

Reproductive performance of women with and without intrauterine adhesions following recurrent dilatation and curettage for miscarriage: long-term follow-up of a randomized controlled trial

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STUDY QUESTION: Are the long-term reproductive outcomes following recurrent dilatation and curettage (D&C) for miscarriage in women with identified and treated intrauterine adhesions (IUA) comparable to women without IUAs.

SUMMARY ANSWER: Reproductive outcomes in women with identified and treated IUAs following recurrent D&C for miscarriage are impaired compared to women without IUAs; fewer ongoing pregnancies and live births are achieved with a prolonged time to a live birth.

WHAT IS KNOWN ALREADY: The Prevention of Adhesions Post Abortion (PAPA) study showed that application of auto-crosslinked hyaluronic acid (ACP) gel, an absorbable barrier in women undergoing recurrent D&C for miscarriage resulted in a lower rate of IUAs, 13% versus 31% (relative risk 0.43, 95% CI 0.22 to 0.83), lower mean adhesion score and significant less moderate to severe IUAs. It is unclear what the impact is of IUAs on long-term reproductive performance.

STUDY DESIGN, SIZE, DURATION: This was a follow-up of the PAPA study, a multicenter randomized controlled trial evaluating the application of ACP gel in women undergoing recurrent D&C for miscarriage. All included women received a diagnostic hysteroscopy 8–12 weeks after randomization to evaluate the uterine cavity and for adhesiolysis if IUAs were present. Here, we present the reproductive outcomes in women with identified and treated IUAs versus women without IUAs, 46 months after randomization.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Between December 2011 and July 2015, 152 women with a first-trimester miscarriage with at least one previous D&C, were randomized for D&C alone or D&C with immediate intrauterine application of ACP gel. Participants were approached at least 30 months after randomization to evaluate reproductive performance, obstetric and neonatal outcomes and cycle characteristics. Additionally, the medical files of all participants were reviewed. Main outcome was ongoing pregnancy. Outcomes of subsequent pregnancies, time to conception and time to live birth were also recorded.

MAIN RESULTS AND THE ROLE OF CHANCE: In women pursuing a pregnancy, 14/24 (58%) ongoing pregnancies were recorded in women with identified and treated IUAs versus 80/89 (90%) ongoing pregnancies in women without IUAs odds ratio (OR) 0.18 (95% CI 0.06 to 0.50, *P*-value <0.001). Documented live birth was also lower in women with IUAs; 13/24 (54%) with versus 75/89 (84%) without IUAs, OR 0.22 (95% CI: 0.08 to 0.59, *P*-value 0.004). The median time to conception was 7 months in women with identified and treated IUAs versus 5 months in women without IUAs (hazard ratio (HR) 0.84 (95% CI 0.54 to 1.33)) and time to conception leading to a live birth 15 months versus 5.0 months (HR 0.54 (95% CI: 0.30 to 0.97)). In women with identified and treated IUAs,

premature deliveries were recorded in 3/16 (19%) versus 4/88 (5%) in women without IUAs, *P*-value 0.01. Complications were recorded in respectively 12/16 (75%) versus 26/88 (30%), *P*-value 0.001. No differences were recorded in mean birth weight between the groups.

LIMITATIONS, REASONS FOR CAUTION: In the original PAPA study, randomization was applied for ACP gel application. Comparing women with and without IUAs is not in line with the randomization and therefore confounding of the results cannot be excluded. IUAs, if visible during routine hysteroscopy after randomization were removed as part of the study protocol; the influence of IUAs on reproductive outcome may therefore be underestimated. Women undergoing a recurrent D&C for miscarriage were included, a specific group likely to generate clinically significant adhesions. The findings should therefore not be generalized to all women undergoing D&C for miscarriage.

WIDER IMPLICATIONS OF THE FINDINGS: As IUAs have an impact on reproductive performance, even after hysteroscopic adhesiolysis, primary prevention is essential. Expectative and medical management should therefore be considered as serious alternatives for D&C in women with a miscarriage. In case D&C is necessary, application of ACP gel should be considered.

STUDY FUNDING/COMPETING INTEREST(S): The original PAPA study (NTR 3120) was an investigator initiated study that was funded by the Foundation for scientific investigation in Obstetrics and Gynaecology of the Saint Lucas Andreas Hospital (currently renamed OLVG Oost), SWOGA. The syringes containing ACP gel were received from Anika Therapeutics, the manufacturer of Hyalobarrier® Gel Endo. The current follow-up study was also an investigator-initiated study without funding. The funder and sponsor had no role in the design of this follow-up study, data collection, data analysis, data interpretation, trial design, patient recruitment, writing of the report or any aspect pertinent to the study. ABH, RAL, JAFH and JWRT have no conflict to declare. HAMB reports being a member of safety board research Womed.

TRIAL REGISTRATION NUMBER: Netherlands Trial Register NTR 3120.

Key words: intrauterine adhesions / Asherman syndrome / reproductive outcome / dilatation and curettage / miscarriage / hyaluronic acid / pregnancy / conception

Introduction

Intrauterine adhesions (IUAs) are considered one of the main reproductive system diseases in women worldwide, characterized by endometrial fibrosis with partial to complete obliteration of the uterine cavity and/or cervical canal (McCulloch *et al.*, 1995; Katz *et al.*, 1996; Bosteels *et al.*, 2014; Johary *et al.*, 2014). Any event that causes damage to the endometrium may lead to the development of IUAs, resulting in menstrual disturbances, infertility and (recurrent) pregnancy loss (Capella-Allouc *et al.*, 1999; Yu *et al.*, 2008). The terms IUAs and Asherman syndrome are often used interchangeably, although the syndrome requires the constellation of signs and symptoms (Deans and Abbott, 2010).

IUAs formation is multifactorial, with multiple predisposing and causal factors; the pregnant uterus being the most important predisposing factor (Schenker and Margalioth, 1982; Valle and Sciarra, 1988; Yu *et al.*, 2008). IUAs are encountered in one in five women following a miscarriage; the risk increases after repeated surgical interventions (Hooker *et al.*, 2014). IUAs have a debilitating impact on the health and quality of life in women of childbearing age while the economic burden is substantial (Yu *et al.*, 2008; Deans and Abbott, 2010; Conforti *et al.*, 2013; Bosteels *et al.*, 2014).

