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ORIGINAL ARTICLE

Hormonal support in women with Asherman syndrome does not lead to better outcomes: A randomized trial

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Abstract

Purpose: The purpose of the study was to investigate if adjuvant hormones after successful adhesiolysis lead to a reduction in spontaneous recurrence of adhesions and influence reproductive outcomes.

Methods: A single-blind randomized controlled trial comparing administration of oral estrogen (the usual care group) with not giving estrogen (no estrogen) in women after successful adhesiolysis for Asherman syndrome. Women were included between September 2013 and February 2017, with a follow-up of 3 years to monitor recurrences and reproductive outcomes. Analyses were based on an intention to treat analyses. This study was registered under NL9655.

Results: A total of 114 women were included. At 1 year, virtually all patients (except 3) were either having a recurrence or were pregnant. Women who did not receive estrogen did not have more recurrences of adhesions in the first year prior to pregnancy (66.1% in the usual care group, 52.7% in the no-estrogen group, $p = 0.15$). Of the women in usual care, 89.8% got pregnant within 3 years, and 67.8% got a living child; this was 83.6% and 60.0%, respectively, in the no-estrogen group ($p = 0.33$ and $p = 0.39$, respectively).

Conclusion: Usual care does not lead to better outcomes as compared with not giving exogenous estrogen but is associated with side effects.

KEYWORDS
estrogen, fertility, gynartresia, hysteroscopy, pregnancy

1 | INTRODUCTION

Asherman's Syndrome (AS) is a condition characterized by the presence of hysteroscopically confirmed intrauterine adhesions (IUA), which are caused by two clinical entities: unintended trauma, severe infection, or hypoxia of the endometrium in a gravid uterus, and IUA that cause symptoms like hypomenorrhea, amenorrhea, subfertility, cyclic abdominal pain, or recurrent pregnancy loss.[1–5] In the general population, AS occurs in around 1.5% of all women,[5] but this number is as high as 21.5% in women who have had a postpartum uterine curettage.[5,6]

Transcervical hysteroscopic adhesiolysis (TCA) is the preferred technique for managing intrauterine adhesions. The success rate of restoring the uterine anatomy can be as high as 95%.[1] However, there is a very high rate of spontaneous recurrence of up to 60%.[7,8]

It has been shown that the insertion of an intrauterine device (IUD) reduces the risk of spontaneous recurrences.[9,10]

Estrogen has been used as a standard post-operative treatment after adhesiolysis for decades.[11] Estrogen is thought to promote re-epithelization of the scarred surface and stimulate regeneration of the endometrium in women with AS.[12] In 1993, Farhi et al. described estrogen and progestin therapy during the first menstrual cycle after dilatation and curettage. In the estrogen group, patients had a significantly thicker endometrium and a higher endometrial volume than patients who did not receive estrogen. However, reductions in recurrences or increased pregnancy rates were not demonstrated in the estrogen group.[13]

To our knowledge, most studies have focused on comparing different dosages of estrogen therapy. One study from Liu et al. compared high dose estrogen (10 mg) to low dose estrogen therapy (4 mg) and suggested that both higher and lower dosages were equally effective in preventing adhesion reformation.[14] Another prospective trial from Guo et al. compared the results of different doses of estrogen (2 mg versus 6 mg) and showed that there was no difference in the amount of IUA present at follow-up between high- and low-dose estrogen therapy.[15]

However, it could be questioned whether exogenous estrogen is needed, as women with an ovulatory cycle produce their own endogenous estrogen. Exogenous estrogen results in side effects, and for many women with AS with a child wish, taking exogenous estrogen feels peculiar.

In this randomized controlled trial, the investigators are seeking to compare the incidence and severity of spontaneous recurrence of adhesions and reproductive outcomes in women without estrogen after treatment for AS with women receiving standard care (4 mg of estrogen for 6 weeks) after treatment for AS. By comparing the outcomes between the two groups, the investigators will be able to determine whether not taking estrogen is as effective as standard care in preventing adhesion formation and improving reproductive outcomes in women with AS. This information could potentially lead to changes in the standard of care for AS, providing a more personalized approach to treatment based on individual patient needs and preferences.

