·Clinical Research·

Potential of new self-crosslinked hyaluronic acid gel on the recovery of endometrium after artificial abortion: a multicenter, prospective randomized controlled trial

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[**Abstract**] **Objective** To evaluate the impact of self-crosslinked hyaluronic acid (SCH) gel on endometrium recovery after artificial abortion. **Methods** A multicenter, prospective randomized controlled trial was conducted across 18 hospitals from December 2021 to February 2023, involving 382 women who underwent artificial abortion. Participants were randomly allocated to receive either treatment with SCH gel (SCH group) or no treatment (control group) in a 1∶1 ratio. The primary outcome was endometrium thickness in 14 to 18 days after the first postoperative menstruation. Secondary outcomes included changes in menstrual volume during the first postoperative menstruation, menstruation resumption within 6 postoperative weeks, time to menstruation resumption, duration of the first postoperative menstruation, and incidence of dysmenorrhea. **Results** Baseline characteristics of participants were comparable between the two groups (all $P>0.05$), with 95.3% (182/191) in SCH group and 92.7% (177/191) in the control group completed the study. The postoperative endometrial thickness in SCH group was significantly greater than that in the control group [(9.78±3.15) vs (8.95±2.32) mm; $P=0.005$]. SCH group also had significantly fewer participants with reduced menstrual volume [23 cases (12.6%, 23/182) vs 31 cases (17.5%, 31/177); $P=0.038$]. Although SCH group experienced less dysmenorrhea during the first postoperative menstrual period, this difference was not statistically significant [28.5%(51/179) vs 37.1%(65/175); $P=0.083$]. Outcomes were similar between SCH group and the control group regarding the proportion of participants who resumed menstruation within 6 weeks postoperatively, time to menstruation resumption, and duration of the first postoperative menstruation ($P=0.792$,0.485, and 0.254, respectively). No serious adverse events were observed during the study period, and no adverse events were attributed to SCH gel treatment. **Conclusion** The application of SCH gel after artificial abortion is safe and might aid in the recovery of the endometrium.

[**Key words**] Hyaluronic acid; Abortion, induced; Endometrium; Randomized controlled trial; Self-crosslinked hyaluronic acid gel

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The endometrium plays a crucial physiological role in embryo implantation, the maintenance of pregnancy after implantation, and the formation of menstruation during non-pregnant periods. [1] The induced abortion procedure may cause damage to the endometrium, and the repair process of this damage could result in the formation of fibrotic scar tissue [2-3]. Damage to the basal layer of the endometrium may delay regeneration, promote the formation of fibrous tissue, and ultimately lead to endometrial fibrosis and adhesions [4]. This may result in partial or complete adhesions in the uterine cavity and/or cervical canal, clinically presenting as menstrual abnormalities, infertility, recurrent miscarriage, and other pregnancy complications. This condition is referred to as "intrauterine adhesions" or "Asherman syndrome". Studies have reported that the prevalence of intrauterine adhesions among women after abortion is as high as approximately 20% [4-5]. Globally, from 2015 to 2019, there were approximately 73 million cases of induced abortion (including surgical and medical abortions) annually [6]. Therefore, protecting the endometrium after induced abortion has become a major focus and challenge in global clinical research. The use of materials to promote endometrial repair and prevent intrauterine adhesions after the procedure is an important adjunctive treatment [7].

In recent years, various materials for preventing intrauterine adhesions have been developed both domestically and internationally, but their clinical performance after induced abortion requires further evaluation through clinical trials. Hyaluronic acid has been shown to promote scarless wound healing by reducing inflammation and promoting epithelial regeneration [8-9]. Additionally, crosslinking modifications can increase the viscosity of hyaluronic acid and delay its degradation, thereby prolonging its retention time in the body. As a result, self-crosslinked hyaluronic acid gel has become a bioactive barrier that effectively prevents intrauterine adhesions [10-14]. The self-crosslinked hyaluronic acid (SCH) gel used in this study is a new type of self-crosslinked hyaluronic acid gel, and it is a domestically produced product. This study is a multicenter, prospective randomized controlled trial aimed at evaluating the safety and efficacy of SCH gel in promoting endometrial repair after induced abortion, with the goal of better protecting the endometrium and preserving female fertility.