Hysteroscopic adhesiolysis is the standard treatment aiming 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 (March, 1995; AAGL Elevating Gynecologic Surgery, 2017).

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 disorders and obstetric complications in subsequent pregnancies (Valle and

Sciarra, 1988; Katz *et al.*, 1996; Pabuçcu *et al.*, 1997; Capella-Allouc *et al.*, 1999; Yu *et al.*, 2008). However, the association is primarily based on retrospective cohort studies, making it difficult to compare women with and without IUAs. The aim of the current study was to compare reproductive performance of women with identified and treated IUAs versus women without IUAs.

Materials and methods

Study design

This study was a follow-up of the Prevention of Adhesions Post Abortion, acronym the PAPA study; a multicenter, women- and assessors-blinded randomized controlled trial (RCT). The manuscript was constructed according to the STROBE guidelines.

For the essentials of the PAPA study, we refer to the original publication of the study (Hooker *et al.*, 2017). In brief, 152 women who experienced a first-trimester miscarriage (less than 14 weeks) with at least one dilatation and curettage (D&C) in history were randomized to D&C alone or D&C with the application of auto-crosslinked hyaluronic acid (ACP) gel, an absorbable barrier, immediately after the D&C procedure. A diagnostic hysteroscopy was performed 8–12 weeks after the D&C procedure to evaluate the uterine cavity. Both the women and hysteroscopic examiner were unaware of the allocation.

IUAs were classified according to the American Fertility Society (AFS) classification of IUAs (American Fertility Society, 1988) and the European Society of Gynecological Endoscopy (ESGE) classification of IUAs version 1998 (Wamsteker and DeBlok, 1998). The AFS classification 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 classification is based on a

combination of type of adhesions, site and extent of cavity involvement and the presence of amenorrhea or pronounced hypomenorrhea; the severity is classified in seven grades.

In women with identified IUAs, adhesiolysis was executed in all cases. Adhesiolysis was performed in the same setting, independent of symptoms. In case of intolerance or discomfort, a new procedure under local, spinal or general anesthesia was performed at the discretion of the hysteroscopic surgeon without the application of ACP gel into the uterine cavity. IUAs were removed, as it was considered unethical not to perform adhesiolysis due to the possible negative effects (Schenker and Margalioth, 1982; Valle and Sciarra, 1988; Capella-Allouc et al., 1999; Yu et al., 2008). A follow-up hysteroscopy in case IUAs were detected to verify anatomic outcome was not mandatory and was not included in the study protocol but in clinical practice women with moderate to severe IUAs received a follow-up hysteroscopy to establish if re-adhesion occurred. Adhesiolysis was performed in all cases with moderate to severe IUAs until a normal cavity was established.

Study population

The study population consisted of participants of the PAPA study. To evaluate reproductive performance, obstetric and neonatal outcomes and cycle characteristics, participants of the PAPA study were approached between December 2017 and April 2018. Respondents were divided in two groups based on the hysteroscopic findings; in a group with identified and treated IUAs and in a group without IUAs. In order to allow analysis, IUAs were classified in three clinical categories mild, moderate and severe based on the scale of the AFS and ESGE classification systems of IUAs (Hooker et al., 2014).

Recruitment and follow-up

For this follow-up study, eligible participants of the PAPA study were approached by post or email. Questionnaire were sent, even if no answer had been obtained to previous questionnaires and consisted of 45 items in six domains (received interventions, complications, menstrual pattern, contraceptive use, desire to become pregnant, conception and outcome of subsequent pregnancies). To minimize lost to follow-up, non-responders received up to three reminders. The medical records of the participants were reviewed to cross-checked obtained outcomes. Data were handled confidential, anonymously and in comply with the European General Data Protection Regulation.

Ethical approval

The RCT and follow-up study was conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects and registered at the Dutch Clinical Trial Registry (NTR 3120). The study protocol was approved by the National Central Committee in Research involving Human Subjects (CCMO-NL 35693.029.10.), by the ethics committee of the Amsterdam University Medical Center (2011/2562011/256) and by the boards of directors of all participating hospitals before start of inclusion. Written and signed informed consent for randomization and follow-up was provided by all participants before randomization.

Outcome measures

The main outcome of the current study was ongoing pregnancy. Conception and outcome of subsequent pregnancies: miscarriage, ectopic pregnancy, live birth and termination of pregnancy (TOP), time to conception, time to pregnancy resulting in live birth were secondary outcomes. Outcome of all subsequent pregnancies that occurred during the entire follow-up period in both groups were compared. Furthermore, menstrual characteristics and obstetrics and neonatal events, including preterm delivery, intra-uterine fetal death, type of delivery, obstetric complications and birth weight, were also recorded.

Definitions

Pregnancy was defined as a positive HCG pregnancy test, an ectopic pregnancy as an embryo implanted outside the uterine cavity and TOP as the termination of a pregnancy with fetal cardiac activity verified by ultrasonography because of congenital malformations. A miscarriage was defined as an intrauterine pregnancy that ended in pregnancy failure before 14 weeks of gestation and an ongoing pregnancy as the presence of fetal cardiac activity verified by ultrasonography beyond 14 weeks of gestation. Live birth indicated the delivery of at least one live fetus beyond 24 weeks of gestation.

Statistical analysis

Categorical data were summarized as absolute numbers and percentages (%). Normally distributed continuous variables were summarized as means, with SDs and non-normally distributed continuous variables as medians with quartiles.

Proportions were compared between groups, in women with identified and treated IUAs and in women without IUAs, using χ^2 test or Fisher's exact test in the case of low cell counts. Since age could have influenced reproductive outcomes, correction for age was performed using logistic regression analysis. Kaplan–Meier analyses and log-rank tests were used to compare time to conception and time to conception resulting in a live birth. Cox regression analysis (both crude and adjusted for age) was used to calculate hazard ratio (HR), together with their 95% CIs. Reproductive outcomes were analyzed for the entire group and for the group of women pursuing a pregnancy. Within the group of patients with IUAs, additional subgroup analyses were performed according to both the AFS and ESGE classification of IUAs.

Time to conception was calculated as the time between randomization and the first day of the menstruation cycle before pregnancy. For comparison of time to conception only the first pregnancy that occurred was taken into account per patient. For the comparison of time to conception resulting in a live birth, we included only the first pregnancy per patient that resulted in a live birth in our analyses. Statistical analyses were performed using SPSS (version 20). A two-sided significance level of 5% was used for all statistical tests.