2 | METHODS

2.1 | Setting

This study was conducted at the Asherman Expertise Center of the Gynecology Department at Spaarne Gasthuis (SG) in Haarlem, The Netherlands. This hospital is a university-affiliated teaching hospital, associated with the University of Amsterdam and Vrije University Amsterdam. The department has specialized in treating patients with Asherman's Syndrome (AS) for over 25 years. The study was approved by the Medical Ethical Committee Noord Holland (number NL41190.094.13), the institutional review board (number 2013.0033), and registered at trialregister.nl (NL9655).

2.2 | Design

This is a single-center, prospective, randomized controlled trial. The inclusion period ran from September 2013 to February 2017, and the follow-up continued until 2020. The two surgeons who performed the hysteroscopy were blinded to the treatment allocation of the patients.

2.3 | Patients

The inclusion criteria were women aged ≥18 years, diagnosed with AS. Patients in the cohort were diagnosed with AS if they had one or more clinical features of AS, such as amenorrhea (absence of menstrual periods), hypomenorrhea (light or infrequent menstrual periods), subfertility (difficulty conceiving), recurrent pregnancy loss, or a history related to abnormal placentation, including placenta previa and accreta. In addition to the clinical features, the diagnosis of AS also required the presence of intrauterine adhesions (IUA), which were diagnosed by hysteroscopy. By using these criteria to diagnose AS, the patients in this cohort can be classified as having clinically significant IUA. The women underwent transcervical hysteroscopic adhesiolysis (TCA). The exclusion criteria were suspected AS due to tuberculosis or schistosomiasis, uncorrected anovulation, amenorrhea or oligomenorrhea prior to AS, uterine anomalies, use of hormonal supplementation, and contraindications for estrogen and/or gestagen. Women who had a cycle length shorter than 24 or longer than 30 were also excluded. Women scheduled to undergo TCA were asked to participate in the trial. After consent and successful treatment, women were randomized to receive hormonal support in addition to an IUD (the usual care group) or an IUD alone (the no-estrogen group).

2.4 | Procedure

The TCA was performed under general anesthesia or spinal anesthesia. TCA in our center is a combination of operative hysteroscopy and intraoperative fluoroscopy.[16–18] As described earlier,[1] the procedure was repeated in several cases, sometimes up to 3 times, until the normal anatomy of the uterine cavity was restored following recommended guidelines.[19,20] A normal uterine cavity was defined as visualization by hysteroscopy of 3 landmarks: the isthmic area, and the left and right tubal ostium, or normal tubal patency by fluoroscopy. The fluoroscopy was used as a guidance method and not to confirm tubal patency. If tubal patency could be assessed, it was recorded.

During the procedure, the grade of IUA was scored and reported by the surgeons. Two classification scoring systems were used. First, the scoring system by the American Fertility Society (AFS)[21] and second, the classification of the European Society of Gynecological Endoscopy (ESGE).[22] After successful TCA, an IUD

was placed inside the uterine cavity to prevent the immediate recurrence of adhesions.[9] Only copper IUDs were used, and the copper wire was removed before placement. A Flexi-T+ 300, 32 mm long and 28 mm wide, or Multiload, 28 mm long and 35 mm wide, were used.

The women in the usual care group received postoperative estrogen (Zumenon Mylan BV) oral 2 mg tablets twice a day for 35 days and Norethisteron (Primolut Bayer BV) oral tablets 5 mg twice a day for 10 days in total to induce withdrawal bleeding.

2.5 | Randomization

The research coordinator assigned eligible women with AS. An independent statistician generated opaque envelopes with study numbers to determine the study intervention allocated to the randomized patients prior to the study period. Allocation only occurred in consented patients who fulfilled all inclusion criteria after a successful procedure and after recovery from the anesthesia. The time between the actual procedure and randomization never exceeded more than one day. Surgeons, research coordinators, and attending care teams were blinded to treatment allocation.

2.6 | Follow up

Eight to ten weeks after the initial surgery, a second-look hysteroscopy was performed in all cases in an office setting without anesthesia. Two weeks before the procedure, the IUD was removed. If adhesions were visualized during this second-look hysteroscopy, this was called spontaneous recurrence of adhesion (SRA) post TCA. These adhesions were removed in the same procedure by hysteroscopy using conventional instruments. After the second-look hysteroscopy, women tried to conceive. If women had symptoms during the follow-up period, such as diminished menstrual blood flow, they were scheduled for another hysteroscopy. If IUA was visualized during this procedure, it was reported and defined as symptomatic SRA. These adhesions were staged and removed in the same procedure.

