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Reproductive outcomes after surgical treatment of Asherman syndrome: A systematic review



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Systematic review

A B S T R A C T

In this systematic review, we analysed the reproductive outcomes of hysteroscopic adhesiolysis in women with Asherman syndrome (AS). We searched PubMed, Web of Science and Cochrane Library (from database inception to April 2018) and selected studies that quantitatively described the reproductive outcomes. We assessed study quality and pooled rate data for each outcome.

There were 54 studies (4640 women) of varying quality. The pooled rate of pregnancy was 50.7% (95% CI [confidence interval]: 49.1 to 52.3) in 53 studies, early pregnancy loss was 17.7% (95% CI: 15.9 to 19.6) in 31 studies, ectopic pregnancy (EP) was 4.2% (95% CI: 2.8 to 6.3) in 9 studies, mid-trimester loss (MTL) was 11.5% (95% CI: 7.6 to 17.8) in 7 studies, cervical incompetence was 12.5% (95% CI: 3.3 to 33.5) in 2 studies and placenta accreta syndrome was 10.1% (95% CI: 8.6 to 11.8) in 23 studies. The pregnancy rate in women with severe adhesion was significantly lower than that in women with mild adhesion ($P = 0.021$).

These results can be used to counsel women with AS before surgical treatment and for planning antenatal care after conception.

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Introduction

Asherman syndrome (AS) is a consequence of trauma to the basal layer of the endometrium, which commonly occurs after dilation and curettage (D&C) of a gravid uterine [1,2]. It is characterised by the presence of intrauterine adhesions (IUA) or fibrosis in women of reproductive age [1]. IUA is not the same as AS; the former may not be associated with any symptomatology and so does not on its own qualify for the diagnosis of AS, which refers to the presence of IUA or fibrosis along with symptoms attributable to the uterine pathology. The prevalence of IUA after miscarriage is approximately 20% [3], which increases to 40% in those who underwent repeated D&C for retained products of conception [4].

Hysteroscopy is accepted as the gold standard for the diagnosis of IUA; women without any symptom do not warrant surgical intervention, but those who experience symptoms should be considered for hysteroscopic surgery to remove the adhesions [5,6].

The reproductive outcome after hysteroscopic adhesiolysis in women with AS has been reported in a number of studies. Unfortunately, the results are variable owing to a number of reasons. First, there are a number of confounding variables including the age of subjects, severity of IUA, duration of follow-up and co-existence of any other infertility factors. Second, many of the reported studies consisted of small numbers with a relatively wide confidence interval. A systematic review is therefore desirable to combine the observations of various studies. The aim of this review was to analyse the literature reports on the outcome of hysteroscopic surgery with regard to the various stages of pregnancy to provide an update for clinicians providing care for women who conceive after surgical treatment of AS.

Methods

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for reporting a systematic review as a template [7].

Search strategy

Studies were searched through electronic databases including PubMed, Web of Science and Cochrane Library in April 2018 without restriction of regions, publication types or languages. The combined search terms were performed: ('Asherman Syndrome' OR 'Intrauterine adhesion' OR 'uterine adhesion' OR 'uterine synechiae') AND ('pregnancy' OR 'pregnancy rate' OR 'miscarriage' OR 'reproductive outcomes' OR 'pregnancy outcomes'). Both retrospective and prospective cohort studies were included. It was supplemented with manual searches of the reference lists of all retrieved studies.

Inclusion criteria

Both randomised controlled trials (RCTs) and observational studies concerning the reproductive outcome after hysteroscopic adhesiolysis were considered eligible.

We excluded reviews, abstracts, case reports, animal studies, letters to editors, and studies that mentioned pregnancy outcome but did not provide any data.

The inclusion criteria were established before the literature search. We selected studies following a two-stage process: all the titles and abstracts were screened by two authors (CPW and GJ) separately, and then, a second full-text review of the articles was performed. Another person further screened the full text to avoid duplication or overlapping population. Any disagreements were resolved after discussion with a third reviewer (TC Li).

We included studies on pregnancy after IUA, which included complications in the antenatal, intrapartum and postnatal periods as well as neonatal complications.

Preamble/definitions

We focused on published studies in humans analysing the maternal and foetal outcomes. Definitions used in this review are primarily based on World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG) and Royal College of Obstetricians and Gynaecologists (RCOG).

- Term birth: It is defined as deliveries occurring at any time after 37 completed weeks of gestation and up until 42 completed weeks of gestation (260–294 days) [8].
- Preterm birth (PTB): It is defined as birth between 20 0/7 weeks of gestation and 36 6/7 weeks of gestation [9].

Pregnancy losses

- Early pregnancy loss: It is defined as a non-viable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or a foetus without foetal heart activity within the first 12 6/7 weeks of gestation [10].
- Ectopic pregnancy (EP): It is defined as a pregnancy that occurs outside of the uterine cavity [11].
- Mid-trimester loss (MTL): It is defined as the pregnancy loss during the second trimester (i.e. 13–27 weeks of gestation) [12].
- Stillbirth: It is also known as foetal death and defined as the delivery of a foetus with no signs of life, with a gestation at birth after 24 completed weeks of pregnancy [13].
- Neonatal death (NND): It is defined as the death of a newborn of any gestation or birth weight within 28 days of live birth when heartbeat, respiration or other signs of life were observed after the birth is completed [14].

