Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-019-05368-6

GENERAL GYNECOLOGY

Cross-linked hyaluronan gel to improve pregnancy rate of women patients with moderate to severe intrauterine adhesion treated with IVF: a randomized controlled trial

Xiaoyan Mao[1] · Yu Tao[1] · Renfei Cai[1] · Jie Zhang[1] · Hongyuan Gao[1] · Qiuju Chen[1] · Yanping Kuang[1] · Shaozhen Zhang[1]

Received: 13 June 2019 / Accepted: 30 October 2019

Abstract

Purpose To evaluate whether the cross-linked hyaluronan (cHA) gel can improve the clinical pregnancy rate of patients with moderate to severe intrauterine adhesion (IUA) who underwent operative hysteroscopy followed by embryo transfer.

Methods Women with moderate to severe IUA desiring to undergo embryo transfer were recruited in this randomized controlled trial. The patients were randomized on the day of receiving hysteroscopy. The control group received standard hysteroscopy, while cHA gel was applied to the treatment group at the end of hysteroscopy and 5–7 days after operation. All patients were expected to undergo in vitro fertilization (IVF)/intracytoplasmic sperm injection and frozen-thawed embryo transfer (FET).

Results A total of 306 patients were enrolled in this study, of which 202 were assigned to the treatment group and 104 to the control group. Both the clinical pregnancy rate (26.3% [49/186] vs. 15.3% [13/85], $P=0.045$), the implantation rate (17.7% [57/322] vs. 9.8% [15/153], $P=0.025$), and the endometrial thickness on the day of embryo transfer (7.97 ± 1.37 vs. 7.50 ± 0.60 mm, $P<0.001$) were significantly higher in the treatment group compared to the control group. In addition, histological assessment of the paired endometrial tissues collected before and after operation revealed a relatively higher number of tubular glands after operation (15.1 ± 13.2 vs. 28.8 ± 30.4, $P=0.166$).

Conclusions To conclude, the application of cHA gel in patients with moderate to severe IUA during hysteroscopy can improve the quality of endometrium and uterine receptivity and consequently enhance the clinical pregnancy rate after IVF/CSI and FET.

Keywords Asherman syndrome · Cross-linked hyaluronan gel · Embryo transfer · Hysteroscopy · Intrauterine adhesion · Uterine receptivity

Introduction

Intrauterine adhesions (IUAs), first described by Fritsch H in 1894 [1], are the fibrous structure that is formed in the uterine cavity as a result of endometrial trauma caused mainly by dilatation and curettage for miscarriage or induced abortion [2]. Severe IUA can lead to menstrual disturbances, pelvic pain, and even complete obliteration of the uterine cavity, which could affect the reproductive function in women [3]. Hysteroscopy currently remains the standard of care for IUA diagnosis and treatment. This minimally invasive technique allows the direct visualization of the uterine cavity and adhesiolysis mechanically. Nonetheless, it has been reported that a high rate of adhesion reformation occurs after operation, especially for patients with severe IUA [4, 5]. Repeated

The abstract of this paper was presented at The European Society of Human Reproduction and Embryology 2017 annual meeting as a poster presentation with interim findings.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00404-019-05368-6) contains supplementary material, which is available to authorized users.

✉ Shaozhen Zhang
15001867500@163.com

[1] Department of Assisted Reproduction, The Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine, Shanghai, China

Published online: 27 December 2019

surgery several times is generally required to achieve a normalized anatomy for implantation. Thus, the key to a successful surgery is to prevent the reformation of adhesions after operation.

Anti-adhesion therapies such as intrauterine device or balloon, hormonal treatments, and barrier gels have been claimed to improve the adhesion conditions after operative hysteroscopy [6]. Hyaluronan is a water-soluble glycosaminoglycan with viscoelastic nature that can physically support the endometrial lining and prevent adhesion reformation. Its high biocompatibility makes it an ideal candidate of biomaterial used to generate barrier gel. There is no safety concern with its use in human and it is even used for the preservation of fertilized eggs. However, hyaluronan gel is rapidly degraded in the human body. To circumvent this issue, cross-linked hyaluronan gel (cHA) has been invented to prolong the half-life of the gel. Through the auto cross-linking technology, linear hyaluronan molecules are activated and modified into a three-dimensional web-like structure, which greatly enhances its stability. Previous studies had demonstrated the efficacy and feasibility of cHA gel in animals [7, 8], but there is a lack of large scale, systematically designed clinical trial to prove the clinical performance, in particular, the improvement in clinical pregnancy rate, of cHA gel in human.

