 of the 84 patients (38.1%; 95% CI: 28.4–48.8%). The extent and degree of the adhesions were reported in seven studies accounting for 124 women with adhesions, 67.8% of all women with adhesions. The adhesions were classified according to the ESH/ESGE, AFS and March systems in four, one and one studies, respectively, while in one study the classification system was not stated (Table II). In one article (Römer et al, 1996), the moderate and severe adhesions of seven patients were not separately reported; we considered these patients to have moderate adhesions. The extent of the reported IUAs is reported in Table III; in 72 patients (58.1%) mild adhesions were reported, in 35 (28.2%) the adhesions were moderate and in 17 (13.7%) the adhesions were severe.

**Numbers of miscarriages**

Results of the meta-analysis are summarized in Fig. 2. The data of seven prospective studies were pooled to compare the prevalence of IUAs in women with more than one versus one miscarriage (Fig. 2A). There were 63 cases of IUAs among 270 women with more than one miscarriage compared with 37 cases among 155 women with one miscarriage, OR 1.99 (95% CI: 1.32–2.99), $I^2 = 21\%$, $P = 0.001$. Excluding two studies with significant loss to follow-up resulted in an OR 2.08 (95% CI: 1.25–3.48). Women with more than one miscarriage had statistically significantly more IUAs compared with women with one miscarriage. The vast majority of the patients were managed surgically.

IUAs were detected in 17 of 77 women with three or more miscarriages compared with 21 cases among 111 women with two miscarriages (Fig. 2B), OR 1.52 (95% CI: 0.68–3.38), $I^2 = 0\%$, $P = 0.30$. Excluding one study with significant loss to follow-up resulted in an OR 1.38 (95% CI: 0.67–3.31). No significant differences in IUAs were found between women with two or three miscarriages. Relative to women with one miscarriage, women with two miscarriages showed no statistically significant risk OR 1.41 (95% CI: 0.78–2.5) but women with three or more miscarriages showed a statistically significantly increased risk of IUAs OR 2.1 (95% CI: 1.09–4.1). Figure 2E shows the reported prevalence of IUAs per study as well as the pooled estimates across the three groups.

**Type of miscarriage and numbers of D&C procedures**

In four studies, there were 68 cases of IUAs among 234 women with an incomplete miscarriage compared with 37 cases of IUAs among 155 women with a delayed miscarriage (Fig. 2C), with an OR of 1.22 (95% CI: 0.76–1.96), $I^2 = 21\%$, $P = 0.41$. Excluding two studies with...
**Table II** Characteristics of the included studies reporting the prevalence of post-miscarriage intrauterine adhesions (IUAs).