Results

Participants

Between December 2017 and April 2018, questionnaires were posted to 140 eligible participants: 30 women with identified and treated IUAs and 110 women without IUAs. Nine women were lost to

follow-up, four in the group with identified and treated IUAs and five in the group without IUAs, they were not included in the current analysis. The response rate was 26/30 (87%) in the group with identified and treated IUAs and 105/110 (96%) in the group without IUAs (P -value 0.10).

Baseline characteristics

The mean duration of the follow-up was comparable in both groups, 46 months (quartiles 38, 57) in the group with identified and treated IUAs versus 46 months (quartiles 37, 58) in the group without IUAs (P -value 1.00). The demographic characteristics of the study populations were comparable, except that significant more women in the group with identified and treated IUAs had three or more previous D&C procedures (Table I). No significant differences were reported in menstrual cycle length, but significant more women with identified and treated IUAs reported less blood loss compared to women without IUAs, respectively 39% versus 9% (P -value 0.001), Table I.

Reproductive outcomes

When all responders were included, a total of 24/26 (92%) women with identified and treated IUAs conceived versus 88/105 (84%) women without IUAs, odds ratio (OR) 2.48 (95% CI: 0.54 to 11.45, P -value 0.24).

Reproductive outcomes are shown in Table II. Significantly less ongoing pregnancies were recorded in women with identified and treated IUAs, 14/26 (54%) versus 80/105 (76%), OR 0.38 (95% CI: 0.16 to 0.93, P -value 0.045). The live birth rate was significantly lower in women with identified and treated IUAs, 13/26 (50%) versus 75/105 (71%) in women without IUAs, OR 0.40 (95% CI 0.17 to 0.96, P -value 0.04). Miscarriage rates were respectively 11/26 (42%) versus 27/105 (26%), OR 2.12 (95% CI 0.87 to 5.17, P -value 0.10). More ectopic pregnancies were recorded in women with identified and treated IUAs (P -value 0.04), TOP rates were similar (Table II). When adjusted for age, the results did not change significantly (Supplementary Table SI).

Women pursuing pregnancy

When only women pursuing a pregnancy were included, pregnancy was recorded in 24/24 (100.0%) women with identified and treated IUAs versus 88/89 (99%) women without IUAs, P -value 1.00. Significant less ongoing pregnancies were reported in women with identified and treated IUAs versus women without IUAs, respectively 14/24 (58%) women versus 80/89 (90%) women, OR 0.18 (95% CI 0.06 to 0.50, P -value <0.001). The live birth rate was also significantly lower in women with identified and treated IUAs, respectively 13/24 (54%) versus 75/89 (84%) women, OR 0.22 (95% CI: 0.08 to 0.59, P -value 0.004). Miscarriage rates were respectively 11/24 (46%) versus 27/89 (30%), OR 1.94 (0.77 to 4.88, P -value 0.22). Significantly more ectopic pregnancies were reported in women with identified and treated IUAs (P -value 0.04), Table II. When adjusted for age, the results did not change significantly (Supplementary Table SI).

Time to conception

The median time to conception was 7 months (95% CI 5 to 8) in women with identified and treated IUAs versus 5 months (95% CI:

4 to 6) in women without IUAs, HR 0.84 (95% CI 0.54 to 1.33, P -value 0.46), Fig. 1A. The median time to conception leading to a live birth was 15 months (95% CI: 4 to 25) in women with IUAs versus 5 months (95% CI: 4 to 6) in women without IUAs, HR=0.54 (95% CI: 0.30 to 0.97; P -value 0.04), Fig. 1B. When adjusted for age, the results did not change significantly (Supplementary Table SI).

Number of pregnancies

When all pregnancies during the follow-up period were examined, the pregnancy rates were similar, respectively 1.48 (34/23) in the group with identified and treated IUAs versus 1.50 (132/88) in the group without IUAs. Significant less ongoing pregnancies were noted during the follow-up period in the group of women with identified and treated IUAs, respectively 47% (16 of 34) versus 71% (93 of 132), P -value 0.023. A lower but nonsignificant difference was encountered in live births in women with identified and treated IUAs, 47% (16 of 34) versus 67% (88 of 132), respectively (P -value 0.067). Significantly more miscarriages were encountered in women with identified and treated IUAs, respectively 47% (16 of 34) versus 28% (37 of 132), P -value 0.011. The rate of ectopic pregnancies and termination of pregnancy were comparable, respectively 6% (2 of 34) versus 0% (0 of 132), P -value 0.20 and 0% (0 of 34) versus 3% (4 of 132), P -value 1.00.

Obstetric and neonatal outcomes

Significantly more premature deliveries were recorded in women with identified and treated IUAs, 19% (3 of 16) versus 5% (4 of 88), P -value 0.01. Furthermore, significant more complications were noted, respectively 75% (12 of 16) versus 30% (26 of 88), P -value 0.001 (Table III). There were no significant differences in the mode of delivery and mean birth weight between the groups.

Reproductive outcomes according to clinical categories

The identified and treated IUAs were classified in three clinical categories: mild, moderate and severe (according to both the AFS and ESGE classification) and compared to women without IUAs. Because of the relative small samples, the moderate and severe IUAs were grouped.

Outcomes according to the AFS classification of adhesions

Reproductive outcomes according to the AFS classification are reported in Table IV. When all responders were included, significant more miscarriages were encountered in women with moderate to severe IUAs (P -value 0.02) and significant more ectopic pregnancies in women with mild IUAs compared to women without IUAs (P -value 0.02). In women pursuing a pregnancy, significant less ongoing pregnancies and live births were recorded in women with moderate to severe IUAs (P -value 0.003 and 0.002, respectively), and in women with mild IUAs (P -value 0.013 and 0.012, respectively), compared to women without IUAs. Significant more ectopic pregnancies were encountered in women with mild IUAs (P -value 0.02).

The median time to conception was 5 months (95% CI: 4 to 6) in women without IUA, 7 months (95% CI 3 to 10) in women with mild

Table I Baseline characteristics of the women.

