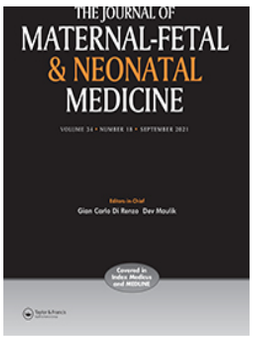

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REVIEW ARTICLE

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Reproductive outcomes in women with mild intrauterine adhesions; a systematic review and meta-analysis

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ABSTRACT

Background: Moderate to severe intrauterine adhesions (IUAs) may greatly impact fertility, predisposing to pregnancy and obstetric complications. The impact of mild IUAs on reproductive performance remains unclear. A systematic review and meta-analysis was performed to examine the long-term reproductive outcomes in women with hysteroscopic identified and treated mild IUAs mild intrauterine adhesions (IUAs)

Methods: An electronic literature search was conducted using MEDLINE and EMBASE from inception to June 2019. All prospective cohort, cross-sectional studies or randomized controlled trials Clinical trials in which reproductive outcomes of women with mild IUAs, were reported were included.

Results: Five studies, reporting on reproductive outcomes of 229 women with hysteroscopic identified and treated mild IUAs, were included. The pregnancy rate was 62.3% (142 of 228; 95% CI: 0.55–0.72, I^2 25%, $p = .21$) and in 86.6% (123 of 142) a live birth was encountered (95% CI: 0.71–0.97) with 83.1% (108 out of 130) term deliveries (95% CI: 0.53–0.95). A miscarriage was reported in 10% (13 of 130; 95% CI: 0.02–0.26). Due to the lack of a control group, reproductive outcomes were compared to a general population. Pregnancy and live birth rates were significantly lower in women with identified and treated mild IUAs, 90% versus 62.3% and respectively 99.5% versus 86.6%. The miscarriage rate was similar. Data on obstetric and neonatal outcomes are lacking.

Conclusions: Women with hysteroscopic identified and treated mild IUAs seem to have lower pregnancy and live birth rate compared to the general population. Future studies consisting of a large cohort of women with hysteroscopic identified and treated IUAs with structural follow-up and a control group are needed to confirm our findings.

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KEYWORDS
Intrauterine adhesions; reproductive outcome; hysteroscopy; fertility; live birth rate

Introduction

Intrauterine adhesions (IUAs) were first described by Fritsch in 1894 [1]. In 1948, Joseph Asherman was the first to describe the etiology of IUAs, since then known as the Asherman's syndrome [2,3]. The terms IUAs and Asherman's syndrome are often used interchangeably, although the syndrome requires a constellation of symptoms [4]. The reported prevalence of IUAs varies between 2.9% and more than 50%, depending on the studied population, applied diagnostic methods, and classification system used [5,6].

IUAs are abnormal fibrous connections joining surfaces of the uterine cavity and develop following the destruction of the basal layer of the endometrium [7]. In the healing process, opposing walls of the uterus adhere together causing partial or complete obliteration of the uterine cavity [8,9]. The pathophysiological process is still undetermined, but IUAs formation is multifactorial with multiple predisposing and causal factors.

IUAs are mainly reported after intrauterine surgery following a miscarriage, termination of pregnancy, retained products of conception (RPOC), and delivery [6,8,10]. Infection and inflammation, retention of trophoblastic tissue, and constitutional factors have also been implicated in the etiology of IUAs [8,11].

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The presence of IUAs can be asymptomatic and often remain undiscovered, but IUAs are commonly associated with menstrual disorders, infertility, and recurrent pregnancy loss [8,12,13]. IUAs can have a major impact on a woman's life.

Nowadays, hysteroscopic adhesiolysis is widely considered the golden standard for diagnosing and treatment of IUAs, but the management remains challenging. There are several classification systems in use to evaluate the extent and degree of IUAs. IUAs are categorized in clinical categories to outline prognosis and results of treatment, defined as mild, moderate, or severe based on the scoring of the classification systems used [6].