In the present study, we aimed to examine the efficacy of a new cHA gel-MateRegen® gel in preventing adhesion reformation and facilitate the success rate of embryo transfer in patients with moderate to severe IUAs.

Materials and methods

Study design

This is a single-center prospective randomized controlled trial. The study protocol has been approved by the Ethics Committee of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine (reference no.: [2014]#31), and all the patients provided written informed consent prior to entry into this study.

Study population

The study was conducted at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine. A total of 306 patients with moderate to severe IUA were recruited from January 2016 to May 2017 (Supplementary Figure 1). The inclusion criteria included: (1) diagnosed as moderate to severe IUA (score $\geq$ 5) according to a classification system recommended by the American Fertility Society (AFS; 1988 version); (2) infertility for at least 1 year; (3) expected to undergo IVF/ICSI and FET; and (4) had at least one good quality embryo left. Patients with uterine malformations, endometrial diseases, endometriosis, and adenomyosis were excluded. The enrolled patients were randomized (2:1) on the day of receiving hysteroscopy, in which 202 were assigned to the treatment group and 104 to the control group. An administrative staff generated the random number list using SPSS and provided the treatment allocation to the physician in a sealed envelope.

Intervention

The control group received standard hysteroscopy, while cHA gel (MateRegen® gel; BioRegen Biomedical Ltd., Inc., Changzhou, China) was applied to the treatment group during hysteroscopy and 5–7 days after operation. Detailed workflow of cHA gel application is shown in Supplementary Figure 2. The MateRegen® gel used in this study is a hyaluronan gel modified through the auto cross-linking technology to enhance its stability. It has been approved by the China NMPA for clinical application.

Hysteroscopy

Hysteroscopy was performed by one of two experienced hysteroscopic surgeons using a 2.9-mm rigid hysteroscope (Karl Storz, Germany) that was equipped with hysteroscopic scissors (Karl Storz). The procedure was performed under local anesthesia with lidocaine. Saline solution was injected to distend the uterine cavity. A 300-W light source with a xenon bulb, a digital camera (Karl Storz), and a 21-inch color video monitor were used in the operation. The exploration of the uterine cavity consisted of a panoramic view of the cavity, followed by a thorough evaluation of the endometrium. The endocervical canal, uterine cavity, tubal orifices, and endometrium were inspected methodically and the findings were recorded. During hysteroscopy, both the anterior and posterior uterine walls were thoroughly examined by moving the hysteroscope along the endometrial surface to get a view parallel to the endometrial surface. In this way, any irregularity of the endometrial surface can be easily identified. Adhesions, micro polyps, and polypoid endometrium were divided or removed with the use of the hysteroscopic scissors until a normal uterine anatomy was achieved. For patients in the treatment group, the cHA gel was applied through intrauterine injection into the uterine cavity after hysteroscopic adhesiolysis.

All patients had biopsies of the endometrium for the pathological examination at the time of initial hysteroscopy. All hysteroscopies were performed in the follicular phase and images were recorded in digital format. Adhesion score was also assessed according to the AFS classification.

After hysteroscopy, all patients received 150 mg tosufloxacin tosilate (Zhuhai Pharma, Guangdong, China) tid orally for 3 days.

Embryo transfer

Embryo transfer was performed 2 months after hysteroscopy. Embryo and endometrial synchronization in cryopreserved embryo transfer cycles were performed as described by Kuang et al. [9, 10].