Materials and Methods

I. Data Sources

1. Study Design: This study adopted a prospective randomized controlled design and was conducted at 18 hospitals across China. The study was approved by the Ethics Committees of each participating hospital (HS-3031B) and registered with the Chinese Clinical Trial Registry (ChinCTR2100053851; https://www.chictr.org.cn/showprojEN.html?proj=141329).

2. Data Collection: Inclusion Criteria: Women aged 18 to 40 who underwent induced abortion; a history of no more than 2 previous abortions; normal liver and kidney function, and no major systemic diseases; ultrasound confirmed that the gestational sac diameter was greater than 1.0 cm and the embryo length was less than 3.0 cm. Exclusion Criteria: Women with gynecological diseases (such as uterine fibroids, adenomyosis, or a history of intrauterine adhesions), menstrual disorders, or a history of polycystic ovary syndrome. All participants signed an informed consent form before joining the clinical trial. Participants were randomly assigned in a 1:1 ratio to two groups: one group received only induced abortion (control group), and the other group received induced abortion followed by intrauterine injection of SCH gel (SCH group). The randomization sequence was generated using an envelope-based method, which was derived from a cross-over randomized design treatment allocation table. To minimize any bias from the operating surgeon, randomization and group assignment were determined immediately after the completion of the surgical procedure. The randomization envelope was opened by an assistant to decide whether SCH gel should be injected into the uterus. The study did not blind the operating surgeons but blinded the participants and the ultrasound technicians who performed follow-up examinations.

II. Treatment Plan and Follow-up

1. Surgical Procedure and Gel Application: All induced abortions were performed under general anesthesia using ultrasound-guided vacuum aspiration.

The gynecological surgeons performing the procedure were qualified in family planning surgery and had at least two years of experience. At the end of the induced abortion procedure, 2.5 mL of SCH gel (produced by BioRegen Biomedical (Changzhou) Co., Ltd., trade name: MateRegen Gel) was injected into the uterine cavity of participants in the SCH group, while the control group did not receive SCH gel treatment. No uterotonic drugs were used during the procedure. Postoperatively, participants were given one of the following traditional Chinese medicines for 7 days: Motherwort Granules, Eleuthero Biochemical Capsules, or Xinshenghua Granules. Postoperative antibiotics of the cephalosporin class were the first choice for anti-inflammatory treatment, and if the participant was allergic, quinolone antibiotics were used, for a duration of 3 days. Short-acting combined oral contraceptives or other steroid hormone treatments were not used postoperatively.

2. Follow-up: Participants were followed up within 6 weeks after the induced abortion to assess the resumption of menstruation and the condition of their first postoperative menstrual period. Transvaginal 3D ultrasound was performed between the 14th and 18th day after the first menstruation.

III. Outcome Measures

1. Efficacy Assessment: The primary efficacy endpoint was the endometrial thickness measured by ultrasound between the 14th and 18th day after the first postoperative menstruation. The secondary efficacy endpoints included the resumption of menstruation within 6 weeks after the procedure, time to menstrual resumption, changes in menstrual volume during the first postoperative menstruation (assessed through patient history inquiry and comparing the current volume with the preoperative baseline; since the participants were outpatient subjects, weight measurement was not feasible, and self-reported weights could lead to missing or inaccurate data, so the study opted to collect menstrual volume data via patient history inquiry), the duration of the first postoperative menstruation, and dysmenorrhea status. Patients who did not experience menstruation within 6 weeks postoperatively due to intrauterine adhesions were excluded from statistical analysis.

2. Safety Assessment: The occurrence rates of complications and adverse events potentially related to the use of SCH gel were observed.

IV. Statistical Methods

Statistical analysis was performed using SPSS 24.0 software. The sample size estimation for this study was based on the primary hypothesis that the SCH group would have a thicker endometrium postoperatively compared to the control group. It was assumed that the difference in postoperative endometrial thickness between the two groups would be 1 mm, with a standard deviation of 3 mm. The two-sided significance level was set at 0.05, with an estimated 20% dropout rate. A total of 354 participants were required, with a 1:1 allocation ratio, to achieve 80% statistical power to detect a difference between the two groups. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$), and compared using independent two-sample t-tests. Non-normally distributed continuous variables were expressed as median (25th, 75th percentiles) [$M(P_{25}, P_{75})$], and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as counts and percentages, and compared using the χ^2 test. A P-value of <0.05 was considered statistically significant.