Moderate or severe adhesions may greatly impact fertility, predisposing to pregnancy and obstetric complications [13–21]. It is generally believed that mild IUAs do not have an impact on reproductive performance [22–24]. Many studies have reported reproductive outcomes following IUAs, but very few systematically analyzed the impact of mild IUAs on reproductive performance. In this study, we aim to review all available literature reporting on reproductive performance and outcomes in women with mild IUAs.

Methods

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. Institutional Review Board approval was not obtained; all data were extracted from previously published data.

Search

We conducted a literature search for published papers in which key reproductive indicators in women with IUAs were reported. The MEDLINE (Ovid) and EMBASE (Ovid) electronic databases were searched from inception to June 2019. The search terms used were intrauterine adhesions, gynatresia, uterine synechiae, Asherman's syndrome, pregnancy, abortion, fertility, infertility, pregnancy rate, reproductive outcome, and synonyms, restricted to title, abstract, and keywords. We modified the search terms according to database requirements (Supplemental Appendix 1). In addition, we manually searched reference lists of included studies to identify cited articles not captured by the electronic searches.

Paper selection procedure and eligibility criteria

All prospective cohort, cross-sectional studies, or randomized controlled trials (RCTs) reporting on reproductive outcomes in women with IUAs were considered for inclusion. Original articles had to be published as full papers in peer-reviewed journals while language restrictions were not applied. Studies that included less than ten patients, studies published before 1980, reviews, opinion papers, proceedings, editorials, and animal studies were excluded. The presence of IUAs had to be confirmed by hysteroscopy, and adhesiolysis was mandatory for inclusion. Studies in which other diagnostic methods were used for the evaluation of IUAs were not included. To be able to establish the effect on IUAs on reproductive performance and to reduce bias, we excluded studies that reported on reproductive outcomes of women with other infertility factors or after assisted reproductive technology (ART).

Three authors (FJM, ABH, ZF) independently selected the studies in a two-stage process. First, eligibility was assessed based on title and abstract, agreement of two out of the three authors was necessary. Full manuscripts were obtained for all studies that were selected. In the second step, an examination of the full manuscript was carried out to determine eligibility. Disagreement was discussed until consensus was reached. An attempt was made to contact study authors when additional information was needed.

Population

All examined full manuscripts were also screened to establish if an eligible control group was available, a group with predisposing or causative factors who received a diagnostic hysteroscopy in which no IUAs were encountered. The lack of an eligible control group has been established earlier by others; they compared reproductive outcomes of women with IUAs with a general population [26]. Given this fact, we also choose to compared the reproductive performance of women with identified and treated mild IUAs with that of a general population, because we anticipated that an adequate control group will still be lacking. The reproductive outcomes of the general Dutch population were considered reliable and were established by searching hospital guidelines, the data of the Dutch College of General Practitioners, the national statistical office named Statistics Netherlands (CBS), and the perinatal audit and registration data Netherlands (PERINED) . The PERINED database describes the data of all pregnancy factors and complications per year in the Netherlands. The available data from 2018 were used in the current analysis [27].

Extent and degree of intrauterine adhesions

Several scoring and classification systems are used to categorize the severity of adhesions but none have received universal endorsement [28–31]. The severity of IUAs was categorized in three clinical categories defined as mild, moderate, or severe depending on the scale of the classification and scoring systems used [6].

Outcomes

IUAs had to be evaluated hysteroscopically and treated (adhesiolysis). The studies had to report pregnancy outcomes as a primary or secondary outcome parameter. The outcome of subsequent pregnancies, miscarriage, ectopic pregnancy, live birth, and termination of pregnancy (TOP) were considered secondary outcomes. Furthermore, we recorded term delivery, time to conception and obstetric complications if available.

Data extraction and assessment of methodological quality

We extracted the following data: publication year, study design, inclusion and exclusion criteria, characteristics of the patients (age, number of miscarriages in history, number of dilatations and curettage (D&C) procedures in history, nullipara or multipara) severity of adhesions, treatment received, treatment after adhesiolysis, duration of follow-up, the time between treatment and second-look hysteroscopy, reproductive outcomes, time to conception, pregnancy rates, miscarriage rates and live birth rates and if available, obstetric complications. Data extraction was performed by two authors independently (FJM, ZF).