The occurrence of side effects was monitored in women receiving hormones. Women were asked to keep a diary until the second-look hysteroscopy visit. The endometrial thickness was measured with transvaginal ultrasound at the second-look hysteroscopy visit. This was between cycle days 15 and 28 in the secretory phase. Women were diagnosed as pregnant after a positive biochemical test or an ultrasound with a gestational sac visualized. The variable "at least one live birth" was defined as a pregnancy and delivery of a newborn after adhesiolysis. Miscarriage was defined as a spontaneous pregnancy loss before 22 weeks of gestational age. Ectopic pregnancies were recorded. Women were offered a diagnostic hysteroscopy after miscarriage or delivery to assess the uterine cavity.

2.7 | Statistical analysis

After data collection and coding, statistical analyses were performed using the Statistical Package for the Social Sciences 24.0 (IBM SPSS Statistics for Windows, version 22). Rates, averages, medians, percentages, and standard deviations were analyzed for the usual care and the no-estrogen groups and compared using a *t*-test or chi-square test. Dichotomous outcomes were adjusted for confounding factors using logistic regression analyses, while the number of recurrences was adjusted using negative binomial regression analyses. The time to recurrence or pregnancy was calculated using Kaplan-Meier and Cox regression analyses. Becoming pregnant and having SRA are competing events, so we performed competing risk incidence analyses, where we adjusted one analysis for the other. Differences in the risk of miscarriage and pregnancy complications were assessed using linear and logistic regression analyses. We presented 95% confidence intervals and adjusted for potential confounding factors.

2.8 | Power analysis

Assuming a 15% (55% to 40%) reduction of adhesion formation, with a noninferiority limit of 10% and an alpha of 0.05, using a chi-square test, and considering a dropout rate of 10%, (100 + 10) 110 patients needed to be included to reach a power of 80%.

3 | RESULTS

Between September 2013 and February 2017, 130 women were included in the trial. Among them, 16 women were excluded (Figure 1). Two women had a hysterectomy during the trial; 9 cases had no

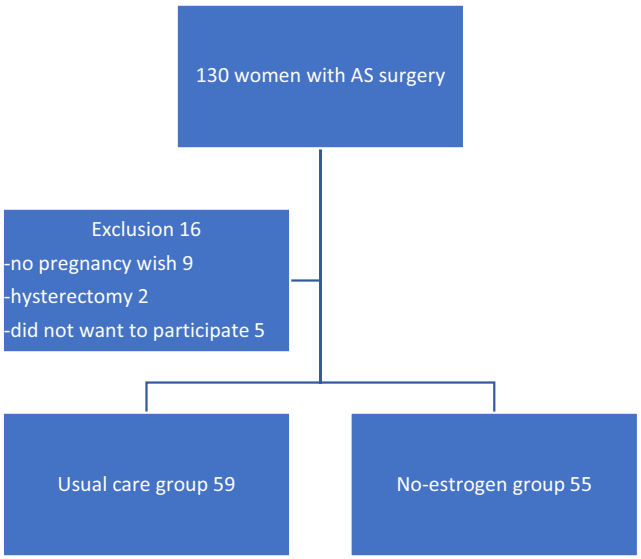

FIGURE 1 Flowchart of the inclusion of patients.

pregnancy wish and received an IUD 8 weeks after surgery; and 5 cases no longer wanted to participate in the study.

A total of 114 cases were analyzed; 59 cases were allocated to the usual care group and 55 cases to the no-estrogen group. The mean age and BMI of the women in the two groups were not significantly different. Most of the patients suffered from menstrual disorders (mainly amenorrhea). The vast majority had suffered from one or more miscarriages. There were no differences in pregnancies, deliveries, or miscarriages before adhesiolysis between the usual care group and the no-estrogen group. The causal procedure and grade of IUA were evenly distributed. There was no difference seen between the two groups in the use of ART to become pregnant (Table 1).

TABLE 1 Demographic information.