Obstetrical haemorrhage

- Placenta praevia: It is defined as a placenta that is implanted in the uterus in such a position that it obscures the internal cervical os [15,16].
- Placental abruption: It is defined as the separation of the placenta (partially or totally) from its implantation site before delivery [17].
- Post-partum haemorrhage (PPH): It is defined as cumulative blood loss greater than or equal to 1000 mL or blood loss accompanied by signs or symptoms of hypovolaemia within 24 h after birth process regardless of the route of delivery [18].

Obstetrical complications

- Preterm premature rupture of membranes (Preterm PROM): It is defined as the spontaneous rupture of the foetal membranes before 37 completed weeks and before labour onset [19].
- Cervical insufficiency: It is also known as cervical incompetence and defined as the inability of the uterine cervix to retain a pregnancy in the absence of signs and symptoms of clinical contractions, labour, or both in the second trimester [20].
- Intrauterine growth restriction (IUGR): It is also known as foetal growth restriction (FGR) and defined as a foetus with an estimated foetal weight (EFW) that is less than the 10th percentile for gestational age [21].

Placental abnormalities

- Placenta accreta syndrome: It is defined as the abnormally implanted, invasive or adhered placenta. Variations in placenta accrete syndrome are classified by the depth of trophoblastic growth [22].
 - 1) Placenta accreta: The villi are attached to the myometrium;
 - 2) Placenta increta: The villi actually invade the myometrium;
 - 3) Placenta percreta: The villi penetrate through the myometrium and to or through the serosa.

Data extraction

Data were extracted and summarised from the articles independently by two authors (CPW and GJ); only data concerning reproductive outcome were extracted. Information extracted included first author, study design, mean age (year), severity of adhesion, surgery technique, post-surgery ancillary treatment, mean period of follow-up (months), menstruation pattern after surgery, pregnancy rate and obstetric complications. The primary outcomes are pregnancy rate and pregnancy loss rate.

Fifty-four studies including 4953 (4640 follow-up) cases fulfilled the inclusion criteria and were included in the final analysis. All the publications were full-text studies. Agreement between the two reviewers was 96% for study selection.

Statistical analysis

We used extracted data to calculate estimated pooled incidences; then, we compared the incidence of maternal and perinatal complications in pregnant women after surgical treatment of IUA to pregnancies in the general population. Data were analysed using SPSS statistical software, version 21. For comparison of pregnancy characteristics, the Mann–Whitney *U* test was performed for independent variables between two groups, whereas the Kruskal–Wallis test was used for more than two groups. For comparing categorical data, the chi-square test was performed. A probability value (*P* value) of less than 0.05 was considered statistically significant.

Results

Selection of literature

As shown in the flow chart (Fig. 1), a total of 564 studies (PubMed = 87; Cochrane = 20; Web of Science = 457) were identified as relevant after search, and 452 of them were excluded from the first screen of titles and abstracts, as 411 were irrelevant, 33 studies were applied in animals and 8 were duplicated. As a result, 112 full-texts were read, and 58 of these papers were excluded due to different reasons (reviews, editorials or letters, duplications, non-English, case reports or full-text articles could not be found).

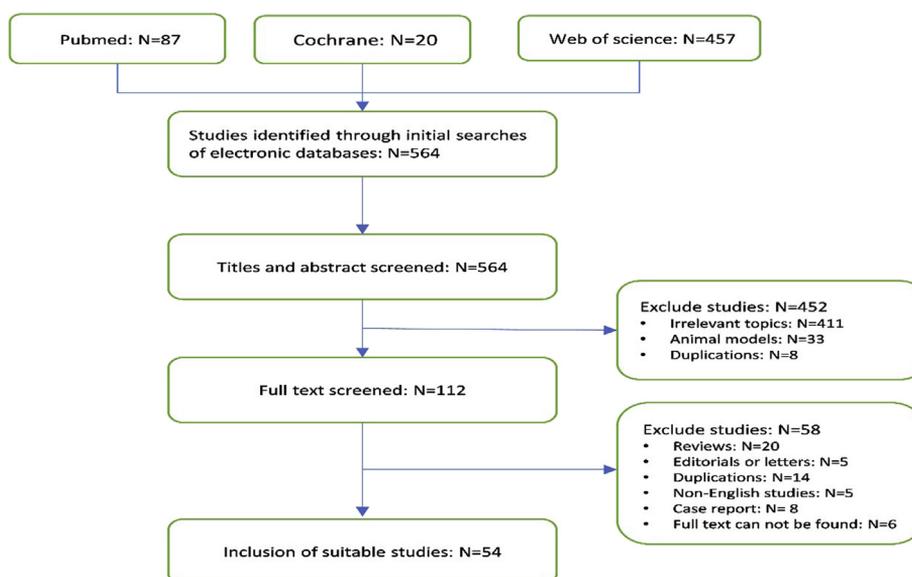


Fig. 1. Flow chart of the study.