The methodological quality of the selected papers was evaluated independently by two reviewers (ABH and ZF) using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement-checklist [32]. The checklist consists of key elements that should be transparently addressed and reported. During the evaluation, items are rated "1" if the content is transparently and adequately described, "0" if items are inadequately or insufficiently reported, and "NA" if not applicable. The final score is the number of items scored "1," with a maximum of 34. Discordant ratings were adjusted through consultation by the two reviewers.

Data synthesis and Meta-analysis

All analyses were performed in R, version 3.4.0 (R foundation for statistical computing platform, Vienna, Austria) using the packages Meta and Metafor to conduct the meta-analyses [33,34]. We calculated the proportion with 95% confidence interval (CI) of the different outcomes for each study. We used the inverse variance method to combine all proportions in a meta-analysis. Because we expect clinical heterogeneity in the observational studies, we used a random effects model. We assessed statistical heterogeneity by visual inspection of the forest plot, and applied the Q test for heterogeneity and calculated the I^2 statistic. An I^2 of 0–40% was considered as low, 30–60% as moderate, 50–90% as substantial, and 75–100% as considerable heterogeneity [35]. When interpreting the results of the I^2 statistic and the test for heterogeneity, we took the size of the studies that were included in the meta-analysis into account.

Results

Selection of literature

The search performed in June 2019 resulted in 712 Medline (Ovid) studies and 171 Embase (Ovid) studies. The flowchart of the study selection is shown in Supplemental Figure 1. After removing eight duplicates, and 105 studies published before 1980, 770 studies were screened on title and abstract. After excluding 647 articles, 123 full-text articles were screened. An overview of the excluded full-text studies is shown in Supplemental Table 1. Five studies fulfilled all inclusion criteria and were included in the review [36–40].

Description of included studies

One prospective and four retrospective cohort studies were included [36–40]. Characteristics of the included studies are summarized in Table 1. A total of 686 women with IUAs were included in the five studies, ranging from 72 to 357 per study.

The mean age ranged from 27.3 to 35 years. The reported predisposing or causative factors that lead to IUAs formation were trauma to the gravid uterus, especially D&C for termination of pregnancy, miscarriage, or RPOC. Furthermore, trauma to the non-gravid uterus (hysteroscopic surgery, myomectomy) or no obvious reason was also reported. IUAs were classified according to the American Fertility Society (AFS) classification in two studies and in three studies according to the (modified) European Society of Gynecological Endoscopy (ESGE) classification system.

In all studies, IUAs were treated by hysteroscopic adhesiolysis. In one study concomitant laparoscopy

Table 1. Characteristics of the studies reporting on reproductive outcomes of women with hysteroscopic identified and treated mild IUAs.

Author	Study design	Case no.	Mean age (sd)	Age (range)	Postoperative treatment	Device removal (d)	Hormonal treatment	Second-look hysteroscopy	Follow-up	Classification system
Hui	Retro	76	35	<45	IUI	NA	NA	NP	NR	ESGE
Chen	Retro	357	28.4 (6.1)	20–40	NA	NA	Yes	NP	27 months	AFS
Sanad	Pro	72	27.3 (4.8)	<37	Foley	10	Yes	3	33.5 months	AFS
Roy	Retro	96	28.4	21–37	IUD	30	Yes	2	24.5 months	ESGE
Yu	Retro	85	31.1	22–43	IUD	90	Yes	3	3.9 years	ESGE

Abbreviations. AFS: American Fertility Society; ESGE: European Society of Gynecological Endoscopy; HA: hysteroscopical adhesiolysis (HA); Hys: hysteroscopy; IUAs: intrauterine adhesions; IUD: intrauterine device; IUI: intrauterine insemination catheter; Pro: prospective cohort study; Retro: retrospective cohort study; NA: not available (NA); NP: not performed (NP); NR: not reported.

was performed in all cases to guide adhesiolysis [39]. One study did not report post-operative treatment [37]. The ancillary post-operative treatment in the remaining four studies was different: an intrauterine device was inserted in two studies [36,39], a foley catheter in one study [38]. Hormone treatment was provided in four studies [36,38–40]. A second look hysteroscopy to verify the integrity of the uterine cavity following adhesiolysis was performed in three studies [36,38,39].