Results

From December 2021 to February 2023, a total of 400 participants who met the inclusion criteria were evaluated in this study. Eighteen participants were excluded for violating the randomization protocol, leaving 382 participants who were randomly assigned to either the SCH group or the control group in a 1:1 ratio. Each group consisted of 191 participants who received the respective interventions, forming the full analysis set and safety analysis set. A detailed participant allocation and process flow can be seen in Figure 1. In this study, no participants withdrew due to adverse events. However, 23 participants (9 from the SCH group and 14 from the control group) were unable to complete the follow-up within the specified timeframe (i.e., they did not undergo post-operative transvaginal 3D ultrasound examination). As a result, a total of 359 participants [182 from the SCH group (95.3%, 182/191) and 177 from the control group (92.7%, 177/191)] completed the statistical analysis for this study.

The baseline characteristics of the two groups, including age, weight, number of pregnancies, number of deliveries, menstrual history, dysmenorrhea history, fertility intentions, and history of uterine surgery, were compared, and no statistically significant differences were found ($P > 0.05$ for all). Furthermore, during the induced abortion procedure, no significant differences were observed between the two groups in terms of blood loss and surgery duration ($P = 0.756$, 0.669). See Table 1.

I. Primary Efficacy Endpoint

The primary efficacy endpoint was the endometrial thickness measured between the 14th and 18th day after the first menstrual period following surgery. A total of 359 participants (182 in the SCH group and 177 in the control group) were included. The postoperative endometrial thickness in the SCH group was (9.78 ± 3.15) mm (95% *CI*: 9.32–10.24 mm), while in the control group it was (8.95 ± 2.32) mm (95% *CI*: 8.61–9.29 mm). The endometrial thickness in the SCH group was significantly greater than that in the control group, with a statistically significant difference between the two groups ($t = 2.85$, $P = 0.005$). Moreover, the lower limit of the 95% *CI* in the SCH group (9.32 mm) was higher than the upper limit of the 95% *CI* in the control group (9.29 mm).