Description of studies

A total of 54 studies were selected for final inclusion in this review [6,23–75]. The characteristics of the included studies are presented in Table 1.

- Types of studies

A total of 54 studies were included in this review, and only 5 of them were RCTs [45,47,55,70,71]. The sample size varied among studies, ranging from 4 to 683 subjects. Of these 54 studies, only 1 study compared the pregnancy outcomes between IUA and non-IUA [52]. The lack of a sufficient number of cohort studies precludes a proper meta-analysis presently. The quality of papers was assessed as shown in Fig. 2. (Information about quality is presented as 100% stacked bars, and data in the stacks represent the number of studies).

- Classification of IUA

A classification of IUA is essential when evaluating the degree and extent of IUA. Unfortunately, no standardised uniform classification of IUA has been used in reporting the severity of intrauterine adhesion [1]. Different classification systems had been used in the various included studies including March classification system, the American Fertility Society (AFS), European Society of Hysteroscopy (ESH), Sugimoto's criteria, European Society of Gynaecological Endoscopy (ESGE) and Toaff and Ballas classification. A total of 4 studies chose to report the severity of adhesion with a combination of 2 classification systems [44,48,49,51], and 7 studies did not mention which classification system was used [24,32,43,52,54,56,71]. In addition, the severity of the reported adhesion varied greatly among studies; among the 54 studies, 10 had severe IUA [6,26,30,35,39,41,43,52,63,65], 1 had mild to moderate IUA [71], 8 had moderate to severe IUA [34,36,38,54,59,63,69,75] and 19 had mild to severe IUA [6,28,30,35,40,44,45,48,51,53,60–62,66,67,72–75], whereas 16 did not provide any information about the severity of adhesion [23–27,29,31,39,41,43,52,55–57,64,65]. We have attempted to incorporate the various classification systems into a single clinical grading as recommended by Yu et al. [1] to facilitate the comparison of outcomes (Table 2) (see Table 3).

- Surgical instruments

Various surgical instruments and techniques were used, including hysteroscopic forceps, blunt curettage, hysteroscopic scissors or micro-scissors, hysteroscopic electrode, hysteroscopic resectoscope, mini-resectoscope, hysteroscopic Collin's knife, electrode needle and Versapoint electrosurgical system.

- Post-operative treatments

Post-operative anti-adhesive agents varied widely among studies. One study did not administer any post-operative adjuvant treatment to reduce adhesion reformation [42], but the other 53 studies all employed one or more of the following adjuvant methods: IUD, balloon, hyaluronic acid gel, amnion graft or hormone therapy. Nevertheless, 9 studies provided fewer details of how the adjuvant treatments were used [6,23,28,32,52,62,67,71,74].

Outcome measures

Preamble

All studies reported on crude pregnancy rate; none of the studies reported on cumulative conception rate (pregnancy rate at different duration of follow-up).

Table 1
Basic information of included papers.