The follow-up time was not reported in one study [40]. The mean follow-up time in the four remaining studies ranged between 24.5 months and 3.9 years [36–40]. The participants in all included studies were screened for other infertility factors and were excluded in case of other fertility factors besides IUAs to exclude the impact of these factors. Of the 686 included participants, 72 (10.5%) were lost to follow-up, ranging between 5.0% and 15.3% in the included studies. Of the 614 remaining participants, 229 (37.3%) had mild IUAs and were included in the analysis.

The results of the assessment of the methodological quality of the five included prospective studies using the STROBE checklist are reported in Supplemental Table 2. The included studies had a mean item score of 17 (from 31 relevant items), ranging between 10 and 20.

Reproductive outcomes in women with mild IUAs

All five included studies reported on the spontaneous pregnancy rate and the outcome of subsequent pregnancies (Table 2). The results of the meta-analysis are summarized in Figure 1. A spontaneous pregnancy occurred in 143 of the 229 women with mild IUAs, resulting in a pooled proportion of 62.3% (95% CI: 0.55–0.72, I^2 25%, $p = .21$), Figure 1(A). Live birth was reported in five studies, in 123 of the 142 women, resulting in a pooled live birth rate of 86.6% (95% CI: 0.71–0.97), Figure 1(B). Four studies reported data on term delivery; a total of 108 term deliveries were reported out of 130 pregnancies, the pooled term delivery rate was 83.1% (95% CI: 0.53–0.95), Figure 1(C). In four studies data on miscarriage were reported. Overall, a miscarriage was reported in 13 of the 130 women, resulting in a pooled miscarriage rate of 10% (95% CI: 0.02–0.26), Figure 1(D).

Control group

As anticipated, no studies were identified reporting on reproductive performance of a control group.

Table 2. Reproductive outcomes of women with hysteroscopic identified and treated mild IUAs.

Author	Case no.	Cases with mild IUAs (%)	Conception rate (%)	Ongoing pregnancy rate (%)	Live birth rate (%)	Miscarriage rate (%)
Hui	47	22 (50.0)	12/22 (54.5)	NR	10/12 (83.3)	NR
Chen	332	135 (40.7)	82/135 (60.7)	3/82 (3.7)	75/82 (91.5)	4/82 (4.9)
Sanad	61	24 (39.3)	20/24 (83.3)	NR	14/20 (70.0)	6/20 (30)
Roy	89	31 (34.8)	18/31 (58)	NR	17/18 (97.4)	1/18 (5.5)
Yu	85	17 (20.0)	11/17 (62.5)	1/11 (10)	8/11 (70)	2/11 (20)
Total	614	229 (37.3)	143/229 (62.4)	4/93 (4.3)	124/143 (86.7)	13/131 (9.9)

Abbreviations. IUAs: intrauterine adhesions; NR: not reported.

When reproductive outcomes of women with mild IUAs were compared to the general Dutch population, the pregnancy rate was lower, 64% after 24.5 months to 3.9 years in women with mild IUAs versus 90% after two years in the general population [41]. The live birth rate was, respectively 86.6% versus 99.5% [28]. The miscarriage rate was similar, 10–15% versus 10% [42,43].

Obstetric and neonatal outcomes

Data on obstetrics outcomes, including postpartum hemorrhage, placenta accreta, manual placenta removal, ectopic pregnancies, pre-term delivery, and neonatal outcomes including intrauterine growth restriction were lacking or insufficient, making it not possible to analyze these parameters.

Discussion

To our knowledge, this is the first published systematic review and meta-analysis reporting reproductive outcomes in women with mild IUAs after adhesiolysis. Hysteroscopic adhesiolysis aims to restore uterine architecture and consists of removal of IUAs, restoration of the volume, shape, and endometrial lining of the uterine cavity and cervical canal, to facilitate communication between the cavity, cervical canal, and fallopian tubes to allow both normal menstrual flow and adequate sperm transportation [44,45].