In this study, hormone replacement treatment was used for endometrial preparation. Oral ethinyl estradiol (25 mg; Shanghai Xinyi Pharma, Shanghai, China) tid or two red femoston tablets (Solvay Pharma, Belgium; each tablet contains 2 mg E2) bid was administered starting on day 3. For patients with thin endometrial lining, a white femoston tablet or a tadalafil tablet (Eli Lilly, Indiana, USA) was administered per vaginum as prescribed by an experienced gynecologist. Once the endometrial lining thickness was > 6.5 mm, the following medications were started: two yellow femoston tablets (each tablet contains 2 mg E2 and 10 mg dydrogesterone) bid and vaginal progesterone soft capsules (Laboratoires Besins International, France; 200 mg) bid.

The timing of embryo warming and transfer was determined on the third day after femoston administration. The maximum number of transferred embryos was two per patient. At day 14 after embryo transfer, a positive β-hCG test was performed to determine chemical pregnancy. When a pregnancy was diagnosed by means of a positive β-hCG test, femoston administration was continued and ultrasonic examination was performed 2 weeks later (Day 28) to confirm pregnancy and to determine singleton/multiple pregnancy. The progesterone supplementation was continued until 12 weeks of gestation.

It should be noted that, at our center, intervention is performed before embryo transfer in the case of patients with hydrosalpinx. Fallopian tube embolization is used when the degree of hydrosalpinx is relatively small and salpingectomy or laparoscopic tubal ligation is performed, when there is severe hydrosalpinx.

Outcome measures

Outcome measures of this study included: (1) ratio of thawed highest quality embryos = number of embryos implanted: number of thawed cycles; (2) chemical pregnancy rate = number of positive β-hCG results ÷ number of thawed cycles; (3) clinical pregnancy rate = number of pregnancy as confirmed by ultrasonic examination ÷ number of thawed cycles; (4) ectopic pregnancy rate = number of ectopic pregnancies ÷ number of clinical pregnancy; (5) singleton pregnancy rate = number of singleton pregnancies ÷ number of clinical pregnancy; (6) multiple pregnancy rate = number of multiple-fetus pregnancies ÷ number of clinical pregnancy; and (7) implantation rate = number of embryos implanted ÷ number of embryos transferred. Clinical pregnancy rate was the primary outcome measure of this study. Other outcome measures were considered as secondary outcomes.

Some patients refused implantation after hysteroscopy due to personal reasons, whereas the others had two implantations within 6 months after hysteroscopy. All implantation outcomes within 6 months after hysteroscopy were included in this study.

Histological assessment

Biopsy of the endometrium was collected from the fundus of uterus under hysteroscopy using the endometrial curette by an experienced gynecologist after intrauterine recavity. The biopsy tissue was a full thick endometrium at about 2–3 mm in diameter and was fixed in 4% paraformaldehyde. In case of severe intrauterine adhesion with an almost obliterated cavity, the suspending tissues from the fundus of uterus after recavity were collected as the biopsy of endometrium. Endometrium biopsy was done again in the treatment group during the follow-up endoscopic examination to obtain paired samples (i.e. preadministration and postadministration of cHA gel) for assessment. Eight paired samples were selected to evaluate the number of tubular glands. Endometrium biopsy samples were embedded in paraffin and sectioned at 5–7 µm thickness. For each sample, 3–5 sections were cut at the interval of 100 µm and stained with hematoxylin and eosin. The stained sections were observed under light microscopy. The morphology of the endometrium was evaluated and the number of tubular glands was counted using ImageJ program in a computer that is synchronized with the microscopic images.

Under the objective lenses' magnification of ten times, 2–3 scopes on the diagonal lines of each section were chosen for analyses. The number of tubular glands in each scope was counted and recorded, and the average number of glands in each section was calculated. The number of tubular glands in the endometrial tissue before and after the application of cHA gel was compared using paired *t* test for the paired samples collected from the eight selected patients.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistical software, version 22 (IBM Corp., New York, USA). Variables were expressed as mean ± standard deviation or median (range) and compared using unpaired *t* test, Mann–Whitney test, Fisher's exact test, or Chi-squared test as appropriate. All analyses were two-tailed. Statistical significance was regarded as $P < 0.05$.