	Intrauterine adhesions		P-value ¹
	Present (n = 26)	Absent (n = 105)	
Baseline characteristics			
Age at entry (years; mean ± SEM)	38 ± 4.8	38 ± 5.3	0.72
White ethnic origin	23 (89)	93 (89)	1.00
Gravidity			0.60
2	6 (23)	31 (30)	
3	7 (27)	34 (32)	
≥4	13 (50)	40 (38)	
Parity			0.80
0	11 (42)	47 (45)	
1	12 (46)	39 (37)	
2	2 (8)	15 (14)	
≥3	1 (4)	4 (4)	
Number of previous D&C procedures [#]			0.04
1	15 (58)	78 (74)	
2	6 (23)	22 (21)	
≥3	5 (19)	5 (5)	
Number of previous miscarriages			0.69
0	5 (19)	25 (24)	
1	9 (35)	43 (41)	
2	9 (35)	24 (23)	
≥3	3 (12)	13 (12)	
Number of prior pregnancy terminations			0.65
0	19 (73)	71 (68)	
≥1	7 (27)	34 (32)	
Prior infertility treatment	1 (4)	13 (12)	0.30
Prior cesarean section	3 (12)	14 (13)	1.00
Menstrual characteristics			
Cycle length (days)			1.00
<24 days	1 (4)	7 (7)	
24–36 days	21 (81)	82 (78)	
>37 days	4 (15)	16 (15)	
Menstrual blood loss			0.001
Less	10 (39)	9 (9)	
Equal	16 (62)	84 (80)	
Increased	0 (0)	12 (11)	
Dysmenorrhea	6 (23)	26 (25)	1.00
Yes, always	3 (12)	19 (18)	0.56
Yes, since the D&C	3 (12)	7 (7)	0.42
Fertility intention			
Contraception use	1 (8)	12 (11)	0.46
Sterilization	1 (4)	4 (4)	1.00
Pursuing pregnancy	24 (92)	89 (85)	0.53

Data are n (%) unless stated otherwise.

¹Analyzed with Fisher's exact test, the independent-samples *t*-test was used for the outcome age. [#] Dilatation and curettage (D&C) was performed for miscarriage, termination of pregnancy or retained products of conception.

Table II Reproductive outcomes of women with and women without intrauterine adhesions (IUAs).

	Intrauterine adhesions		P-value
	Present (n = 26)	Absent (n = 105)	
Conceived	24/26 (92)	87/105 (83)	0.36
Ectopic pregnancy	2/26 (8)	0/105 (0)	0.04
Termination of pregnancy	0/26 (0)	4/105 (4)	0.58
Miscarriage	11/26 (42)	27/105 (26)	0.15
1	6/26 (23)	19/105 (18)	0.58
≥2	5/26 (19)	8/105 (8)	0.013
Ongoing pregnancy	14/26 (54)	79/105 (75)	0.05
Live birth	13/26 (50)	75/105 (71)	0.04
1	10/26 (39)	64/105 (61)	0.05
≥2	3/26 (12)	11/105 (11)	1.00
Women pursuing a pregnancy (n = 24)	(n = 24)	(n = 89)	
Conceived	24/24 (100)	88/89 (99)	1.00
Ectopic pregnancy	2/24 (8)	0/89 (0)	0.04
Termination of pregnancy	0/24 (0)	4/89 (5)	0.58
Miscarriage	11/24 (46)	27/89 (30)	0.22
1	6/24 (25)	19/89 (21)	0.78
≥2	5/24 (21)	6/89 (7)	0.05
Ongoing pregnancy	13/24 (54)	80/89 (90)	<0.001
Live birth	13/24 (54)	75/89 (84)	0.004
1	10/24 (42)	64/89 (72)	0.008
≥2	3/24 (13)	11/89 (14)	1.00

Values are number (percentages); analyzed with Fisher's exact test.

IUAs (HR 0.82, 95% CI 0.47 to 1.42, *P*-value 0.48) and 7 months (95% CI 4.4 to 10.3) in women with moderate to severe (HR 0.89, 95% CI 0.44 to 1.77, *P*-value 0.73), [Figure 2A](#). The median time to conception leading to a live birth was respectively 5 months (95% CI: 4 to 6), 8 months (95% CI 2 to 13), (HR 0.59, 95% CI 0.29 to 1.17, *P*-value 0.13) and 15 months (95% CI 0.18 to 29.20), (HR 0.45, 95% CI 0.16 to 1.23, *P*-value 0.12), [Fig. 2B](#).

Outcomes according to the ESGE classification of adhesions

Reproductive outcomes according to the ESGE classification are reported in [Table IV](#). When all responders were included, significant more miscarriages were reported in women with moderate to severe IUAs compared to women without IUAs (*P*-value 0.04). In women pursuing a pregnancy, significant less ongoing pregnancies were recorded in women with moderate to severe and mild IUAs in comparison to women without IUAs (*P*-value 0.04 and 0.001, respectively). In women with moderate to severe IUAs significant less live births were reported, *P*-value 0.007.

The median time to conception was 5 months (95% CI: 4 to 6) in women without IUA, 10 months (95% CI 0 to 26.0) in women with mild IUAs (HR 0.91, 95% CI 0.42 to 1.97, *P*-value 0.81) and 7 months