Summary of the evidence

After extensive review of the literature, only five cohort studies were identified in which key reproductive indicators were reported in women with hysteroscopic identified and treated mild IUAs. Despite the extensive literature search, we were unable to find a proper control group. In the five studies a pregnancy rate of 62.3% and live birth of 86.6% were encountered in women with hysteroscopic identified and treated mild IUAs, which is significantly lower compared to 90% and 99.5% in the general Dutch population. The miscarriage rate was similar.

Strengths and limitations

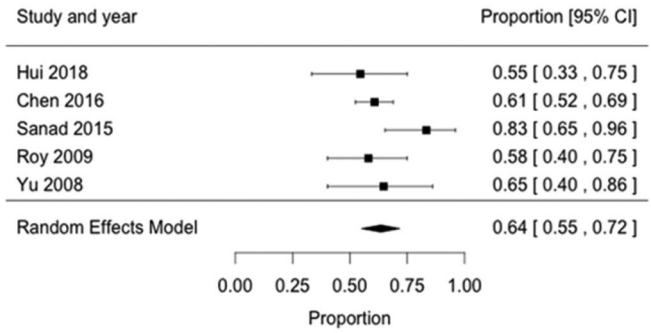
Our study has several points to be highlighted. We performed a systematic review of the literature and included only studies in peer-reviewed journals and individually analyzed the methodology and quality of the included studies. We deliberately excluded studies in which other infertility factors were present or ART was applied, to be able to establish the impact of mild IUAs on reproductive outcome. In all studies, hysteroscopy was the method used to detect, classify, and treat IUAs.

This study has also several weaknesses. Unfortunately, no randomized controlled trials were available, only one prospective and four retrospective cohort studies were encountered. Given the non-randomized design, selection bias is expected to have played a role in the included studies. Cohort studies are less reliable to determine treatment-associated factors.

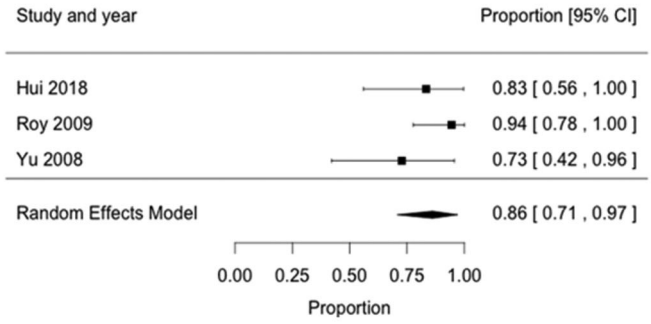
There are possible confounders for the existence of IUAs or reproductive function, such as parity, gravidity, number of prior termination of pregnancies and miscarriages, previously existing IUAs, prior uterine surgery, and surgical interventions. Age is a well-known factor that influences reproductive performance and outcome [46–49]. The age of included women in the studies varied significantly. The aforementioned factors were insufficiently reported; no adjustments were made in the studies for these confounding variables. The individual studies have a limited number of participants and the number of participants lost to follow-up ranged from 0 to 15.3%. Despite meta-analysis, the sample sizes in the (sub) groups were relatively small.

The studies, assessed by the STROBE statement checklist, resulted in an average score of 17 of a maximum of 34, the quality of the studies is poor to average. In addition, there were significant differences in post-operative management. Furthermore, a second-look hysteroscopy was performed, and in case of adhesion reformation, hysteroscopic adhesiolysis was again performed.