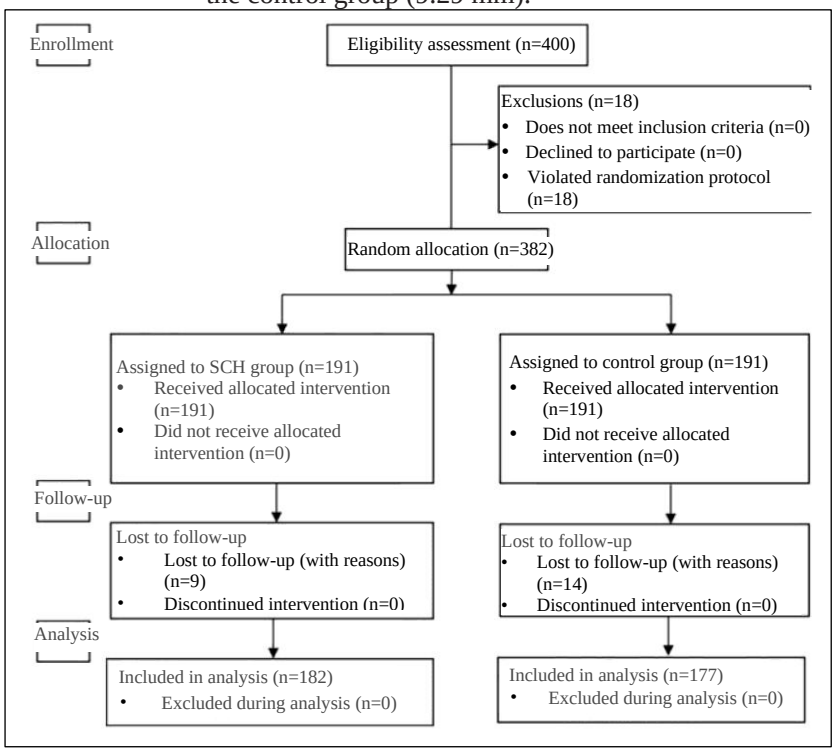

Fig. 1 Flowchart of the Allocation of Subjects in this Study

II. Secondary Efficacy Endpoints

The incidence of reduced menstrual flow in the SCH group was lower than that in the control group, with a statistically significant difference between the two groups (P = 0.038). However, there were no significant differences between the two groups in terms of the number of participants who had menstrual resumption within 6 weeks postoperative, time to menstrual resumption, and the duration of menstruation (all $P > 0.05$). Although the SCH group experienced less dysmenorrhea during the first postoperative menstruation, the difference did not reach statistical significance (P = 0.083). All 359 participants in the study completed the final follow-up, with no cases of absent menstrual resumption. The longest follow-up time was 94 days. See Table 2.

III. Safety Assessment: Results

Three cases of surgical complications were observed in the SCH group, all of which were incomplete induced abortion. Postoperative B-ultrasound examination showed heterogeneous or mixed echogenicity within the uterine cavity. However, the amount of residual tissue was minimal, and treatment with traditional Chinese medicine (TCM) was administered orally. The residual tissue was completely expelled after the first postoperative menstruation. In the control group (no SCH gel), there was 1 case each of mild rash and lower abdominal pain postoperative. These were adverse drug reactions (unrelated to the SCH gel used as a control) and surgical complications. Both cases were mild and resolved after appropriate care.

Table 1. Comparison of General Characteristics Between Two Groups of Participants Undergoing Induced Abortion

Category	SCH Group (n=182)	Control Group (n=177)	Statistic Value	*P*-Value
Age (years, $\bar{x}\pm s$)	30.3±5.3	30.3±5.1	t=0.06	0.955
Weight (kg, $\bar{x}\pm s$)	57.1±8.9	57.7±9.1	t=0.57	0.567
Gravidity (n, %)			χ^2=1.14	0.286
0 pregnancies	31 (17.0)	38 (21.5)		
1–5 pregnancies	151 (83.0)	139 (78.5)		
Parity (n, %)			χ^2=1.18	0.277
0 births	76 (41.8)	84 (47.5)		
1–3 births	106 (58.2)	93 (52.5)		
Previous menstrual duration (days, $\bar{x}\pm s$)	6.5±4.8	6.2±4.0	t=0.59	0.554
Fertility intention (n, %)			χ^2=0.35	0.552
No intention	93 (51.1)	96 (54.2)		
Has intention	89 (48.9)	81 (45.8)		
Dysmenorrhea history (n, %)			χ^2=2.34	0.126
No	128 (70.3)	111 (62.7)		
Yes	54 (29.7)	66 (37.3)		
Previous uterine surgery history (n, %) [a]			χ^2=1.31	0.726
0 surgeries	111 (61.0)	110 (62.9)		
1 surgery	54 (29.7)	50 (28.6)		
2 surgeries	17 (9.3)	15 (8.6)		
Intraoperative blood loss (ml, $\bar{x}\pm s$)	11.2±5.8	11.4±7.8	t=0.31	0.756
Intraoperative duration (min, $\bar{x}\pm s$)	7.9±4.5	8.1±4.6	t=0.43	0.669

Note: [a] Two cases in the control group did not provide data, resulting in missing values. SCH = Self-Crosslinked Hyaluronic Acid.

Table 2. Comparison of Secondary Efficacy Endpoints Between Two Groups of Participants Undergoing Induced Abortion

Category	SCH Group (n=182)	Control Group (n=177)	Statistic Value	*P*-Value
Menstrual volume (n, %)			χ^2=6.54	0.038
No reduction	159 (87.4)	146 (82.5)		
Reduction	23 (12.6)	31 (17.5)		
Menstrual resumption within 6 weeks (n, %)			χ^2=0.07	0.792
No	19 (10.4)	17 (9.6)		
Yes	163 (89.6)	160 (90.4)		
Time to menstrual resumption (days, $\bar{x}\pm s$)	36.1±9.3	35.5±7.4	t=0.70	0.485
Dysmenorrhea during first postoperative menstruation (n, %) [a]			χ^2=3.01	0.083
No	128 (71.5)	110 (62.9)		
Yes	51 (28.5)	65 (37.1)		
Duration of first postoperative menstruation (days, $\bar{x}\pm s$)	5.8±1.5	6.0±1.6	t=1.14	0.254