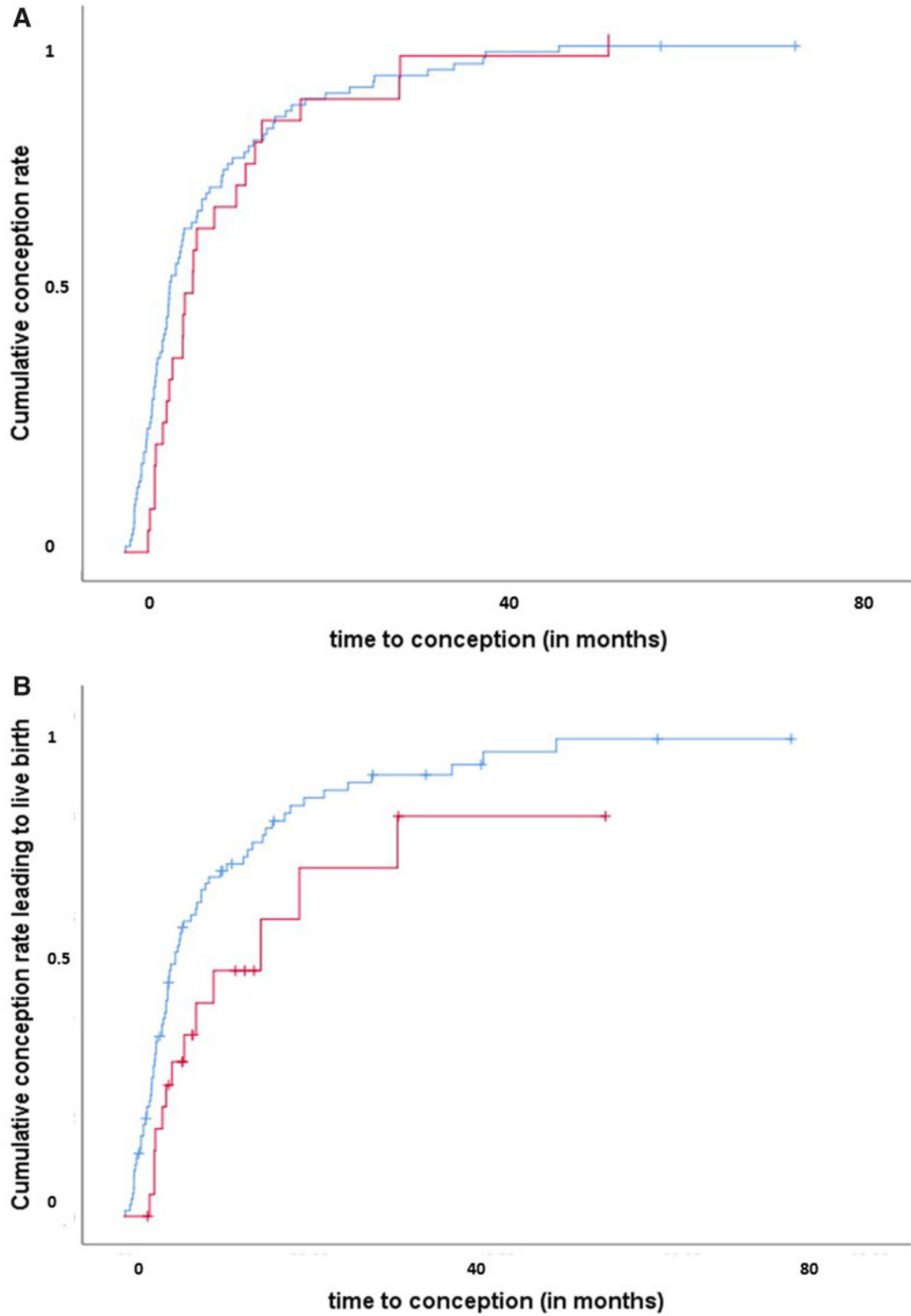


Figure 1. Time to conception (A) and time to conception leading to a live birth (B) in women with identified and treated intrauterine adhesions (IUAs) and women without IUAs. Vertical marks indicate where a participant was lost to follow-up (censored).

Table III Obstetric and neonatal outcomes of the women with and women without intrauterine adhesions (IUAs).

Deliveries	Intrauterine adhesions		P-value
	Present (n = 16)	Absent (n = 88)	
<i>Obstetric outcome</i>			
Term delivery	13/16 (81)	83/88 (96)	0.10
Premature birth	3/16 (19)	4/88 (5)	0.01
<i>Mode of delivery</i>			
Vaginal	14/16 (88)	58/88 (67)	0.14
Caesarean section	2/16 (13)	25/88 (28)	0.23
Primary	0/16 (0)	13/25 (52)	<0.001
Secondary	2/2 (100)	12/25 (48)	0.481
Instrumental	0/6 (0)	4/8 (5)	1.00
<i>Complications</i>			
Total	12/16 (750)	26/88 (30)	0.001
Hemorrhage (\geq 1000 ml)	3/16 (19)	11/88 (13)	0.45
Manual placental removal	3/16 (19)	8/88 (9)	0.37
Preterm pre-labor rupture of the membranes	3/16 (19)	2/88 (2)	0.03
Cervical insufficiency	1/16 (6)	1/88 (1)	0.29
Placental remnant	1/16 (6)	1/88 (1)	0.29
Other	1/16 (6)	3/88 (3)	0.50
<i>Neonatal outcome Median (quartiles)</i>			
Gestation (weeks)	40 (37–41)	39 (38–41)	0.58
Birth weight (g)	3506 (2968–3695)	3500 (3258–3650)	0.80

Values are number (percentages); analyzed with Fisher's exact test, unless otherwise stated.

(95% CI 5 to 8) in women with moderate to severe IUAs (HR 0.82, 95% CI 0.49 to 1.38, *P*-value 0.46), Fig. 2C. The median time to conception leading to a live birth was respectively 5 months (95% CI: 4 to 6), 10 months (95% CI 0 to 21), (HR 0.75, 95% CI 0.30 to 1.86, *P*-value 0.54) and 19 months (95% CI 4 to 34), (HR 0.45, 95% CI 0.22 to 0.94, *P*-value 0.03), Fig. 2D.

Number of pregnancies

When all pregnancies during the follow-up period were examined, the pregnancy rates were similar. Significant more miscarriages, less ongoing pregnancies and live births were encountered during the entire follow-up period in women with moderate to severe IUAs compared to women without IUAs according to both the AFS and ESGE classification systems (Table IV).

Discussion

To the best of our knowledge, this is the first published study reporting reproductive performance of women with identified and treated

IUAs compared to women without IUAs after recurrent D&C for miscarriage.

Main findings

After a mean follow-up of 46 months, significant less ongoing pregnancies and live births were encountered in women with identified and treated IUAs compared to women without IUAs when all responders were included. The difference in ongoing pregnancy and live birth rates increased when only women pursuing a pregnancy were included. The median time to conception was similar but the median time to live birth was significantly longer in women with identified and treated IUAs, 14.7 versus 5.0 months. There was no differences in mode of delivery, but significantly more premature deliveries and complications were recorded in women with identified and treated IUAs. When all pregnancies that occurred during the follow-up period were analyzed, significant less ongoing pregnancies and live births were recorded and significant more miscarriages in women with IUAs.