Baseline characteristics	Usal care group	No-estrogen group	*p*
Total	59	55	
Age	33.2 (4.3)	33.6 (4.1)	0.62
BMI	23.4 (4.3)	24.6 (4.01)	0.15
Symptoms			0.219
Infertility	15	8	
Menstrual disorder	44	46	
Other	0	1	
Menstrual pattern			0.723
Eumenorrhoe	4	2	
Oligomenorrhoe	7	5	
Hypomenorroe	12	15	
Amenorrhoe	36	33	
Pregnancies before TCA (Gravida)			0.731
1	30	24	
2	16	18	
3–5	13	13	
Deliveries (Para) before TCA			0.703
0	30	32	
1	23	19	
2	6	4	
Miscarriages before TCA			0.099
0	15	5	
1	29	32	
2 or more	15	18	
Causal procedure			0.095
First trimester	44	47	
Post-partum	15	7	
Grade Adhesions ASF and ESGE score			0.079
Mild (grade 1,2)	4	2	
Moderate (grade 2a)	23	33	
Severe (grade 3,4,5)	32	20	
Use of ART			0.201
Spontaneous	46	35	
IUI	1	2	
Clomid	1	1	
IVF	2	0	
Not reported	9	17	

At the second-look hysteroscopy at 8–10 weeks after surgery, 16 women in the usual care group (27.1%), and 14 women in the no-estrogen group did have SRA (25.5%), $p=0.84$. The administration of estrogen did not affect the grading of the SRA (ESGE) seen at the second-look hysteroscopy post-TCA ($p=0.76$) (Table 2).

Prior to pregnancy and within the first year, 62.7% of the patients in the usual care group and 53% of the patients in the no-estrogen group had a symptomatic SRA after a mean of 4.4 (SD 2.1) months in the usual care group and 3.9 (SD 2.0) months in the no-estrogen group ($p=0.97$) (Figure 2). The risk of recurrence was 1.51 times higher (95% CI 0.71 to 3.18, $p=0.28$) for the usual care group, as compared with the no-estrogen group. The administration of estrogen did not affect the grading of the SRA (ESGE) ($p=0.29$), nor the number of SRA ($p=0.50$) (Table 3). Menstrual pattern changes were the most common reason women were scheduled for a new hysteroscopy.

Out of the 59 women in the usual care group, 53 (89.8%) got pregnant within 36 months (mean 6-month SD 5.5). This was 46 of the 55 women not using hormones (83.6%, mean 4.0 months, SD 2.5) ($p=0.33$). Survival analysis did not show a significant difference in time to pregnancy (0.95 95% CI 0.64–1.42), and also not after adjustment for age and prior pregnancies (HR 0.89 95% CI 0.60–1.33), (Table 4).

In the usual care group, 40 (67.8%) women had a living child, compared to 33 (60.0%) women in the no-estrogen group ($p=0.39$). The first pregnancy ended in miscarriage for 15 women in the usual care group and 19 times in the no-estrogen group. Multiple miscarriages were recorded for five women. One case in the no-estrogen group had a late termination of pregnancy because of congenital malformations (Table 4).

At 1 year, almost all patients (except 3) were either experiencing a recurrence or were pregnant (see Figure 3). The administration of hormones, age, BMI, causal procedures, the number of intrauterine

TABLE 2 Spontaneous Recurrence of Adhesions (SRA) directly post TCA.

SRA post TCA	Usual care group (59)	No-estrogen group (55)	*p*
IUA			0.84
Yes	16 (27.1%)	14 (25.5%)	
No	43 (72.9%)	41 (74.5%)	
ESGE Grade of IUA			0.76
1	5 (31.3%)	7 (50.0%)	
2	4 (25.0%)	3 (21.4%)	
2a	2 (12.5%)	1 (7.18%)	
3	5 (31.3%)	3 (21.4%)	
4 or 5	0 (0%)	0 (0%)	