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Period</th>
<th>Characteristics of the patients</th>
<th>Treatment</th>
<th>n</th>
<th>Mean age (range)</th>
<th>System†</th>
<th>Follow-up hysteroscopy</th>
<th>Lost to follow-up (%)</th>
<th>IUAs (%)</th>
<th>Other abnormalities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congendez et al. (2011)</td>
<td>PCS</td>
<td>2005–2007</td>
<td>Women with a miscarriage during the first 20 weeks of gestation</td>
<td>D&amp;C</td>
<td>151</td>
<td>28.6 (18–42)</td>
<td>AFS</td>
<td>End of first menstruation</td>
<td>0</td>
<td>14 (9.3%)</td>
<td>45 (29.8%)</td>
</tr>
<tr>
<td>Wang et al. (2011)</td>
<td>PCS</td>
<td>NR</td>
<td>Women with early pregnancy loss after IVF-ET.</td>
<td>NR</td>
<td>84</td>
<td>NR</td>
<td>NR</td>
<td>Prior to next treatment</td>
<td>0</td>
<td>32 (38.1%)</td>
<td>26 (31.0%)</td>
</tr>
<tr>
<td>Kuzel et al. (2011)</td>
<td>PCS</td>
<td>NR</td>
<td>Women with a delayed miscarriage</td>
<td>D&amp;C</td>
<td>100</td>
<td>32 (21–43)</td>
<td>ESH</td>
<td>4–12 weeks</td>
<td>0</td>
<td>7 (7%)</td>
<td>18 (18%)</td>
</tr>
<tr>
<td>Salzani et al. (2007)</td>
<td>CSS</td>
<td>NR</td>
<td>Women with a miscarriage</td>
<td>D&amp;C</td>
<td>109</td>
<td>28.4 (18–45)</td>
<td>ESH</td>
<td>3–12 months</td>
<td>169 (60.8%)</td>
<td>41 (37.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Yasar et al. (2004)</td>
<td>RCT</td>
<td>NR</td>
<td>Women with a delayed miscarriage</td>
<td>D&amp;C</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>8 weeks</td>
<td>0</td>
<td>13 (22.4%)</td>
<td>NR</td>
</tr>
<tr>
<td>Tam et al. (2002)</td>
<td>PCS</td>
<td>1995–1998</td>
<td>Women with a miscarriage</td>
<td>Exp, D&amp;C, MIS</td>
<td>70</td>
<td>29 (15–44)</td>
<td>AFS</td>
<td>6 months</td>
<td>56 (44.1%)</td>
<td>2 (2.9%)</td>
<td>NR</td>
</tr>
<tr>
<td>Römer et al. (1996)</td>
<td>PCS</td>
<td>1991–1995</td>
<td>Women with an incomplete or delayed miscarriage and who had a desire of further pregnancy</td>
<td>D&amp;C</td>
<td>80</td>
<td>27.7, SD 5.4</td>
<td>ESH</td>
<td>8–12 weeks</td>
<td>43 (35.6%)</td>
<td>20 (25%)</td>
<td>20 (25%)</td>
</tr>
<tr>
<td>Römer (1994)</td>
<td>PCS</td>
<td>1991–1993</td>
<td>Women with an incomplete or delayed miscarriage with desire of further pregnancy</td>
<td>D&amp;C</td>
<td>53</td>
<td>27.5, SD 5.4</td>
<td>ESH</td>
<td>6–12 weeks</td>
<td>0</td>
<td>16 (30.2%)</td>
<td>14 (26.4%)</td>
</tr>
<tr>
<td>Friedler et al. (1993)</td>
<td>PCS</td>
<td>1990</td>
<td>Women with an incomplete or delayed miscarriage between the 7th and 12th week of pregnancy</td>
<td>D&amp;C</td>
<td>147</td>
<td>34 (19–41)</td>
<td>March</td>
<td>After first menstruation</td>
<td>10 (6.8%)</td>
<td>28 (19.0%)</td>
<td>10 (6.8%)</td>
</tr>
<tr>
<td>Golan et al. (1992)</td>
<td>PCS</td>
<td>NR</td>
<td>Women with a delayed miscarriage</td>
<td>D&amp;C</td>
<td>60</td>
<td>30 (19–41)</td>
<td>NR</td>
<td>8–12 weeks</td>
<td>0</td>
<td>10 (16.7%)</td>
<td>15 (25%)</td>
</tr>
</tbody>
</table>

PCS, prospective cohort study; CSS, cross-sectional study; RCT, randomized controlled trial; NR, not reported; Exp, expectant management; D&C, dilation and curettage; MIS, misoprostol treatment.

†AFS, American Fertility Society; ESH, European Society of Hysteroscopy.
concerning the indication for, and the method of, performing D&C was studied in three studies, but was insufficient for analysis. Information on the use of antibiotics was not stated. The effect of estradiol application could not be examined due to insufficient reports of this event while in 15 (25.9%), 10 (17.2%) and 5 (8.6%) women, respectively.

Polyps in 28 of 58 women (48.3%) with an acquired abnormality, followed by the arcuate uterus (19.6%), hypoplastic uterus (3.3%) and the septate uterus or bicorneal uterus in 69 of the 92 women (75.0%), 61.3% of all encountered abnormalities. The most reported anomaly was more than one miscarriage, and the difference was statistically significant, excluding the pooled prevalence did not change significantly, 22.0% \( \text{OR} 2.05 (95\% \text{CI}: 1.35–3.12), P < 0.001. \)

### Intrauterine abnormalities

Seven studies reported on the prevalence of intrauterine abnormalities, other than adhesions, assessed by hysteroscopy. Overall, 150 cases of intrauterine abnormalities were detected in 675 women, resulting in a pooled prevalence of 22.4% (95\% CI: 16.3–29.9%), \( \text{OR} 2.05 (95\% \text{CI}: 1.35–3.12), P < 0.001. \) When the studies with significant loss to follow-up were excluded, the pooled prevalence did not change significantly, 22.0% (95\% CI: 15.3–30.6%). The prevalence of intrauterine abnormalities was 12.5% (34/271) after one m miscarriage and 29.4% (55/187) after more than one miscarriage, and the difference was statistically significant, \( P < 0.0001. \)