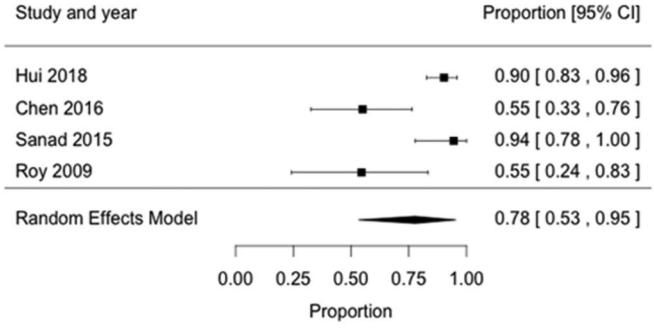
Because of the lack of an eligible control group, we compared women with hysteroscopic identified and treated mild IUAs to a general population, it remains uncertain if the group of women with identified and treated mild IUAs (completely) resembles the general



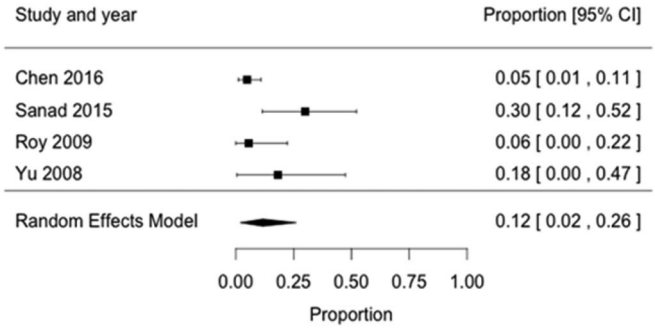
(A) Random-Effects Model, I^2: 24.96%. Q(df = 4) = 5.9195, p-val = 0.2052



(B) Random-Effects Model, I^2: 22.99%. Q(df = 2) = 2.4917, p-val = 0.2877



(C) Random-Effects Model, I^2: 83.61%. Q(df = 3) = 17.4592, p-val = 0.0006.



(D) Random-Effects Model, I^2: 66.82%. Q(df = 3) = 9.5383, p-val = 0.0229.

Figure 1. Summary of meta-analysis presenting pooled proportion with 95% confidence interval (CI) for pregnancy rate (A), live birth rate (B), term delivery rate (C), and miscarriage rate (D) in women with identified and treated mild IUAs.

population. On basis of all the above, we are obliged to interpret the result of this review with caution.

Comparison to the literature

The pathophysiological process that leads to adhesion formation is still not fully elucidated [8,12,36].

The relationship between IUAs and reproductive performance has been frequently described in the literature; moderate and severe IUAs may greatly impact fertility, predisposing to pregnancy and obstetric complication in subsequent pregnancies [12,13,15,36]).

A recent systematic review by Guo et al. reported reproductive outcomes, even after ART in women with hysteroscopic identified and treated IUAs [26]. The distinction could only be made on pregnancy rate between mild, moderate and severe IUAs, the pregnancy rate was 69.1%, comparable to our findings [26].

IUAs are related to obstetric complications, including abnormal placentation, fetal growth restriction, and fetal anomalies, premature delivery, and postpartum hemorrhage [8,12,13]. Unfortunately, we could not analyze obstetric complications and neonatal outcomes. The presence of IUAs should be considered a surrogate indicator; reproductive performance and obstetric and neonatal complications are clinically relevant. The pathophysiologic mechanism by which IUAs impairs reproductive performance and outcomes is complex and still not completely understood but may be related to obstruction of sperm transport, impaired embryo migration, failure of embryo implantation, and diminished receptivity of the endometrium [4,36].

Although the presented result should be interpreted with caution, the pregnancy and live birth rate in women with identified and treated mild IUAs are significantly lower compared to a general population. The reported differences are relevant for women trying to achieve a pregnancy and therefore practitioners should be much more reluctant to perform surgical interventions enhancing IUAs formation. Intrauterine surgical interventions, especially following the miscarriage, termination of pregnancy, delivery, and RPOC should be avoided as much as possible and expectative and medical management should be considered alternatives. Furthermore, patients should be properly informed about the possible risks. Good counseling is of the essence when discussing the need for intrauterine surgery.

Conclusion

Mild IUAs seem to have an impact on reproductive outcomes, a lower pregnancy and live birth rate were encountered compared to a general population. Prevention of IUAs is crucial because of the possible implications on reproductive performance. To accurately define reproductive performance and obstetric complications, prospective follow of a large cohort of women with and without IUAs is needed with structural follow-up.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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