Note: [a] Data missing for 3 cases in the SCH group and 2 cases in the control group. SCH = Self-Crosslinked Hyaluronic Acid

Furthermore, no postoperative infections were reported in either group. During the clinical trial, no serious adverse events occurred, such as hemorrhagic shock, uterine perforation, vascular embolism, or sepsis. Additionally, there were no cases of prolonged hospitalization or repeat surgeries due to adverse events. No adverse events attributable to SCH gel treatment were reported in this study.

Discussion

I. The Role of Hyaluronic Acid in Endometrial Repair

Hyaluronic acid promotes the proliferation and differentiation of endometrial epithelial cells and facilitates endometrial repair by downregulating inflammatory responses and promoting angiogenesis [15]. However, liquid hyaluronic acid degrades too quickly in vivo and cannot remain in the uterine cavity during the critical period of re-epithelialization—5 to 7 days after endometrial injury [16]. This rapid degradation has raised questions about its efficacy. A cohort study indicated that the efficacy of hyaluronic acid in preventing reformation of intrauterine adhesions after hysteroscopic adhesiolysis was inferior to inert barriers (such as intrauterine devices and balloon catheters), with significant differences between the two ($P < 0.001$) [17].

Self-crosslinked hyaluronic acid prolongs its retention time in vivo by increasing viscosity and delaying degradation, while retaining the beneficial properties of standard hyaluronic acid. During the critical period of endometrial repair, the appropriate use of self-crosslinked hyaluronic acid can effectively separate multiple injury sites on the endometrium, preventing adhesion formation by keeping damaged areas from adhering to each other, thus promoting postoperative endometrial repair. In a randomized controlled trial [18], patients with endometrial polyps, uterine fibroids, or uterine septa who received SCH gel after hysteroscopic resection had significantly reduced rates of intrauterine adhesion formation compared to the blank control group (3.66% vs. 10.98%). Additionally, SCH gel significantly improved postoperative pregnancy rates (60.98% vs. 40.54%). These findings suggest that SCH gel is more effective than standard hyaluronic acid in promoting endometrial repair and improving subsequent pregnancy rates.

II. Efficacy Evaluation of SCH Gel in Endometrial Repair After Induced Abortion

1. Efficacy evaluation based on the primary endpoint: This study focused on women undergoing induced abortion. Regarding the primary efficacy endpoint, the postoperative endometrial thickness in the SCH group was (9.78 ± 3.15) mm, compared to (8.95 ± 2.32) mm in the control group without SCH gel. The postoperative endometrial thickness in the SCH group was significantly greater than that in the control group, achieving the primary study endpoint. Study has demonstrated that clinical pregnancy rates and live birth rates show significant differences when the endometrial thickness is around 8 mm [19]. A separate study investigated the impact of SCH gel on pregnancy outcomes. This study included 306 patients undergoing in vitro fertilization (IVF) after intrauterine adhesiolysis surgery. Of these, 202 patients in the treatment group received SCH gel, while 104 patients in the control group received standard treatment without SCH gel. On the day of embryo transfer, the endometrial thickness of the treatment group and the control group was (7.97 ± 1.37) mm and (7.50 ± 0.60) mm, respectively. Although the mean difference between the two groups was only 0.47 mm ($P < 0.001$), the clinical pregnancy rates were 26.3% in the treatment group and 15.3% in the control group ($P = 0.045$), demonstrating significant clinical relevance [20]. Therefore, the nearly 1 mm increase in average endometrial thickness observed in this study highlights the efficacy of SCH gel in promoting endometrial repair. This is particularly significant for patients with an endometrial thickness <8 mm and fertility desires, as it holds substantial clinical importance.