Results

Baseline characteristics

A total of 306 patients with moderate to severe IUA were recruited in this study. As shown in Supplementary Figure 1, the enrolled patients were randomly assigned to the treatment group ($n = 202$) and the control group ($n = 104$) on the day receiving hysteroscopy. cHA gel was applied to the treatment group during hysteroscopy and 5–7 days after operation. Detailed workflow of cHA gel application is shown in Supplementary Figure 2. No adverse reaction was observed in both groups of participants. The baseline characteristics, including age, adhesion score, infertility duration, primary infertility, previous IVF failure, history of hysteroscopy, and endometrial thickness before operation were similar among the two groups ($P > 0.05$, Table 1). In addition, all the participants received the same hormonal replacement treatment for endometrial preparation. An additional treatment with white femoston tablet or tadalafil tablet was given to patients with thin endometrial lining. The number of cycles of additional treatment per the total number of thawed cycles was similar between the two groups (treatment group: 31.2% [58/186]; control group: 32.9% [28/85]).

Table 1 Baseline characteristics of the enrolled patients

Characteristics	Treatment group ($n = 202$)	Control group ($n = 104$)	P value[a]
Age (y)	35.9 ± 5.7	36.7 ± 4.7	0.224
Infertility duration (y)	5 (1–24)	6 (1–24)	0.113
Primary infertility (n)			0.226
Yes	27	9	
No	175	95	
Previous IVF failure (n)	2 (0–10)	2 (0–9)	0.878
History of hysteroscopy (n)	2 (0–12)	2 (0–6)	0.449
Adhesion score	8.24 ± 1.48	7.97 ± 1.41	0.109
Endometrial thickness (mm)	6.33 ± 0.97	6.31 ± 0.68	0.319

Age, adhesion score, and endometrial thickness are present as mean ± standard deviation. Other variables are present as median (range)

IVF in vitro fertilization

[a] P value was calculated by unpaired t test, Mann–Whitney test, or Chi-squared test as appropriate

Clinical outcomes of embryo transfer

As shown in Table 2, the ratio of thawed highest quality embryos (1.73 in the treatment group vs. 1.80 in the control group) was comparable in the two groups. Both the groups had a significant decrease in adhesion score after operation (treatment group: from 9.03 ± 1.15 to 2.00 ± 1.58, $P < 0.001$; control group: from 8.28 ± 1.71 to 2.13 ± 1.76, $P < 0.001$), with the control group showing a relatively higher incidence of readhesion (75.0% vs. 72.4%, $P = 0.845$). The incidence of adhesion score ≥ 5 at follow up was also relatively higher in the control group (9.4% vs. 6.9%, $P = 0.483$). The treatment group showed a relatively larger average percentage change in adhesion score (− 78.0% vs. − 75.6%, $P = 0.536$). Significant increases in the endometrial thickness were observed in both groups (treatment group: from 6.35 ± 0.92 to 7.97 ± 1.37, $P < 0.001$; control group: from 6.28 ± 0.69 to 7.50 ± 0.60, $P < 0.001$). Despite there were more patients from the control group canceling embryo transfer due to the thin endometrial lining or hydrohystera ($n = 19$) compared to the treatment group ($n = 16$), the endometrial thickness

Table 2 Clinical circumstances and outcomes of embryo transfer

	Treatment group	Control group	P value[a]
Number of thawed cycles (n)	186	85	
Number of embryos implanted (n)	322	153	
Ratio of thawed highest quality embryos	1.73	1.80	
Adhesion score before operation[b]	9.03 ± 1.15	8.28 ± 1.71	0.089
Adhesion score at follow up[b]	2.00 ± 1.58	2.13 ± 1.76	0.906
Average change in adhesion score[b] (%)	− 78.0%	− 75.6%	0.536
Incidence of readhesion at follow up[b] (%)	72.4 (21/29)	75.0 (24/32)	0.845
Incidence of adhesion score ≥ 5 at follow up[b] (%)	6.9 (2/29)	9.4 (3/32)	0.483
Endometrial thickness before operation[c] (mm)	6.35 ± 0.92	6.28 ± 0.69	0.243
Endometrial thickness on the day of embryo transfer[c] (mm)	7.97 ± 1.37	7.50 ± 0.60	< 0.001
Average change in endometrial thickness[c] (%)	+ 27.5%	+ 20.7%	0.048