Congenital abnormalities were reported in 92 women, accounting for 61.3% of all encountered abnormalities. The most reported anomaly was the septate uterus or bicorneal uterus in 69 of the 92 women (75.0%), followed by the arcuate uterus (19.6%), hypoplastic uterus (3.3%) and uni-corneal uterus in respectively three (3.3%) and two (2.2%) women. The most reported acquired uterine abnormality was uterine polyps in 28 of 58 women (48.3%) with an acquired abnormality, followed by leiomyoma, endometritis and retained products of conception in 15 (25.9%), 10 (17.2%) and 5 (8.6%) women, respectively.

The influence of infection or inflammation on the formation of IUAs could not be examined due to insufficient reports of this event while the use of antibiotics was not stated. The effect of estradiol application was studied in three studies, but was insufficient for analysis. Information concerning the indication for, and the method of, performing D&C was not stated. As such, these possible risk factors could not be examined.

### Long-term fertility and reproductive outcome

A second literature search was performed for relevant articles reporting on long-term reproductive outcomes in women following a miscarriage, especially in women with post-miscarriage IUAs. The study selection and number of included studies are reported in Fig. 3. In summary, 4553 potentially relevant citations were identified, including 715 duplicates. After title and abstract selection 3694 citations were excluded, because it was clear that they did not fulfill the inclusion criteria.

After reviewing the full manuscripts of the remaining 144 articles, 100 were excluded from analysis: 71 articles did not report on follow-up after miscarriage, while 29 articles reported long-term reproductive outcomes in subfertile couples or after assisted conception. Subsequently, 36 articles were excluded including 12 articles reporting on symptomatic women with IUAs, i.e. women with menstrual disturbances and/or infertility (Caspi and Perpinial, 1975; Bergquist et al., 1981; Fedele et al., 1986; Valle and Sciarrà, 1988; Katz et al., 1996; Pabuççu et al., 1997; Capella-Allouc et al., 1999; Fernandez et al., 2006; Adesiyun et al., 2010; March et al., 2010; Roy, 2010; Roy et al., 2010). Eleven studies examined the associations between pregnancy and obstetric complications and past reproductive performance in population-based cohorts and were excluded (David and Smith, 1980; Rachootin and Olsen, 1982; Regan et al., 1989; Knudsen et al., 1991; Thom et al., 1992; Joffe and Li, 1994; Taskinen et al., 1999; Gray and Wu, 2000; Maconochie et al., 2007; Bhattacharya et al., 2008; Hure et al., 2012). Seven articles evaluating women with recurrent pregnancy loss (Cowchock and Smith, 1995; Ruiz et al., 1996; Saitoh et al., 1998; Sheiner et al., 2005; Prakash et al., 2006; Rai and Regan, 2006; Stephenson and Kuteh, 2007), three case reports (Kobayashi et al., 1996; Razi et al., 2000; Sills et al., 2004) and one article (Creinin, 1999) reporting unplanned conceptions following miscarriage were excluded. Furthermore, two retrospective articles reporting on reproductive outcomes following a miscarriage were excluded (Levin et al., 1979; Hassan and Killick, 2005).

### Description and quality of included studies assessing long-term reproductive outcome

Finally, eight prospective studies (Table IV) were identified, in which key reproductive indicators following a miscarriage were reported (Ben-Baruch et al., 1991; Kaplan et al., 1996; Blohm et al., 1997; Adelusi et al., 1998; Graziosi et al., 2005; Tam et al., 2005; Fontanarosa et al., 2007; Smith et al., 2009). A total of 1770 women who had suffered a miscarriage were included in the eight studies.

The results of the assessment of the methodological quality of the eight included prospective studies using the STROBE checklist are reported in Supplementary data, Table SII. The included studies had a mean item score of 14.4 (from 31 relevant items), ranging between 11 and 29.

### Reproductive outcome following intrauterine adhesions

The relationship between IUAs following a miscarriage and subsequent fertility and reproductive outcome could not be assessed, as the presence of IUAs was not studied in the included eight studies.