Authors	Design	No. of subjects	Mean age (yr)	Surgical technique		Post-surgery treatment	Mean duration of follow-up (month)	Pregnancy rate	Method of conception		Pregnancy loss			Obstetrical haemorrhage				Other obstetrical complications			Live birth	TB	PTB	
				IUD	Balloon				HA	HT	Natural	ART	EPL	EP	MTL	Stillbirth	NND	Placental abruption	Placenta praevia	PPH				PROM
Forsman L, 1965 [23]	Retro	35	-	HS (cold)	-	-	60	15/35 (42.9) ^a	-	-	7/24 (29.2)	1/24 (4.2)	1/24 (4.2)	-	-	-	-	-	-	-	2/24 (8.3)	13/24 (54.2)	11/24 (45.8)	4/24 (16.7)
Cominos AC, 1969 [24]	Retro	68	-	Curette	Y	-	-	30/68 (44.1)	-	-	2/30 (6.7)	-	-	-	-	-	-	-	-	-	2/30 (6.7)	28/30 (93.3)	28/30 (93.3)	-
Oelsner G, 1974 [25]	-	41	-	HSG	Y	-	-	16/41 (39.0) ^a	-	-	6/20 (30.0)	-	-	-	-	-	-	-	-	-	-	14/20 (70.0)	-	-
Jewelewitz R, 1976 [26]	Retro	36	-	HS/D&C	Y	Y	-	18/34 (52.9)	-	-	2/18 (11.1)	1/18 (5.6)	4/18 (22.2)	-	1/18 (5.6)	3/18 (16.7)	-	-	-	-	4/18 (22.2)	10/18 (55.6)	8/18 (44.4)	5/18 (27.8)
Sugimoto O, 1978 [27]	Retro	192	-	HS (cold)	Y	-	-	79/192 (41.2)	-	-	29/79 (36.7)	3/79 (3.8)	-	-	-	-	-	-	-	-	8/79 (10.1)	47/79 (59.5)	45/79 (57.0)	6/3
Bergquist CA, 1981 [28]	Pro	25	-	-	-	-	-	19/25 (76.0)	-	-	5/19 (26.3)	-	-	-	-	-	-	-	-	-	-	13/19 (68.4)	-	-
Friedman A, 1986 [29]	Retro	33	-	HS/D&C	Y	Y	36	36/33 (78.8)	-	-	1/24 (4.2)	-	-	1/24 (4.2)	-	-	-	-	-	-	2/24 (8.3)	23/24 (95.8)	20/24 (83.3)	3/24 (12.5)
Valle RF, 1988 [30]	Retro	187	26	HS (cold)	Y	Y	132	143/187 (76.5)	-	-	26/134 (18.2)	-	-	-	-	-	-	-	-	-	1/143 (0.7)	-	114/143 (79.7)	-
Goldenberg M, 1995 [31]	Pro	36	-	HS	Y	Y	21.1	20/35 (57.1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rogge P, 1996 [32]	Retro	102	32.2	HS (cold/hot)	-	-	24.4	28/50 (56.0) ^a	-	-	10/34 (17.7)	-	-	-	1/34 (2.9)	-	-	-	-	-	1/34 (2.9)	24/34 (70.6)	18/34 (52.9)	6/34 (17.7)
Chen FP, 1997 [33]	Retro	7	31	HS	Y	Y	24	3/7 (42.9)	-	-	-	-	-	-	-	-	-	-	-	-	2/3 (28.6)	0/3	-	-
McComb PF, 1997 [34]	-	6	32	HS (cold)	Y	Y	-	5/6 (83.3)	-	-	1/5 (20.0)	-	-	-	-	-	-	-	-	-	-	4/5 (66.7)	2/5 (33.3)	0
Pabuccu R, 1997 [35]	Retro	40	26.4	HS (cold)	Y	Y	16	34/40 (85.0)	-	-	-	-	-	-	-	-	-	-	-	-	-	23/24 (95.8)	-	40/40 (100)
Protapas A, 1998 [36]	Pro	7	37	HS (cold)	Y	Y	12	3/7 (42.9) ^a	-	-	1/4 (25.0)	1/4 (25.0)	-	-	1/4 (25.0)	1/4 (25.0)	-	-	-	-	1/4 (25.0)	1/4 (25.0)	-	1/4 (25.0)
Capella-Allouc S, 1999 [37]	Retro	28	34.7	HS (cold)	-	Y	31	12/28 (42.9) ^a	11/28 (39.3)	1/28 (3.6)	2/15 (13.3)	3/15 (20.0)	-	-	1/15 (6.7)	1/15 (6.7)	-	-	-	-	2/15 (13.3)	9/15 (60)	5/15 (33.3)	-
Feng ZC, 1999 [38]	Retro	365	33.8	HS (cold)	Y	Y	>12	156/186 (83.9)	-	-	11/156 (7.1)	-	-	-	-	-	-	-	-	-	4/156 (2.6)	145/156 (92.9)	-	-
Ortuz AAE, 2003 [39]	Retro	110	26.9	Curette	Y	Y	96	34/110 (30.9)	-	-	8/34 (23.5)	-	-	-	-	-	-	-	-	-	-	18/34 (52.9)	18/34 (52.9)	8/34 (23.5)
Zikopoulos KA, 2004 [40]	Retro	46	33.6	HS (hot)	Y	Y	39.2	20/46 (43.5)	13/46 (28.3)	7/46 (15.2)	-	-	-	-	-	-	-	-	-	-	2/20 (10.0)	10/20 (50.0)	10/20 (50.0)	
Efete ER, 2006 [41]	Retro	71	29.7	HS (hot)	-	Y	-	8/71 (11.3)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fernandez H, 2006 [42]	Retro	71	36.1	HS (cold)	-	Y	41	28/64 (43.8)	25/64 (39.1)	3/64 (4.7)	3/28 (10.7)	4/28 (14.3)	-	-	1/28 (3.6)	-	-	-	-	-	2/28 (7.1)	21/28 (75.0)	-	-
Thomson AJM, 2007 [6]	Retro	30	33.8	HS (cold/hot)	-	Y	-	9/17 (52.9)	8/17 (47.1)	1/17 (5.9)	-	-	-	-	-	-	-	-	-	-	1/9 (11.1)	8/9 (88.9)	-	-
Yasmin H, 2007 [43]	Retro	20	26.1	HS	Y	Y	12	2/19 (10.5)	-	-	1/2 (50.0)	-	-	-	-	-	-	-	-	-	-	1/2 (50.0)	-	-
Yu D, 2008 [44]	Retro	85	31.1	Y	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

(continued on next page)