Adhesion score and endometrial thickness are present as mean ± standard deviation

[a] P value was calculated by Man–Whitney test. [b]Only 29 (treatment group) and 32 (control group) patients that were followed up for 1 month after operation were included in this analysis. [c]Only 186 (treatment group) and 85 (control group) patients that undergo embryo transfer had measured endometrial thickness available and were included in this analysis

on the day of embryo transfer was significantly higher in the treatment group ($P < 0.001$). The average percentage decrease in endometrial thickness was also significantly higher in the treatment group ($P = 0.048$).

The clinical outcomes are shown in Table 3. Outcome measures, including chemical pregnancy rate, clinical pregnancy rate, and implantation rate, were both significantly higher in the treatment group ($P < 0.05$). The two groups showed a similar singleton pregnancy rate, multiple pregnancy rate, ectopic pregnancy rate, abortion rate, and live birth rate ($P > 0.05$).

Histological assessment

Eight selected patients from the treatment group had endometrial biopsy collected during hysteroscopy and the follow-up endoscopic examination. The quality of endometrium in these paired biopsy samples was observed and compared in terms of tissue morphology and the number of tubular glands present. Our results demonstrated that a trend of increasing tubular glands was observed in the endometrium after operation (15.1 ± 13.2 vs. 28.8 ± 30.4, $P = 0.166$, Fig. 1). In addition, more fibrotic tissue was seen in the endometrium before operation compared to that after operation.

Table 3 Clinical outcomes of embryo transfer

	Treatment group	Control group	*P* value[a]
Cancel rate[b] (%)	7.9 (16/202)	18.3 (19/104)	0.007
Chemical pregnancy rate[c] (%)	34.4 (64/186)	22.4 (19/85)	0.046
Clinical pregnancy rate (%)	26.3 (49/186)	15.3 (13/85)	0.045
Ectopic pregnancy rate (%)	2.0 (1/49)	7.7 (1/13)	0.378
Singleton pregnancy rate (%)	81.6 (40/49)	76.9 (10/13)	0.703
Multiple pregnancy rate (%)	16.3 (8/49)	15.4 (2/13)	1.000
Abortion rate[d] (%)	18.4 (9/49)	38.5 (5/13)	0.147
Live birth rate (%)	81.6 (40/49)	61.5 (8/13)	0.147
Implantation rate (%)	17.7 (57/322)	9.8 (15/153)	0.025

[a]*P* value was calculated by Fisher's exact test or Chi-squared test as appropriate. [b]Embryo transfer canceled due to thin endometrial lining or hydrohystera. [c]Chemical pregnancy is defined as positive β-HCG. [d]Abortion due to ectopic pregnancy or embryo arrest (induced labor in one case of the control group due to umbilical hernia)

Discussion

IUA may cause infertility in women. Hysteroscopic adhesiolysis can improve the success rate of embryo transfer on the premise that readhesion is prevented. Hyaluronan gel has shown to be a safe and effective barrier, which can improve clinical pregnancy rate [11–13]. For cHA gel, several studies indicated that it can prevent IUA reformation after operative hysteroscopy [14, 15]. However, there is a lack of evidence that the use of cHA gel can improve the clinical outcomes of infertile women.

In this randomized controlled study, we demonstrated that the application of a new cHA gel can significantly improve the clinical outcomes of patients with moderate to severe IUA, in terms of chemical pregnancy rate, clinical pregnancy rate, singleton pregnancy rate, and implantation rate. The clinical outcomes in our study appeared to be relatively lower than those previously reported [13–15]. This is probably due to the difference in the study population. In our study, all recruited patients had infertility for at least 1 year and suffered from moderate to severe IUA. These could lead to poorer clinical outcomes. In agreement with the previous studies [14, 15], we also recognized that the use of cHA gel after hysteroscopy can significantly reduce the severity of adhesion. Although the adhesion scores at follow up were not significantly different between the two