### Reproductive outcome following miscarriage

In three studies, key reproductive indicators were reported for 430 women after medical management with misoprostol. Cumulative conception rates ranged between 94 and 98% and live birth rates ranged between 79 and 87% (Graziosi et al., 2005; Tam et al., 2005; Smith et al., 2009). A live birth rate of 87% was reported by Graziosi et al. (2005) after medical evacuation and Tam et al. (2005) reported a
Figure 2 Summary of meta-analysis presenting odds ratio (OR) with 95% confidence interval (CI) for number (A and B) or type (C) of miscarriage and number of D&C procedures (D). (E) The reported prevalence per study as well as the pooled estimates across women with one, two and three or more miscarriages. Abbreviations: D&C, dilatation and curettage, IUAs, intrauterine adhesions, Mis, miscarriage.
miscarriage rate of 13%. The percentage of women who received additional surgical treatment was not reported in all studies.

A total of 511 women were evaluated in five studies after surgical treatment. Cumulative conception rates ranged between 75 and 98%, ongoing pregnancy rates ranged between 72 and 87%, live birth rates ranged between 82 and 88% and miscarriage rates ranged between 11 and 28% (Ben-Baruch et al., 1991; Blohm et al., 1997; Graziosi et al., 2005; Tam et al., 2005; Smith et al., 2009).

In 6 studies, 829 women were evaluated after conservative management. Subsequent conception rates between 73 and 91%, live birth rates between 64 and 79% and miscarriage rates between 26 and 30% were reported (Ben-Baruch et al., 1991; Kaplan et al., 1996; Blohm et al., 1997; Adelusi et al., 1998; Fontanarosa et al., 2007; Smith et al., 2009). The proportion of women who received additional medical or surgical treatment could not be reported, as it was not reported in all studies.

The number of previous miscarriages seems predictive of subsequent reproductive outcome. Even when adjusted for age, the live birth rate declined following one, two or three or more miscarriages from 74%, to 67% and 58%, respectively (Smith et al., 2009). There were more viable pregnancies among women who have no previous miscarriages, while the number of pregnancies decreases with an increase in the number of previous miscarriages (Kaplan et al., 1996).

Time to conception was not uniformly defined in the included studies and could not be assessed. Furthermore, the conception rates were reported over different time scales, which made it impossible to compare the results of the different studies.

**Discussion**

To our knowledge, this is the first published systematic review and meta-analysis reporting the prevalence of IUAs after miscarriage and potential risk factors, and long-term reproductive outcome following a miscarriage was also assessed.

Hysteroscopy was considered the gold standard for IUA detection; the uterine cavity can be visualized and the extent, localization and degree of IUAs can be accurately determined, while other intrauterine abnormalities can also be detected (Goldenberg et al., 1997; Cohen...
### Table IV Characteristics of the prospective studies reporting long-term reproductive outcome after miscarriage.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Period</th>
<th>Characteristics of the women</th>
<th>Follow-up (m)</th>
<th>Treatment</th>
<th>n</th>
<th>Conception rate (%)</th>
<th>Live birth rate (%)</th>
<th>Miscarriage rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (2009)</td>
<td>PCS</td>
<td>2005–2007</td>
<td>Women with a miscarriage (&lt;13 weeks) enrolled in a previous RCT comparing expectant, surgical and medical evacuations were followed up by questionnaires.</td>
<td>70</td>
<td>EXP</td>
<td>224</td>
<td>NR</td>
<td>177/224 (79)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MED</td>
<td>230</td>
<td></td>
<td>181/230 (79)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D&amp;C</td>
<td>235</td>
<td></td>
<td>192/235 (82)</td>
<td></td>
</tr>
<tr>
<td>Fontanarosa et al. (2007)</td>
<td>PCS</td>
<td>NR</td>
<td>Women with a symptomatic early miscarriage managed conservatively followed up by telephone survey.</td>
<td>12</td>
<td>EXP</td>
<td>60</td>
<td>18/60 (81)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tam et al. (2005)</td>
<td>PCS</td>
<td>1995–1998</td>
<td>Women enrolled in a previous RCT comparing medical and surgical evacuation were followed up by telephone survey.</td>
<td>48–108</td>
<td>MED</td>
<td>131</td>
<td>128/131 (96)</td>
<td>109/128 (85)</td>
<td>17/128 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D&amp;C</td>
<td>130</td>
<td>127/130 (96)</td>
<td>112/127 (88%)</td>
<td>14/127 (11)</td>
</tr>
<tr>
<td>Graziosi et al. (2004)</td>
<td>PCS</td>
<td>2001–2003</td>
<td>Women with a miscarriage (&lt;14 weeks) enrolled in a previous RCT, comparing surgical and medical evacuation, were followed up by a telephone survey.</td>
<td>12</td>
<td>MED</td>
<td>69</td>
<td>65/69 (94)</td>
<td>60/69* (87)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D&amp;C</td>
<td>57</td>
<td>54/57 (95)</td>
<td>50/57* (87)</td>
<td></td>
</tr>
<tr>
<td>Adelusi et al. (1998)</td>
<td>PCS</td>
<td>1992</td>
<td>Women, who spontaneously aborted after suffering a spontaneous miscarriage in an obstetric clinic, were followed.</td>
<td>6–48</td>
<td>EXP</td>
<td>273</td>
<td>222/273 (81)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blohm et al. (1997)</td>
<td>PCS</td>
<td>1993–1994</td>
<td>Women with a miscarriage enrolled in a previous RCT comparing expectant and surgical management were followed up by questionnaires.</td>
<td>24</td>
<td>D&amp;C</td>
<td>37</td>
<td>33/37 (89)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EXP</td>
<td>76</td>
<td>69/76 (91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaplan et al. (1996)</td>
<td>PCS</td>
<td>NR</td>
<td>Women with first trimester miscarriage (&lt;8 weeks) managed conservatively were followed up on future fertility.</td>
<td>18</td>
<td>EXP</td>
<td>161</td>
<td>118/161 (73)</td>
<td>75/118* (64)</td>
<td>35/118 (30)</td>
</tr>
<tr>
<td>Ben-Baruch et al. (1991)</td>
<td>PCS</td>
<td>1983–1988</td>
<td>Women with a miscarriage (&lt;10 weeks) managed conservatively or surgically were followed up to compare long-term fertility.</td>
<td>12–72</td>
<td>EXP</td>
<td>35</td>
<td>27/35 (77)</td>
<td>19/27 (70)*</td>
<td>7/27 (26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D&amp;C</td>
<td>52</td>
<td>39/52 (75)</td>
<td>28/39 (72)*</td>
<td>11/39 (28)</td>
</tr>
</tbody>
</table>