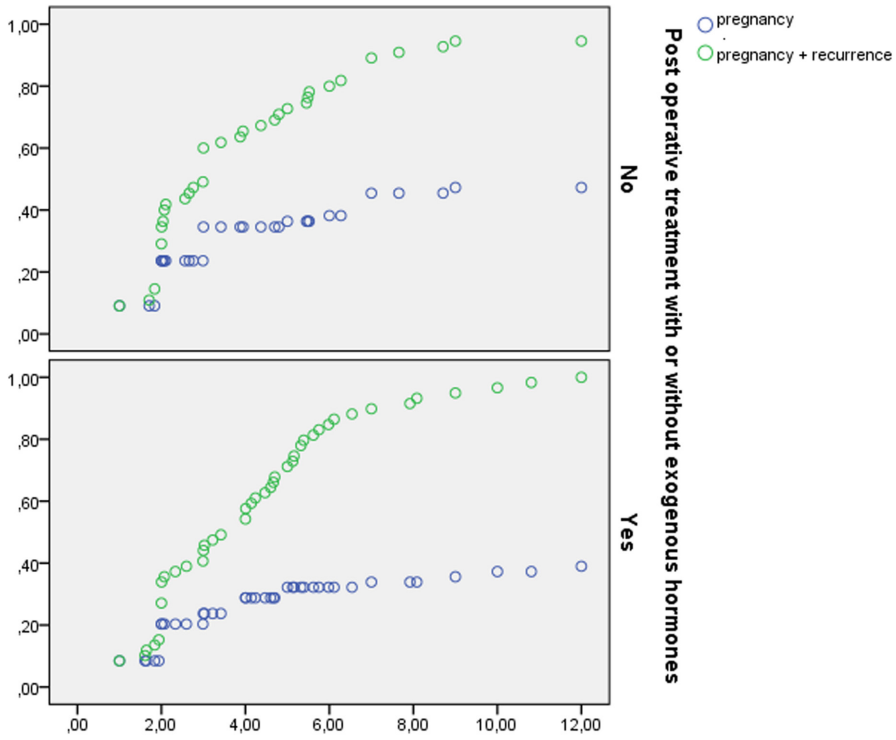

FIGURE 2 Cumulative risk of recurrence and pregnancy (difference between the risk of recurrence and pregnancy) for patients on hormones and those not on hormones.

TABLE 3 Symptomatic Spontaneous Recurrence of Adhesions (SRA) within 1 year prior to pregnancy.

Symptomatic SRA[a]	Usual care group (59)	No estrogen group (55)	OR (95%CI)	*p*	Adjusted
IUA			1.51 (0.71–3.18)	0.28	1.08 (0.61–1.92)
Yes	37 (62.7%)	29 (52.7%)			
No	22 (37.3%)	26 (47.3%)			
Number SRA			Beta (95%CI)	0.50	0.13 (−0.45–0.72)
0	22 (37.3%)	26 (47.3%)	0.19 (−0.36–0.74)		
1	26 (44.1%)	20 (36.4%)			
2	8 (13.6%)	7 (12.7%)			
3 or 4	3 (5.1%)	2 (3.6%)			
ESGE Grade of IUA[b]				0.29	
1	3 (8.1%)	1 (3.4%)			
2	27 (73.0%)	26 (89.7%)			
2a	4 (10.8%)	2 (6.9%)			
3	3 (8.1%)	0 (0%)			
4 or 5	0 (0%)	0 (0%)			

[a]Age, number of miscarriages.
[b]Age, previous recurrence.

procedures, the classification of (re) adhesions during the TCA, and the control hysteroscopy were analyzed. None of these variables had a significant contribution to the model.

At the three-month visit, the side effects of exogenous hormones were recorded. Of the 59 women allocated to the usual care group, 40 (68%) reported one or more side effects. Fluid retention, headaches, and painful or tender breasts were the most frequently reported symptoms. One patient discontinued the intake of estrogen after a week because of intolerable side effects (Table 5).

TABLE 4 Chance of pregnancy within 36 months and a living child.

	Usual care (59)	No-estrogen (55)	*p*-value	Relative risk (OR/HR)	HR adjusted age, prior pregnancies
Number of women getting pregnant	53 (89.8%)	46 (83.6%)	0.33	0.95 (0.64–1.42)	0.89 (0.60–1.33)
Result of the 1e pregnancy			0.38		
Miscarriage	15 (28.3%)	19 (41.3%)			
Late termination	0 (0%)	1 (2.2%)			
Perinatal death	2 (3.8%)	0 (0%)			
Living child	36 (71.7%)	26 (56.5%)			
Chance of Living child (overall)	40 (67.8%)	33 (60.0%)	0.39	1.40 (0.65–3.02)	1.30 (0.60–2.85)
Pregnancy duration (mean)	38+4	38+2	0.59	Difference 2 days (−11 to 7)	