2. Efficacy and Safety Evaluation Based on Secondary Endpoints: In this study, the incidence of reduced menstrual volume during the first postoperative menstruation was significantly lower in the SCH group compared to the control group (12.6% vs. 17.5%; $P = 0.038$). This effect is associated with the ability of SCH gel to promote endometrial repair and increase endometrial thickness. The study also compared the two groups regarding menstruation resumption within 6 weeks post-abortion, time to menstruation resumption, duration of the first postoperative menstruation, and dysmenorrhea. No significant differences were observed between the groups (P-values of 0.792, 0.485, 0.254, and 0.083, respectively). Regarding the safety of SCH gel, no adverse reactions related to SCH gel were identified in this study. These findings suggest that SCH gel's primary benefit for endometrial repair after induced abortion lies in improving endometrial thickness and preserving menstrual physiology. Moreover, its safety profile is comparable to that of conventional treatment.

III. Strengths and Limitations of This Study

1. Strengths: A literature database search

revealed that this study is the first to analyze the effects of SCH gel on endometrial repair after induced abortion through a large-scale, prospective randomized controlled trial. The main strengths of this study lie in its use of randomized controlled and multicenter design, ensuring the reliability of the results. Conducted across 18 hospitals, the study has a certain level of representativeness. Additionally, the adequate sample size (382 participants) and low loss-to-follow-up rate (approximately 6%) ensured sufficient statistical power and reduced potential bias, making the study of high evidence-based medical quality.

2. Limitations: The main limitation of this study is that it only assessed postoperative endometrial thickness and menstrual recovery. Due to the limited follow-up duration, the study did not analyze the long-term impact of SCH gel on intrauterine adhesion incidence or pregnancy outcomes. Compared to other intrauterine surgical procedures, endometrial trauma caused by induced abortion is relatively mild, and tissue healing occurs relatively quickly. In clinical practice, some women resume sexual activity as early as one month after induced abortion. Therefore, this study measured endometrial thickness via transvaginal 3D ultrasound between the 14th and 18th days after the first postoperative menstruation as the primary efficacy endpoint. Based on the study results, the average follow-up time for both groups fully covered the time to menstruation resumption, suggesting that the follow-up period was adequate to observe the primary efficacy endpoint. Given the practical clinical constraints of this study and the fact that other researchers have studied the long-term impact on pregnancy outcomes [20], this study did not include long-term follow-up in its design.

This study did not include other ultrasound imaging features as observation endpoints. First, the ultrasound features of intrauterine adhesions include thin endometrium, disruption of endometrial continuity, heterogeneous endometrial echogenicity, and intrauterine fluid accumulation. However, during the study design phase, a comprehensive literature review did not identify composite indicators that encompass these ultrasound features and effectively characterize intrauterine adhesions. Second, ultrasound examination has certain limitations in diagnosing intrauterine adhesions [21-22]. Diagnoses based on ultrasound are not suitable as primary endpoints for well-designed clinical trials. Finally, a literature review revealed that similar major clinical trials both domestically and internationally have not adopted ultrasound-diagnosed intrauterine adhesions as primary efficacy endpoints. Therefore, this study ultimately selected endometrial thickness, the most representative indicator closely associated with subsequent pregnancy, as the primary efficacy endpoint.

In conclusion, the use of SCH gel after induced abortion promotes postoperative endometrial growth and repair, reducing the incidence of decreased menstrual volume during the first postoperative menstruation. SCH gel is a convenient, safe, and effective medication for promoting endometrial repair after induced abortion.

Conflict of Interest All authors declare no conflicts of interest.

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On the Importance of Citing Domestic Literature

Citing references is an important indicator of a paper's scientific rigor and academic quality. It also reflects the author’s respect for others' research achievements and provides readers with additional relevant information. Authors should limit their citations to key primary sources they have personally read, published in formal publications.

Currently, some authors, when writing papers or reviews, only cite foreign literature (or non-Chinese language literature), as if this practice is trendy or sophisticated. Admittedly, in many fields of medical research, the level of domestic studies does require improvement, and citing foreign literature is indeed necessary.

However, disregarding domestic literature can lead to the following issues: (1) It is highly likely that the author has not read the domestic literature. This results in an incomplete review of the available research, calling into question the scientific rigor and innovation of the paper or review being written. (2) Failure to cite relevant domestic literature prevents a comprehensive and accurate reflection of the level and progress of domestic research. After all, papers and reviews published in this journal are primarily intended for Chinese physicians. (3) Some authors, despite having read domestic literature, choose not to cite or annotate it.

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