PCS, prospective cohort study; NR, not reported; EXP, expectant management; D&C, dilation and curettage; MED, medical treatment; RCT, randomized control trial.

*aOngoing pregnancy rate is reported.
*bReported rate is a combination of live birth rate and ongoing pregnancies.
et al., 2001). Because of the high frequency of false positive and diagnostic errors, hysterosalpingography, ultrasonography and sonohysterography are less suitable for accurate detection of IUAs (Valle, 1980; Raziel et al., 1994; Soares et al., 2000).

Summary of the evidence

The prevalence of IUAs in women treated for a current miscarriage varied between 3 and 38%, with a pooled prevalence of 19%. The majority of women were treated by D&C and women with more than one miscarriage had a significantly higher incidence of IUAs than women with only one miscarriage (P = 0.001). The prevalence of IUAs was not different in women with two compared with three or more miscarriages or in women in incomplete versus delayed miscarriage, although the small number of included women may have played an important role in this finding: the studies were underpowered to detect a significant difference between the groups. Exclusion of the studies with a substantial number lost to follow-up (>30%), did not influence the results of the meta-analysis.

Recent curettage procedures were identified as the most important risk factor for IU formation. Our results are in agreement with earlier observations; Westendorp et al. (1998) and Tsapanos et al. (2002) studied the presence of IUAs in women undergoing a second curettage and reported a prevalence of IUAs of 50%. In our study, no adhesions were encountered in women after a spontaneous miscarriage without any intervention and in women treated medically, although they were a minority (5.1%). The time between treatment and hysteroscopic evaluation for IUAs ranged between 1 and 12 months. In 42% of the reviewed patients, moderate to severe IUAs were encountered and these are of concern as they may have serious reproductive implications.

Besides IUAs, other abnormalities were frequently encountered in women undergoing hysteroscopy after miscarriage, with an overall prevalence of 22.4%. Congenital abnormalities accounted for 61.3% of all encountered intrauterine abnormalities, especially uterine septum or bi-cornuate uterus. Uterine polyps were the most reported acquired abnormality. The prevalence of intrauterine abnormalities was significantly increased in women with more than one miscarriage compared with women with only one miscarriage.