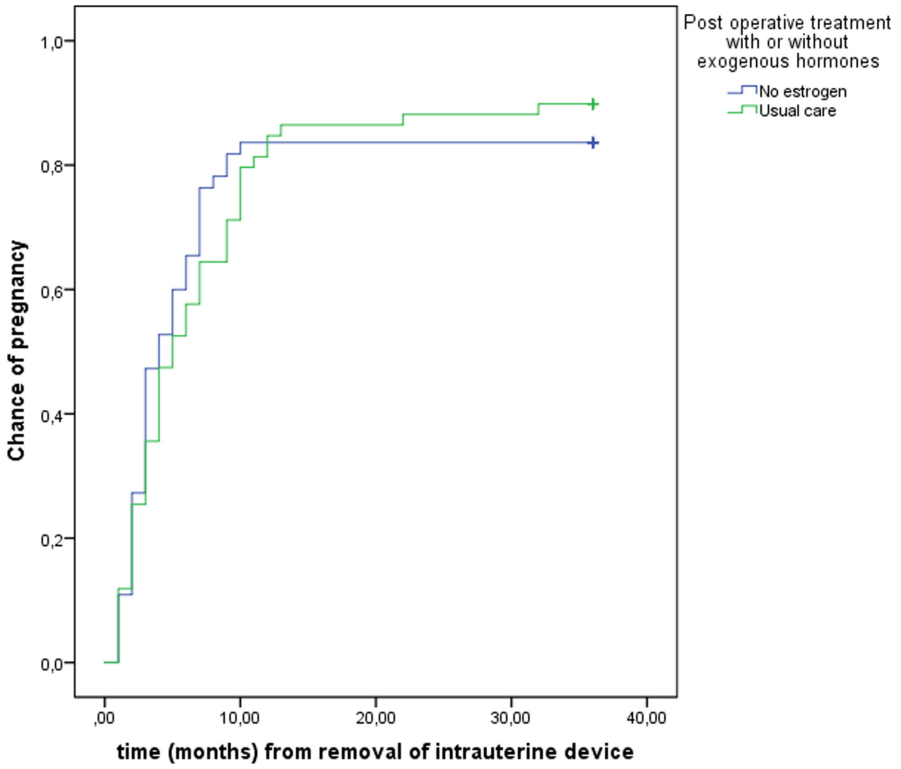

FIGURE 3 Time to pregnancy (months) after successful TCA between the usual care and the no-estrogen group.

4 | DISCUSSION

This trial aimed to evaluate the effect of the incidence and severity of spontaneous recurrence of adhesions (SRA) and reproductive outcomes in AS-treated women who do not receive estrogen after treatment compared to those who receive standard care. The removal of exogenous estrogen from the treatment did not lead to a reduction in SRA, or a difference in the pregnancy rate, or having a living child compared to usual care. However, 70.7% of the women using estrogen reported side effects.

This information could potentially lead to changes in the standard of care for AS, providing a more personalized approach to treatment based on individual patient needs and preferences.

Estrogen, whether exogenous or endogenous, produced by the ovaries, is believed to promote the re-epithelialization of the scarred surface and stimulate the regeneration of the endometrium in women with Asherman's Syndrome (AS).[12] Postoperative estrogen therapy has been widely recommended and used by many guidelines and investigators to prevent adhesion recurrence.[20] The dosage of estrogen used varies widely, ranging from 2 mg to 12 mg per day.[11–15,23] However, randomized clinical trials have not shown the benefits of high-dose estrogen therapy over low-dose therapy.[15]

Nevertheless, no randomized controlled trials have been performed to determine whether exogenous estrogen for necessary in AS patients postoperatively. In this trial, SRA at the second look hysteroscopy 8–10 weeks after surgery was observed in 37 (62.7%) women in the usual care group and 29 (52.7%) women in the no-estrogen group. Our rate of SRA was similar to that of other studies; however, only a few studies have performed a

TABLE 5 Number and percentage of side effects reported in the usual care group.