Chen L, 2017 [67]	Retro	357 (332) ^b	28.4	HS (hot/cold)	-	-	-	Y	27 (9)	160/332 (48.2)	-	-	15/160 (9.4)	-	-	-	-	-	11/160 (6.9)	-	-	9/160 (5.6)	137/160 (85.6)	135/160 (84.4)	5/160 (3.1)
Chen Y, 2017 [68]	Pro	114 (97) ^b	31.06	HS	Y	Y	-	Y	-	43/97 (44.3)	28/97 (28.9)	15/97 (15.5)	16/43 (37.2)	-	-	-	-	-	1/43 (2.3)	2/43 (4.7)	-	1/43 (2.3)	24/73 (62.8)	-	-
Cai H, 2017 [69]	Retro	76	31.64	HS (cold)	Y	-	Y	Y	-	24/72 (33.3)	20/72 (27.8)	4/72 (5.6)	-	-	-	-	-	-	-	-	-	-	13/24 (54.2)	12/24 (50.0)	-
Gan L, 2017 [70]	RCT	80	29.6	HS (hot)	-	Y	-	Y	8.8 (1.6)	16/80 (20.0)	11/80 (13.8)	5/80 (6.3)	7/16 (43.8)	-	-	-	-	-	-	-	-	-	-	-	-
Roy KK, 2017 [71]	RCT	60	29.6	HS (hot)	-	-	-	Y	-	16/60 (26.7)	-	-	3/16 (18.8)	1/16 (6.3)	-	-	-	-	-	-	-	-	9/16 (56.3)	9/16 (56.3)	-
Zhao J, 2017 [72]	Pro	219 (104) ^b	-	HS (hot)	Y	-	-	Y	>24	63/104 (60.6)	60/104 (57.7)	3/104 (2.9)	18/63 (28.6)	2/63 (3.2)	-	-	-	-	-	-	-	-	41/63 (65.1)	-	-
Baradwan S, 2018 [73]	Retro	41	32.24	HS (hot)	-	-	-	Y	24	22/41 (53.7)	15/41 (36.6)	7/41 (17.1)	6/22 (27.3)	6/22 (27.3)	-	-	-	-	-	-	-	-	-	9/22 (40.9)	5/22 (22.7)
Hui CYY, 2018 [74]	Retro	76 (44) ^b	35	HS	-	-	-	-	>24	25/44 (56.8)	-	-	-	-	-	-	-	-	1/25 (4.0)	-	1/25 (4.0)	19/25 (76.0)	15/25 (60.0)	4/25 (16.0)	
Xu WZ, 2018 [75]	Retro	151	30.72	HS (cold)	Y	Y	Y	Y	84	108/151 (71.5)	57/151 (37.7)	51/151 (33.8)	17/108 (15.7)	6/108 (5.6)	5/108 (4.6)	-	-	-	2/108 (1.9)	-	-	15/108 (13.9)	80/108 (74.01)	73/108 (67.6)	7/108 (6.5)

Yr = years old; IUD = intrauterine device; HA = hyaluronic acid; HT = hormone therapy; Preg. rate = pregnancy rate; ART = assisted reproductive technology; EPL = early pregnancy loss; EP = ectopic pregnancy; MTL = mid-trimester loss; NND = neonatal death; PPH = postpartum haemorrhage; PROM = premature rupture of membrane; IUGR = intrauterine growth restriction; PAS = placenta accreta syndrome; TB = term birth; PTB = preterm birth; Retro = retrospective study; Pro = prospective study; Y = yes; HS = hysteroscopy adhesiolysis; HSG = hysterosalpingography; D&C = dilation and curettage.

NOTE: pregnancy rate = women conceived/women tried to conceive; cold = forceps/scissors/knife; hot = laser/needle/electrode/loop.

^a The pregnancy rate refers to pregnant subjects, but some women conceived more than once.

^b Number of women who completed follow-up.

^c Subjects were selected from women who conceived.

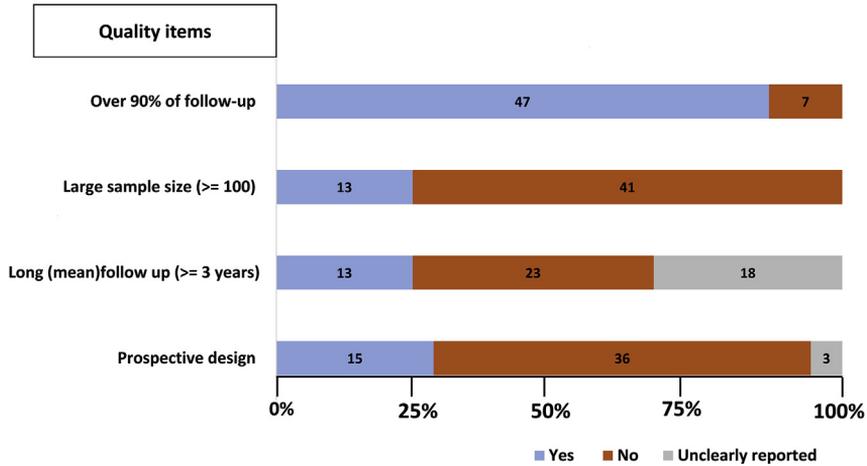


Fig. 2. The quality of papers in the study.

Table 2

A comparison of different classification systems.