After extensive review of the literature, only eight prospective studies were identified in which key reproductive indicators were reported after conservative, medical or surgical treatment for a miscarriage. Despite the extensive literature search, we were unable to find any study that had specifically looked at reproductive outcome or long-term fertility in women with post-miscarriage IUAs. Only symptomatic women with IUAs of different cause were reported in the available studies on this subject.

Similar pregnancy outcomes were reported subsequent to conservative, medical and surgical management of miscarriage, although the number of studies evaluating the long-term reproductive outcome was limited and different time scales were used. The limited number of studies and small sample size of the treatment groups obviously limit the statistical power to detect any difference in reproductive outcomes between the treatment regimes. Due to a large variation in primary outcomes, methodology and populations, we were not able to perform meta-analyses on reproductive outcome after miscarriage. The relationship and impact of IUAs on long-term reproductive outcomes remain undetermined.

The number of previous miscarriages seems to predict subsequent reproductive performance; the live birth rate declines and the risk of miscarriage increases (Knudsen et al., 1991; Kaplan et al., 1996; Smith et al., 2009). As shown by Hure et al. (2012), different groups of women experience different miscarriage rates; factors such as smoking status and fertility problems have great impact on the miscarriage rate, with an 8-fold difference in the group with the lowest versus the highest calculable rate of miscarriage.

Strengths and limitations of the review

Our study has several points to be highlighted. We performed a systematic review of the literature to determine the prevalence of IUAs and to identify risk factors. Furthermore, long-term reproductive outcome in women after miscarriage was assessed. The strength of this report is that the methodology and quality of included studies were individually analyzed and only studies in peer-reviewed journals were included. Only studies in which participants were included prospectively and consecutively were eligible for inclusion. Studies were included if in all the enrolled patients a validated method for IUA ascertainment was used and IUAs were clearly defined or if key reproductive indicators were used to establish long-term reproductive outcome.

We applied this protocol in order to minimize verification bias. For this reason, studies including only symptomatic women after miscarriage were excluded. In addition, we did not include studies reporting the prevalence of IUAs or key reproductive indicators with a retrospective design, or studies in which women were evaluated by hysteroscopy beyond 12 months after miscarriage, given the higher risk of selection bias.

This study has also several weaknesses. Unfortunately, only one randomized controlled trial was available to be included in this systematic review; cohort studies are less reliable especially to determine treatment-associated factors. Only ten prospective cohort studies with IUAs as end-point in women diagnosed with a current miscarriage were encountered. The individual studies with a limited number of patients, a maximum 151, are underpowered to evaluate risk and prognostic factors. Despite meta-analysis, the sample sizes in subgroups remained small.

The methodological quality of the studies included in this review is considered poor to average. The studies reporting on IUAs, assessed by the STROBE statement checklist, resulted in an average score of 17.5 (ranging 14–25), of a maximum of 34. Although all patients had experienced a miscarriage and had a hysteroscopic evaluation within 12 months after miscarriage, eligibility criteria, sources and methods of selection of participant were barely described. There was insufficient information in most studies regarding the number of patients who met all inclusion criteria and the reason for received treatment and there were no explanations of how the study sizes were determined.

In three studies >30% of women were lost to follow-up and these were the studies with the longest period between miscarriage and hysteroscopic evaluation. This could be a relevant source of bias, as women achieving early pregnancy are excluded. A separate analysis, excluding these studies, did not influence the results significantly. Another noticeable point is that only 5.1% of the women were evaluated after a spontaneous miscarriage and expectant management or after medical evacuation.

Variations in different potential influencing factors including maternal age, chromosomal abnormalities, endocrine diseases, mode of
conception and term of pregnancy failure (early and/or late) could not be ruled out. The majority of patients received surgical treatment and no distinction could be made between patients with and without D&C in the subgroups. The indication to perform a surgical treatment (D&C) was not reported. Women requiring surgical treatment (D&C) may differ from those who would be amenable to medical treatment or requiring no treatment at all.

Furthermore, there was lack of information concerning the D&C technique (sharp, blunt, suction or combinations), cervical ripening, skills of the surgeons, indication, signs of infection or inflammation, the use of antibiotics and treatment with estradiol. Because different classification systems were used, the scoring of the adhesions was not uniform while the presence of pre-existing adhesions was not assessed. These factors may have biased the results in an unknown way.