When subgroup analyses was performed in the group with identified and treated IUAs, both mild and moderate to severe IUAs seem to have an impact on reproductive performance and are associated with less ongoing pregnancies in women pursuing a pregnancy according to both the AFS and ESGE classification systems. Significant more miscarriages, less ongoing pregnancies and live births were encountered in women with moderate to severe IUAs compared to women without IUAs when all pregnancies during the follow-up period were analyzed.

As reproductive performance in the groups, including the number of miscarriages, was similar at baseline, the presence of IUAs seems to have a compromising effect on reproductive performance, even after adhesiolysis.

Strength and limitations

The strength of our study include the collection of data after a mean follow-up of 46 months. Although dropouts are unavoidable, less than 10% of the eligible participants were lost to follow-up. The medical records of the respondents were reviewed to cross-check the obtained data. As part of the RCT, all participants received a hysteroscopy, making it possible to establish the presence, extent and degree of IUAs.

The current study compared reproductive outcomes in women with hysteroscopic identified IUAs versus women without IUAs following D&C for miscarriage making it possible to have an adequate control group. Furthermore, the outcomes of the clinical categories of IUAs, mild and moderate to severe, were compared to women without IUAs according to the international most used classification systems. An additional strength of the current study is that we performed additional analyses correcting for age, a potential confounder for reproductive performance.

Potential limitation of the current study include the fact that the PAPA study was designed and powered for the presence of IUAs and not for comparison of long-term reproductive outcomes in women with hysteroscopic identified and treated IUAs versus women without IUAs. As hysteroscopic adhesiolysis was routinely performed, the reported differences in reproductive performance are probably an underestimation of the real differences: a diagnostic hysteroscopy and subsequently adhesiolysis is not a standard treatment regime following

Table IV Reproductive outcomes by severity of intrauterine adhesions (IUAs), classified according to the American Fertility Society (AFS) and European Society of Gynecological Endoscopy (ESGE) classification.

	Women without IUAs	Women with IUAs according to the AFS classification				Women with IUAs according to the ESGE classification			
		Mild IUAs	P-value	Moderate to severe IUAs	P-value	Mild IUAs	P-value	Moderate to severe IUAs	P-value
Conceived	87/105 (82.9)	15/17 (88.2)	0.74	9/9 (100)	0.35	7/9 (77.8)	0.66	17/17 (100)	0.07
Ectopic pregnancy	0/105 (0)	2/17 (11.8)	0.02	0/9 (0)	1	1/9 (11.1)	0.08	1/17 (5.9)	0.14
Termination of pregnancy	4/105 (3.8)	0/17 (0)	1	0/9 (0)	1	0/9 (0)	1	0/17 (0)	1
Miscarriage	27/105 (25.7)	5/17 (29.4)	0.77	6/9 (66.7)	0.02	2/9 (22.2)	1	9/17 (52.9)	0.04
1	19/105 (18.1)	3/17 (17.6)	1	3/9 (33.3)	0.37	1/9 (11.1)	1	5/17 (29.4)	0.32
≥2	8/105 (7.6)	2/17 (11.8)	0.63	3/9 (33.3)	0.04	1/9 (11.1)	0.54	4/17 (23.5)	0.06
Ongoing pregnancy	79/105 (75.2)	9/17 (52.9)	0.08	4/9 (44.4)	0.06	4/9 (44.4)	0.06	10/17 (58.8)	0.24
Live birth	75/105 (71.4)	8/17 (47.0)	0.05	4/9 (44.4)	0.13	4/9 (44.4)	0.13	9/17 (52.9)	0.16
1	64/105 (61.0)	6/17 (35.3)	0.06	3/9 (33.3)	0.16	3/9 (33.3)	0.16	7/17 (41.2)	0.18
≥2	11/105 (10.6)	2/17 (11.8)	1	1/9 (11.1)	1	1/9 (11.1)	1	2/17 (11.8)	1
<i>Women pursuing a pregnancy</i>									
Conceived	88/89 (98.9)	15/15 (100)	1	9/9 (100)	1	7/7 (100)	1	17/17	1
Ectopic pregnancy	0/89 (0)	2/15 (13.3)	0.02	0/9 (0)	1	1/7 (14.3)	0.07	1/17 (5.9)	0.16
Termination of pregnancy	4/89 (4.5)	0/15 (0)	1	0/9 (0)	1	0/7 (0)	1	0/17 (0)	1
Miscarriage	27/89 (30.3)	5/15 (33.3)	0.77	6/9 (66.7)	0.06	2/7 (28.6)	1	9/17 (52.9)	0.09
1	19/89 (21.3)	3/15 (20)	1	3/9 (33.3)	0.42	1/7 (14.3)	1	5/17 (29.4)	0.53
≥2	6/89 (6.7)	2/15 (13.3)	0.33	3/9 (33.3)	0.04	1/7 (14.3)	0.42	4/17 (23.5)	0.05
Ongoing pregnancy	80/89 (89.9)	8/15 (53.3)	0.002	4/9 (44.4)	0.003	4/7 (57.1)	0.04	9/17 (52.9)	0.001
Live birth	75/89 (84.3)	8/15 (53.3)	0.012	4/9 (44.4)	0.013	4/7 (57.1)	0.10	9/17 (52.9)	0.007
1	64/89 (71.9)	6/15 (40)	0.03	3/9 (33.3)	0.03	3/7 (42.9)	0.19	7/17 (41.2)	0.02
≥2	11/89 (13.6)	2/15 (13.3)	1	1/9 (11.1)	1	1/7 (14.3)	1	2/17 (11.8)	1
<i>Number of pregnancies</i>									
Mean pregnancy rate	132/88 (1.50)	20/15 (1.33)		14/9 (1.56)		10/7 (1.43)		24/17 (1.41)	
Ectopic pregnancy	0/132 (0)	2/20 (10)	0.02	0/14 (0)	1	1/10 (10)	0.07	1/24 (4.2)	0.15
Termination of pregnancy	4/132 (3.0)	0/20	1	0/14 (0)	1	0/10 (0)	1	0/24 (0)	1
Miscarriage	37/132 (28.0)	7/20 (35)	0.60	9/14 (64.2)	0.01	3/10 (30)	1	13/24 (54.2)	0.02
Ongoing pregnancy	93/132 (70.5)	11/20 (55)	0.20	5/14 (35.7)	0.01	6/10 (60)	0.49	10/24 (41.7)	0.009
Immature delivery	1/132 (0.8)	0/20	1	0/14 (0)	1	0/10 (0)	1	0/24 (0)	1
Live birth	88/132 (66.7)	11/20 (55)	0.32	5/15 (35.7)	0.02	6/10 (60)	0.73	10/24 (41.7)	0.02

Values are number (percentages); analyzed with Fisher's exact test.