Clinical grade	Classification system			
	March 1978	AFS, 1988	ESH, 1989	ESGE, 1995
Mild	Mild	Stage I	Stage I	Stage I
Moderate	Moderate	Stage II	Stage II, IIa or III	Stage II, IIa or III
Severe	Severe	Stage III	Stage IIIa, IIIb or IV	Stage IV, Va or Vb

Table 3

A comparison of menstruation pattern before and after surgical treatment of AS (based on 22 reports).

Menstruation pattern	Before N (%)	After N (%)	P-value
Normal	420 (20.6)	1414 (70.2)	P < 0.01
Hypomenorrhoea	1057 (51.8)	496 (24.6)	
Amenorrhoea	565 (27.7)	103 (5.1)	

Pregnancy rate and pregnancy profile

• Pregnancy rate

The reported pregnancy rate after hysteroscopic management among the 54 studies ranged from 10.5% (2/19) [43] to 100% (4/4) [58]. The overall pregnancy rate for all subjects included in the 54 studies was 50.7% (1871 of 3690 subjects). Interestingly, when the running average method was employed to calculate the cumulative (crude) pregnancy rate (CPR) according to the date of publication (5-year interval), it seems that the rate had increased slightly from ~44% before 1985 to more than 51% after 1986 (Fig. 3).

• Methods of conception

A total of 21 studies reported the pregnancy rate according to the methods of conception. Among 483 pregnancies in whom the methods of conception were known, 135 (~28%) conceived with the help of assisted reproductive technology (ART).

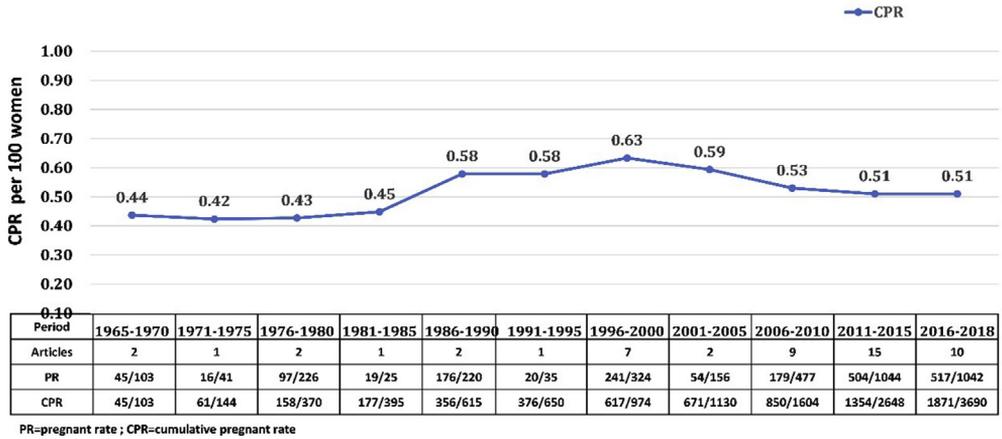


Fig. 3. Cumulative pregnancy rate (CPR) following surgical treatment of AS reported in the literature (grouped at five years interval).

- Severity of adhesions

The relationship between the severity of adhesion and pregnancy rate is shown in Fig. 4; among women with mild, moderate and severe IUA, the median pregnancy rates were 69.1%, 61.3% and 44.3%, respectively. The pregnancy rate was significantly decreased in the severe adhesion group when compared to that in the mild adhesion group ($P = 0.021$) but not in the other two groups (mild vs moderate ($P = 0.222$); moderate vs mild ($P = 0.205$)).

Various pregnancy outcomes (Fig. 5)

1) Live birth

The pooled prevalence of live birth was 64.1% [95% confidence interval (CI): 61.6 to 66.5] among 1543 pregnancies recorded in 41 articles.

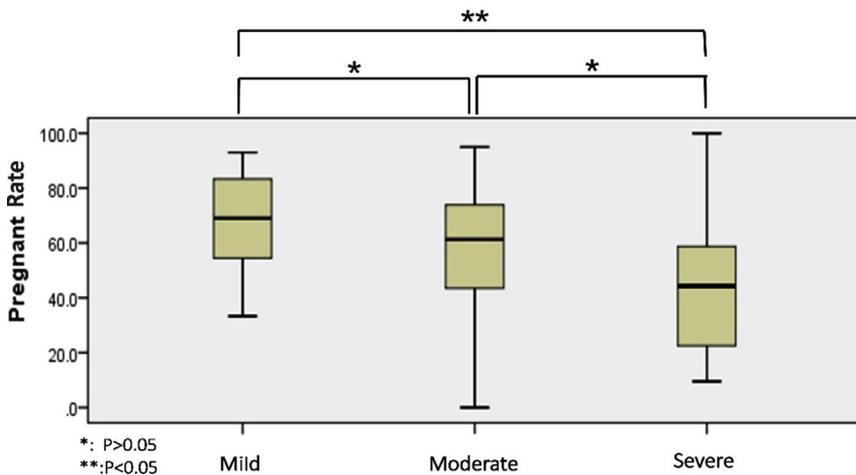


Fig. 4. Box-and whisker plot of pregnancy rate following surgical treatment of AS reported in the literature according to severity of IUA.