The methodological quality of the included studies reporting on long-term reproductive outcome was poor. The average STROBE statement score was 14.4, ranging between 11 and 29. A substantial percentage of patients treated medically or conservatively received additional surgical treatment because of incomplete management. Furthermore, no adjustments were made in the studies for confounding variables such as parity, gravidity, infertility, or number of prior induced abortions and miscarriages. The studies did not report on the prevalence of other pathologies; no adjustments were made for intrauterine abnormalities, although they can be detected frequently and contribute to the incidence of miscarriage. In this regard, the result of this review should be interpreted with caution as the overall quality of the included studies reporting on both post-miscarriage IUAs and in particular on the related long-term reproductive outcomes needs to be considered as poor to average.

The long-term reproductive outcome could not be reported in women with post-miscarriage IUAs due to a lack of studies reporting on key reproductive indicators in these women. A total of 1770 women were included in eight cohort studies, reporting on one or more long-term reproductive indicators in women following a miscarriage, was a limited number and a small overall sample size. Similar outcomes were reported over different time scales in the different treatment groups, while no adjustment was made in the studies for important confounding factors. So, on the basis of the current literature no solid conclusions can be drawn on the link between treatment modality and adhesion formation. The issue of possible impairment of future fertility after miscarriage remains inconclusive on basis of the current literature.

Systematic reviews and meta-analyses rely on aggregated published data to provide estimates of treatment effects or diagnostic tests. It is not possible to perform detailed analyses that take into account patient covariates or other features. A potentially more coherent approach to summarize the evidence is to acquire the original data from the included studies. Meta-analysis based on individual patient data prevents drawbacks and biases compared with conventional review, allowing the possibility of investigating effectiveness in patients with different profiles and offering a more valid outcome (Broeze et al., 2010).

However, to do so, access to original data sets is imperative, which can be a problem in older studies, while authors need to be willing to share their data.

Comparison with previous research

This systematic review and meta-analysis reports the prevalence of IUAs after miscarriage, while no studies were found to report on long-term reproductive outcomes in women with after miscarriage IUAs. The largest study that classified IUAs following different antecedent endometrial trauma, including incomplete or elective abortion and postpartum curettage, showed that the subsequent reproductive outcome after hysteroscopic treatment depends on the extent of IUAs. The pregnancy rate declined from 93% in women with mild to 57% in women with severe IUAs while the term pregnancy rate declined from 88 to 57% (Valle and Sciarra, 1988). Schenker (1996) reported a pregnancy rate of 95% in the mild IUAs group compared with 60% in the severe group after hysteroscopic treatment.

In general, hysteroscopic adhesiolyis is advised when IUAs are detected (Valle and Sciarra, 1988; Katz et al., 1996). Schenker and Margalioth (1982) reported poor reproductive outcome in a cohort of 292 women with IUAs, who did not receive treatment before attempting to conceive. Pregnancy was reported in only 45%, while 40% ended in a spontaneous miscarriage and another 23% were pre-term deliveries. Even after hysteroscopic treatment, the reproductive outcome remains unsatisfactory; the post-operative pregnancy rate varies between 60 and 75% (March, 1995).

Subsequently, miscarriage rates of 15–50% and pre-term delivery rates of 10–23% are reported in patients with IUAs while in 12% obstetric complications, especially related to abnormal placentaion, are encountered (Schenker and Margalioth, 1982; Friedman et al., 1986). In our study the extent of the reported IUAs was mild in 58% of the reviewed patients. The clinical implications and significance of mild IUAs are still under debate, but it is likely that they are of minor importance for fertility and symptomatology (Westendorp et al., 1998). There are no studies comparing expectant management and hysteroscopic adhesiolyis in patients with mild IUAs. Whether hysteroscopic treatment of mild adhesions is beneficial remains unclear, particularly in case of asymptomatic patients.

A high overall prevalence (22.4%) of congenital and acquired uterine abnormalities was encountered in this study. The most reported congenital abnormality was the septate or bi-cornuate uterus. A septate uterus results from incomplete resorption of the utero-vaginal septum and is frequently quoted as the most common congenital anomaly, associated with a high rate (≏60%) of spontaneous miscarriage ( Homeret al., 2000). This can be explained by the inability of the relative avascular septum, with an abnormal overlying endometrium, to provide an adequate blood supply to the developing embryo (Burchell et al., 1978).

An arcuate uterus is considered a normal variant although the association of an arcuate uterus with reproductive failure remains controversial (Salim et al., 2003). The relationship between acquired intrauterine abnormalities and miscarriage remains unclear. The presence of intrauterine polyps and leiomyoma can interfere with implantation and fertility, creating a hostile environment to embryo implantation (Somigliana et al., 2007; Pritts et al., 2009; Sunkara et al., 2010).