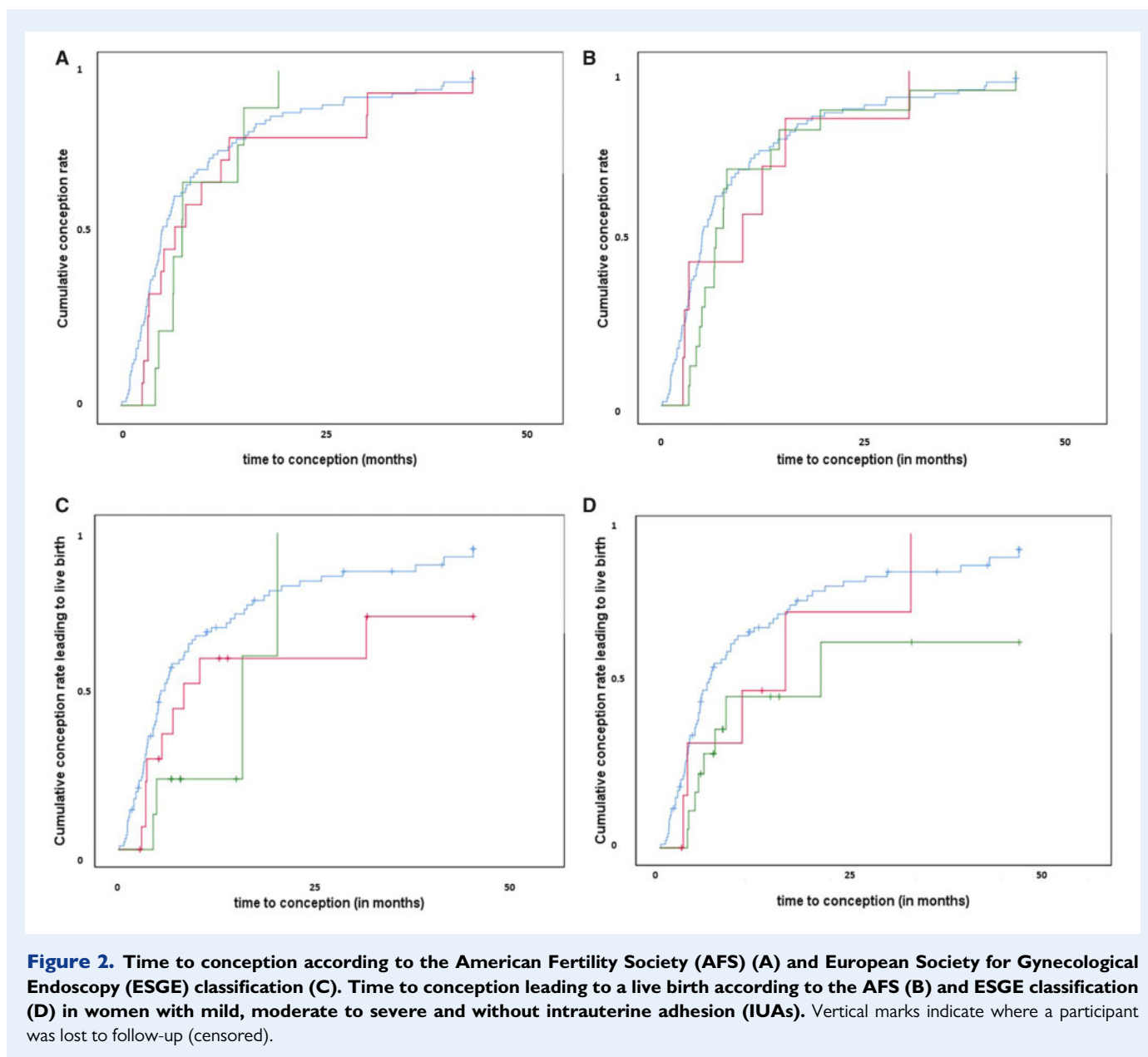
D&C for miscarriage. In clinical practice, adhesiolysis is mainly performed in women with signs or symptoms. Adhesiolysis was performed 8–12 weeks after the D&C-procedure, a short time frame to develop and detect symptoms. In case IUAs were encountered, a follow-up hysteroscopy following adhesiolysis was not mandatory. Nevertheless, all women with moderate to severe IUAs received a follow-up hysteroscopy to establish if re-adhesion occurred and adhesiolysis was performed until a normal cavity was established.

ACP gel was applied in the intervention group of the RCT, which influenced the rate, extent and degree of IUAs (Hooker et al., 2017). The sample size of women with identified and treated IUAs was relatively small. The main limitation is that the influence of other potential or unknown confounding factors on the reported results cannot be ruled out.

Literature

It has been several decades since Joseph Asherman described the syndrome of traumatic IUAs and acknowledge that IUAs do not always result in menstrual disturbances (Asherman, 1948). Since then, IUAs has become one of the main reproductive system diseases in women worldwide, probably due to increasing intra-uterine cavity surgery (Deans and Abbott, 2010; Johary et al., 2014).

Data on the pathophysiology of IUAs remains limited; understanding the causes and related mechanism of adhesion formation is essential for treatment and prevention strategies. Surgical procedures, especially intra-uterine surgery following miscarriage, TOP or delivery have been implicated in the etiology of IUAs. Injury by intrauterine surgery leads to disruption of the basal layer of the endometrium and to IUAs formation; the number of surgical procedures seem to be proportionally



related to the severity and recurrence rate of IUAs (Schenker and Margalioth, 1982; Deans and Abbott, 2010; Hooker et al., 2014). In the current study, significantly more women with identified and treated IUAs had three or more D&C procedures in history.