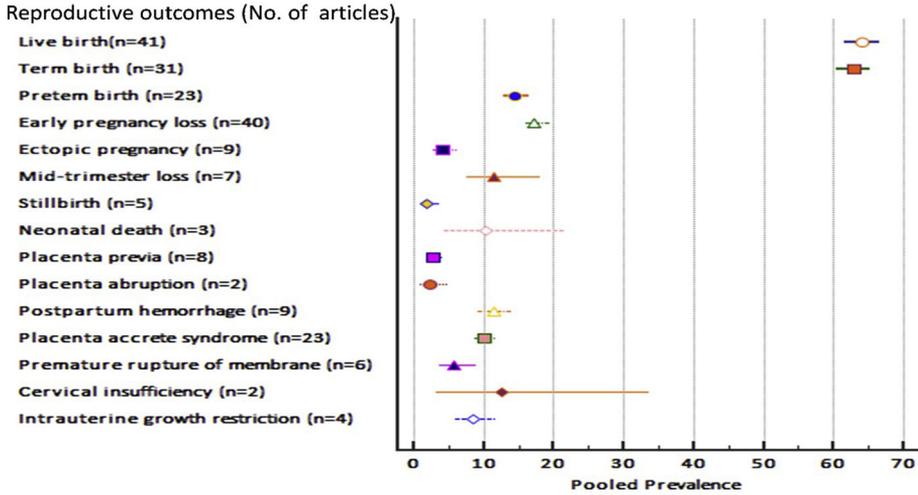


Fig. 5. Forest plot of various reproductive outcomes occurring in a subsequent pregnancy following surgical treatment of AS.

2) Term birth

The pooled prevalence of term birth was 62.8% [95% confidence interval (CI): 60.3 to 65.3] among 1465 pregnancies recorded in 31 articles.

3) Preterm birth (PTB)

The pooled prevalence of PTB was 14.5% (95% CI: 12.7 to 16.5) among 1370 pregnancies recorded in 23 articles.

4) Pregnancy loss

- Early pregnancy loss

The pooled prevalence of early pregnancy loss was 17.7% [95% confidence interval (CI): 15.9 to 19.6] among 1705 pregnancies recorded in 40 articles.

- Ectopic pregnancy (EP)

The pooled prevalence of EP was 4.2% (95% CI: 2.8 to 6.3) among 589 pregnancies recorded in 9 articles.

- Mid-trimester loss (MTL)

The pooled prevalence of MTL was 11.5% (95% CI: 7.6 to 17.8) among 209 pregnancies recorded in 7 articles.

- Stillbirth

The pooled prevalence of stillbirth rate was 1.8% (95% CI: 0.9 to 3.4) among 504 pregnancies recorded in 5 articles.

- Neonatal death (NND)

The pooled prevalence of NND was 10.3% (95% CI: 4.3 to 21.8) among 58 pregnancies recorded in 3 articles.

5) Obstetrical haemorrhage

- Placenta praevia

The pooled prevalence of placenta praevia was 2.8% (95% CI: 1.8 to 4.2) among 832 pregnancies recorded in 8 articles.

- Placental abruption

The pooled prevalence of placental abruption was 2.3% (95% CI: 1.0 to 5.0) among 300 pregnancies recorded in 2 articles.

- PPH

The pooled prevalence of PPH was 11.4% (95% CI: 9.1 to 14.1) among 643 pregnancies recorded in 9 articles.

6) Other complications

- Placenta accreta syndrome

The pooled prevalence of placenta accreta syndrome was 10.1% (95% CI: 8.6 to 11.8) among 1415 pregnancies recorded in 23 articles.

- Premature rupture of membrane (PROM)

The pooled prevalence of PROM was 5.7% (95% CI: 3.6 to 8.7) among 371 pregnancies recorded in 6 articles.

- Cervical incompetence

Table 4

Prevalence of various adverse pregnancy outcomes for women who conceived after surgical treatment of AS compared with the rates in the general population (references in the brackets).

Obstetrical complications	No. of cases	Reported articles	IUA population	General population (%)
			Pooled prevalence (%; 95% CI)	
Pregnancy loss				
Early pregnancy loss	301/1705	40	17.7 (15.9–19.6)	10–25 [78–80]
Ectopic pregnancy	25/589	9	4.2 (2.8–6.3)	1.1–2 [11,81]
Mid-trimester loss	24/209	7	11.5 (7.6–17.8)	1–5 [12,82]
Stillbirth	9/504	5	1.8 (0.9–3.4)	0.5–0.6 [13,83]
Neonatal death	6/58	3	10.3 (4.3–21.8)	1.4–4.1 [84]
Obstetrical haemorrhage				
Placenta praevia	23/832	8	2.8 (1.8–4.2)	0.3–0.5 [16,85]
Placental abruption	7/300	2	2.3 (1.0–5.0)	0.3–1.2 [86,87]
Postpartum haemorrhage	73/643	9	11.4 (9.1–14.1)	5–15 [18,88]
Others				
Placenta accreta syndrome	143/1415	23	10.1 (8.6–11.8)	0.14–0.9 [89,90]
Premature rupture of membrane	21/371	6	5.7 (3.6–8.7)	2–3 [19,91]
Cervical insufficiency	3/24	2	12.5 (3.3–33.5)	1–2 [20]
Intrauterine growth restriction	36/428	4	8.4 (6.0–11.6)	8 [91]
Preterm birth	199/1370	23	14.5 (12.7–16.5)	5–18 [92]

The pooled prevalence of cervical incompetence was 12.5% (95% CI: 3.3 to 33.5) among 55 pregnancies recorded in 2 articles.