Implications for clinical practice

This meta-analysis shows that recurrent miscarriages and D&C procedures should be considered as an important risk factor in IUAs formation. Although considerable advances have been made in the treatment of IUAs, the results are still not satisfactory. This has implications for clinical practice, as D&C should be prevented as much as possible and adhesion formation should be taken into account when treatment options for miscarriage are discussed.
In order to minimize the numbers of D&C, and probably IUAs, in patients after miscarriage, we propose the following strategy. First, expectative management could be emphasized as treatment option in patients diagnosed with a miscarriage. Wieringa et al. (2002) reported that 50% of the patients with a miscarriage evacuated spontaneously and completely within 2 weeks without a significant increase in morbidity, making this an attractive management option. Secondly, medical evacuation should be considered as a serious alternative. Treatment with mifepristone and misoprostol is equally as effective as surgery in achieving complete evacuation with a RR of 0.96 (95% CI: 0.92–1.0), and a success rate of >80% in both treatment groups (Neilson et al., 2010). There was a large and statistically significant reduction in surgical treatment when patients were treated with misoprostol compared with immediate D&C, RR 0.07 (95% CI: 0.03–0.18), without differences in blood transfusion, anemia, pelvic infection or use of pain relief. Moreover, women were satisfied with the treatment they received (Neilson et al., 2010).

When there is a necessity, D&C should be performed in the gentlest manner avoiding unnecessary trauma. Application of materials for the prevention or reduction of adhesion may be effective in the prevention of IUAs, although the evidence is limited and only a minority have been studied in women after miscarriage.

Implications for further research
To accurately define the prevalence of IUAs, a systematic and prospective evaluation is required after spontaneous miscarriage and expectant management, medical evacuation and surgical treatment (D&C). After reviewing the literature, no study was encountered in which this was studied. Several randomized studies have been performed comparing treatment strategies for miscarriage, but without systematic follow-up with IUAs as end-point of interest.

IUAs is a surrogate indicator: long-term fertility, reproductive outcome and obstetric complications are clinically relevant. There is an association between the presence and extent of IUAs and long-term complications but studies addressing the link, especially in women with after miscarriage IUAs, are lacking. Only symptomatic women with IUAs of different causes are reported in the studies available on this subject.

To accurately define the prevalence of IUAs, pregnancy, obstetric and fertility complications, one needs to prospectively follow a large cohort of women after miscarriage for a long period. Subsequently, structural follow-up is necessary to examine cumulative pregnancy, birth and miscarriage rates after conservative, medical and surgical treatment for miscarriage. Furthermore, adjustment should be made for congenital and acquired intrauterine abnormalities as they are frequently encountered and can contribute to miscarriages.

Conclusions
The present review reports IUAs in one of five patients after miscarriage. In >50% the adhesions were of mild severity and extent, but the clinical relevance of these mild adhesions are unknown. Recurrent miscarriage and D&C procedures were identified as the most important risk factors, although other influencing factors could not be ruled out. Data on the link between post-miscarriage IUAs and long-term reproductive outcomes are lacking. Similar reproductive outcomes are reported after conservative, medical and surgical management, although the number of studies and sample size are limited. Furthermore, the quality of the studies was poor to average.

To date, D&C is often performed in clinical practice in women diagnosed with a miscarriage despite the possibility of expectant management and medical treatment and this may account for unnecessary curretages and related IUAs. Further research is urgently needed to analyze treatment modalities in women with a miscarriage in relation to IUAs and to identify risk factors. Subsequently, long-term fertility and preventive measures to avoid adhesion formation following miscarriage can be identified.

Supplementary data
Supplementary data are available at http://humupd.oxfordjournals.org/.

Acknowledgements
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Authors’ roles
A.B.H. was responsible for designing the study. M.L., A.L.T., H.A.M.B., B.W.M. and J.A.F.H. participated in study design and provided knowledge during the analysis and writing of the paper. A.B.H., M.L and J.A.F.H. performed data abstraction and analyzed the data. A.B.H. drafted the first manuscript. M.W.H. and B.C.O. performed the statistical analysis; B.C.O. performed the meta-analysis. All the authors critically revised the manuscript, contributed to the final draft of the manuscript and approved the version to be published.

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Conflict of interest
None declared.

References