Side effects	Group 59 (N, %)
Headache	11(18.6%)
Nausea	7 (11.9%)
Vomiting	1 (1.7%)
Painful or tender breasts	16 (27.1%)
Spotting	7 (11.9%)
Fluid retention	13(22.0%)
Mood swings	4 (6.8%)
Rash	3 (5.1%)
Joint pain	2 (3.4%)
Acne	0
Vertigo	1 (1.7%)
Dizziness (spontaneous report)	1 (1.7%)

control hysteroscopy. Capella-Allouc et al. described that in 10 of 16 patients (62.5%) who had a satisfactory result after the initial adhesiolysis, filmy adhesions were present.[24] Yu et al. and Hanstede et al.[1,5] showed that the occurrence of SRA depended on the severity of adhesions found at surgery. Dan Yu et al.[8] reported rates of reformation of adhesions in women with moderate adhesions (16.7%, 4 out of 24) and severe adhesions (41.9%, 13 out of 31), respectively.

The most important outcome for women is a successful pregnancy. After 3 years of follow-up, the usual care group had a living child rate of 68%, while the no-estrogen group had a living child rate of 60%. Pregnancy rates vary between studies. Fernandez et al.[25] reported pregnancies in 28 of 64 (43.8%) patients and a live birth in 21 of 64 (32.8%) patients with stage 3–4 adhesions. Valle et al.[26] reported a live birth rate of 31.9% (15/47 cases) in severe cases, and the live birth rate in mild and moderate disease was 81.3% (35/43) and 65.9% (64/97), respectively. Barbot et al.[27] reported a live birth rate of 31.5% (23/73 cases).

A second look Hysteroscopy was performed during the secretory phase of the cycle. During the secretory phase, the endometrium becomes thicker and more vascular, and glandular secretions increase. The intention was to minimize damage to the endometrial layer during hysteroscopy to increase the chances of conception in the upcoming cycle.

Estrogen caused side effects in 70.7% of the patients in our intervention group. A plausible explanation for the high rate of side effects can be the fact that the trial was not placebo-controlled and participants were aware of their hormone intake. Having these side effects was generally not a reason for women to stop taking the hormones, except for one woman. Most women were willing to accept the side effects to increase their chances of getting pregnant.

A possible weakness of this study is that the true effect of estrogen on recurrence or reproductive outcomes was not investigated without the insertion of an IUD. We thought it was unethical to perform a study with a third control arm in which the subjects did not receive any intrauterine devices. Previously reported studies suggested that an IUD or balloon significantly reduced postoperative adhesions in Asherman syndrome.[9,10]

The study was conducted in a referral center for AS care, and the centralization of AS care influences the volume of cases and therefore the expertise of the surgeons and the variety of cases, with more difficult cases referred to this center. This can affect external validity. Whether or not women received estrogen was only blinded to the surgeons, which is a potential cause for bias. Another limitation of this study is that only two surgeons performed the surgery and control hysteroscopy. The strong points of the study are the design and follow-up length.

5 | CONCLUSION

The purpose of this trial was to assess whether removing estrogen from the treatment would affect the occurrence and severity of spontaneous recurrence of adhesions (SRA) and reproductive outcomes in women with AS compared to the standard care group. Results showed that the absence of estrogen did not lead to a decrease in SRA, nor did it show any difference in pregnancy rate or having a living child as compared to the usual care group. However, a high percentage of women (70.7%) in the estrogen group experienced side effects. These findings suggest the need for a more personalized approach to treatment based on individual patient needs and preferences, which could potentially change the standard of care for AS.

CONFLICT OF INTEREST STATEMENT

In the interest of transparency, I disclose that there are no relationships, activities, or interests that are related to the content of our manuscript. Conflict of interest: Miriam Hanstede, Jan Molkenboer, Karlijn van Stralen, Sebastiaan Veersema, Mark Hans Emanuel declares that they have no conflict of interest.

HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients before they are included in the study.

APPROVAL BY ETHICS COMMITTEE AND CLINICAL TRIAL REGISTRY SUBSECTIONS

The research protocol has been approved by the Institutional Review Board "Noord-Holland" in The Netherlands (medisch ethische toetsingscommissie Noord-Holland [METC]) (Trial number NL41190.094.13) and the local review board at the Spaarne Gasthuis, Hoofddorp, The Netherlands, and all women gave written informed consent. The trial is registered on trialregister.nl NL9655.

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