The presence of IUAs has long been considered a surrogate outcome. Reproductive performance and obstetrical complications are considered more relevant for clinical perspectives. However, the number of studies comparing the effect of IUAs on reproductive outcomes is limited. The current study shows that IUAs, even after hysteroscopic adhesiolysis are clinically relevant; significantly less ongoing pregnancies and live births were encountered in women with identified and treated IUAs and the time to a live birth was almost three times longer, 15 versus 5 months. Furthermore, significantly more premature deliveries and obstetrical complications were recorded in women with identified and treated IUAs. Consistent

with our results, one previous case-series ($n = 14$) study reported a significant increase of premature deliveries and obstetrical complications in women with identified and treated IUAs but contrary to our findings, lower birth weights were recorded after adhesiolysis (Baradwan et al., 2018b).

The mechanisms of compromised fertility in case of IUAs is not completely understood, but the underlying mechanism may be related to obstruction of sperm transport, impaired embryo migration, or failure of embryo implantation owing to endometrial insufficiency, adhesion reformation while the receptivity of the endometrium seems to play an important role in fertilization and implantation (Yu et al., 2008; Deans and Abbott, 2010). The subsequent pregnancy rate in women pursuing pregnancy between groups (including the different clinical categories of IUAs) was similar. The rate of ongoing pregnancy and live birth were significantly lower in women with identified and treated

IUAs and when classified in clinical categories, deteriorated by increasing severity.

It seems that in case of IUAs conception can be normally achieved, implantation seems to be the most important mechanism in case of IUAs: the altered endometrium lining, architecture and the obliterated uterine cavity may predispose to diminished placentation (Baradwan *et al.*, 2018b). Furthermore, adhesion reformation has been reported in up to 66% after adhesiolysis (Valle and Sciarra, 1988; Capella-Allouc *et al.*, 1999; Hanstede *et al.*, 2015; AAGL Elevating Gynecologic Surgery, 2017), which could also be a plausible explanation for the impaired implantation function. The ability to develop a functional endometrium with correct morphology seems to be crucial; the receptivity of the endometrium is critical for fertilization and implantation (Polishuk *et al.*, 1977; Fedele *et al.*, 1986; Pabuçcu *et al.*, 1997; Lo *et al.*, 2008; Simón, 2012).

The endometrial pattern and thickness have been identified as independent and critical factors for implantation failure (Shufaro *et al.*, 2008; Gleicher *et al.*, 2011; Zhao *et al.*, 2012; Baradwan *et al.*, 2018a). In case of midcycle endometrial thickness ≤ 5 mm, significant lower pregnancy rates (38% vs 80%) and significant higher miscarriages rates (50% vs 8%) are reported compared to women with >5 mm endometrial thickness. These phenomenon could (partly) explain the high impact of impaired reproductive function and diminished outcomes.

Our study shows that even mild IUAs according to both the AFS and ESGE classification systems seem to be associated with significant less ongoing pregnancies in women pursuing a pregnancy. Previous studies were not able to study the effect of mild adhesions due to the lack of an adequate control group of women without IUAs. In our study, according to both the AFS and ESGE classification systems mild IUAs have a compromised impact on reproductive performance compared to women without IUAs, the impact increases in women with moderate to severe IUAs. Although complex, this phenomenon could be explained by minimal scar tissue with preserved endometrial function in case of mild disease whereas in moderate to severe IUAs there is enhanced intra-uterine scarring without or with minimal endometrial function.

Our study indicates that the presence of IUAs should be considered an important and clinical relevant indicator, as even after hysteroscopic adhesiolysis reproductive performance remains compromised. It is worth noticing that reproductive performance at baseline was similar, without significant difference in gravidity, parity, number of previous miscarriage and terminations of pregnancy between the groups. This seems to imply that a priori there were no signs for impaired placentation. Given the fact that women in the group with identified and treated IUAs had significant more previous D&C procedures with similar number of miscarriages, implies that IUAs seem to be the most important etiologic factor. Other possible relevant factors, like constitutional characteristics, inflammation, and infection (Yu *et al.*, 2008), could not be assessed in the current study.

The presented results emphasize that primary prevention is essential and crucial. D&C-procedures must be prevented as much as possible in women with a miscarriage while expectative and medical management should be considered serious alternatives (Wieringa-De Waard *et al.*, 2002; Neilson *et al.*, 2017). If a D&C is indicated, the application of ACP gel should be considered since it has proven to reduce the amount and severity of IUAs in women with and without previous history of D&C undergoing D&C for miscarriage (Hooker *et al.*, 2017; Li

et al., 2019). A diagnostic hysteroscopy following the D&C procedure should be strongly considered, especially in women pursuing a pregnancy. The best post-operative management in case of IUAs remains unclear, as there is no consensus on the best management to prevent adhesion reformation.

Hyaluronic acid improves tissue hydration, enhances cell resistance to mechanical injury and reduces post-traumatic granulation and fibrous tissue formation: due to the biocompatibility and enzymatic biodegradation it is suitable for prevention of postoperative tissue adhesion (Salwowska *et al.*, 2016; Hong and Ding, 2017). In a systematic review and meta-analysis of clinical randomized controlled trials, the application of hyaluronic acid gel following intrauterine operations significantly reduced the incidence and severity of IUAs compared to intrauterine surgery alone; the reduction was not affected by type of surgery (D&C or hysteroscopy) or by disorders/diseases (Zheng *et al.*, 2020).

Conclusion

For women pursuing a pregnancy, live birth rate is the only important clinical outcome. IUAs is an acquired condition and the current study indicates that reproductive outcomes of women of childbearing age with IUAs, even mild remains limited and inefficient in comparison to women without IUAs, even after hysteroscopic adhesiolysis. Significant more premature deliveries and complication were recorded in women with IUAs, emphasizing that primary prevention is essential. Identified and treated IUAs should be considered a clinical important prognostic indicator for reproductive performance. The current data provides us tools to inform and counsel women undergoing intra-uterine surgery, especially during (early) pregnancy or recent pregnancy. Future studies are needed to study the pathophysiology of IUAs, to evaluate (primary) preventive measures in regard to fertility and reproductive outcomes.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

ABH, RAL, HAMB and JAFH conceived and designed the trial. ABH and RAL design the questionnaires. JWRT performed all statistical analysis. All authors collected, analyzed and interpreted the data. ABH drafted the first version the manuscript. All authors edited the

manuscript, read and approved the final submitted version and are guarantors for the study.

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Conflict of interest

ABH, RAL, JAFH and JWRT have none to declare. HAMB reports being a member of safety board research Womed.

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