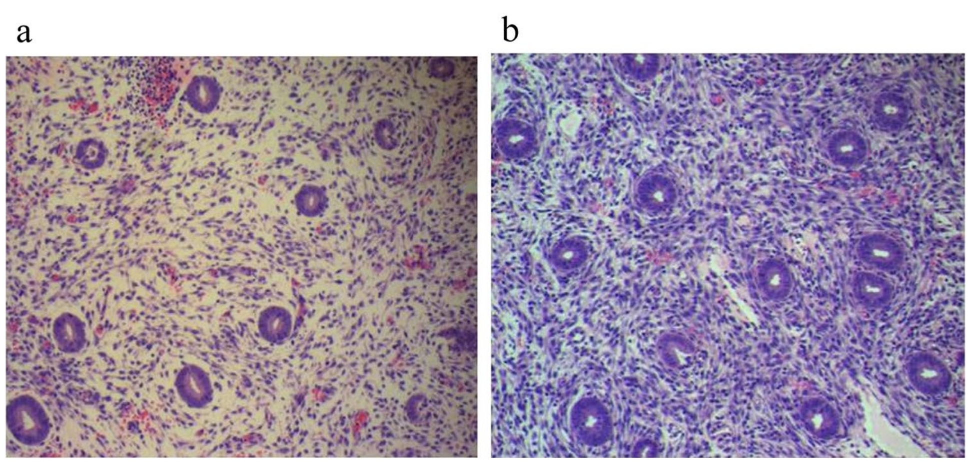

Fig. 1 Representative images of the histological assessment of the paired endometrium biopsy samples: quality of endometrium (**a**) before and (**b**) after operation

groups, the treatment group displayed a lower incidence of readhesion after operation.

To further investigate the rationale of the beneficial effect brought by cHA gel, we examined the endometrial thickness and the quality of endometrium of the recruited patients. Thin endometrial lining has been well characterized to be a major risk factor for implantation failure [16]. Zhang et al. proved that endometrial thickness can be used as a predictive factor of the endometrial receptivity in a retrospective study [17]. Theoretically, the quality of endometrium in terms of mucous gland number is also an indicator of the endometrial receptivity [18, 19]. Our results revealed that the treatment group treated with cHA gel exhibited a significantly thicker endometrial lining compared to the control group and a trend of increase in the number of glands was observed in the treatment group after operation. These supported that the cHA gel can improve the endometrial receptivity and subsequently lead to a better performance in embryo transfer.

The potential limitations of this study were listed as follow: (1) only two surgeons were assigned to perform hysteroscopy; (2) the clinicians were not blinded for the use of the gel; and (3) the small sample size of participants that finally undergo embryo transfer. These factors may affect the study quality, and thus further studies are required to validate our results.

The cHA gel used in this study-MateRegen® gel has been shown to facilitate the regeneration of nasal mucus [20]. The gel can degrade into water and completely be eliminated from the body. Thus, it is effective and safe to be used in the human body.

To the best of our knowledge, this is the first randomized controlled clinical trial reporting the use of cHA gel in a specified population, infertile woman with moderate to severe IUA, with reproductive outcomes. Adequate data such as adhesion score, endometrial thickness, and the number of glands were evaluated to support the rationale of improving endometrial receptivity with cHA gel. Together, we proved that the use of cHA gel can effectively prevent readhesion and improve the endometrial receptivity, which eventually facilitates embryo transfer in patients with moderate to severe IUA.

Acknowledgements We thank BioRegen Biomedical Ltd., Inc. for providing the MateRegen® gel and technical support in this study.

Authors' contribution Shaozhen Zhang: protocol development, data collection, data analysis, manuscript writing. Jie Zhang: data collection, manuscript proofreading. Yu Tao: data collection, manuscript proofreading. Xiaoyan Mao: protocol development, data collection, data analysis, manuscript writing. Yanping Kuang: data collection, manuscript proofreading. Hongyuan Gao: data collection, manuscript proofreading. Qiuju Chen: data collection, manuscript proofreading. Renfei Cai: data collection, manuscript proofreading.

Funding This work was supported by the National Natural Science Foundation of China (Grant number 81501334, 2016–2018).

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine; reference no.: [2014]#31) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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