- Intrauterine growth restriction (IUGR)

The pooled prevalence of IUGR was 8.7% (95% CI: 6.2 to 12.0) among 403 pregnancies recorded in 4 articles.

Menstruation pattern after surgery

A total of 33 studies reported the menstruation pattern after surgery, and 22 of them provided detailed information about pre- and post-operative menstruation pattern. Overall, the proportion of women with amenorrhoea, hypomenorrhoea and normal period before and after adhesiolysis were 27.7%, 51.8% and 20.6% and 5.1%, 24.6% and 70.2%, respectively.

Discussion

This systematic review of 54 studies including 4953 subjects (4640 subjects with follow-up information) showed that pregnancy occurring in women after surgical treatment of IUA was associated with a number of obstetric complications including EP, cervical incompetence, MTL, placenta praevia, placental abruption, PROM, placenta accreta syndrome, NND and stillbirth when compared with the general population (Table 4). The findings of this systemic review showed that women who conceive following surgical treatment of AS require increased surveillance during their pregnancy.

Women should be offered an earlier ultrasound examination at 6 weeks of gestation to verify foetal viability and to confirm the location of the pregnancy; the fallopian tube is the most common location of EP (~95%); however, implantation in the abdomen (<1%), cervix (1%), ovary (1–3%) and caesarean scar (1–3%) can occur and often results in greater morbidity if the diagnosis and treatment are delayed [11,76]. Further scan may be repeated at 8–10 weeks of gestation to confirm viability given the slight increase in early pregnancy loss. If miscarriage does occur, the management requires careful consideration and discussion of the various treatment options. Expectant treatment, on the one hand, may be the preferred option, but failure rate may be somewhat higher, given that the intrauterine adhesions could have recurred and endometrial fibrosis could have persisted at the time of conception. Surgical treatment, on the other hand, may also be complicated by the presence of residual adhesions or fibrosis, hence leading to a more adherent placenta. Any surgical intervention could incur further damage to the endometrium and must therefore be gently performed, preferably under ultrasound guidance, to minimise injury and to ensure completeness of the procedure.

In the second trimester, regular cervical scan should be considered to monitor cervical length and to look for sign of funnelling, which is an early indication of cervical incompetence.

In the third trimester, foetal growth should be checked at regular intervals for early detection of foetal growth restriction. The placenta should be examined for signs of placenta accreta based on a standardised description of combined ultrasound markers (grey-scale and colour Doppler) proposed by the European Working Group on Abnormally Invasive Placenta (EW-AIP) [77].

The lack of consensus with regard to the use of post-operative adjuvant treatment to prevent adhesion reformation and the paucity of well-planned RCT in this area is evident. Tertiary referral centres that manage a high volume of cases should be encouraged to set up a registry to facilitate the collection of valuable audit data and to conduct RCT to examine the effectiveness, if any, of the various adjuvant treatments in the prevention of recurrence.

On the other hand, the observation in this systemic review that the pregnancy rate appeared to be negatively correlated with the severity of the IUA confirmed the finding of a number of earlier reports [6,31,60,66,68,72].

In summary, pregnancies following surgical treatment for AS are associated with a number of adverse outcomes including EP, cervical incompetence, MTL, placenta praevia, placental abruption,

PROM, placenta accreta syndrome, NND and stillbirth. An enhanced surveillance should be provided to all affected women during various stages of pregnancy.

Practice points

- Pregnancies following surgical treatment of IUA should be managed as high risk’.
- Women who conceived after surgical treatment for IUA should be advised of the risks associated with the pregnancies and offered additional monitoring.
- Delivery should be conducted in a hospital setting by an experienced obstetric team.

Research agenda

- To set up a central registry of women who suffered from Asherman syndrome to audit the outcome of treatment and to enable detailed and more accurate follow-up data to be collected.
- Matched cohort studies, separately for women who conceive spontaneously and those who conceive following assisted conception, should be conducted to compare subjects with and without IUA to confirm the findings reported in this systematic review.
- The observed increase in the prevalence of cervical incompetence in women with Asherman syndrome requires confirmation and the underlying cause for the association merits further study.
- The reason for the observed increase in placenta accreta syndrome and its possible relationship with the reduction of uNK in the (damaged) endometrium, which controls the invasiveness of the implanting trophoblast, should be investigated.

Conflict of interest

None.

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