Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2025**; 52(7): 36477
https://doi.org/10.31083/CEOG36477

Review

The Efficacy of Self-Cross-Linked Sodium Hyaluronate Gel in the Prevention of Intrauterine Adhesions: A Literature Review

Mingjiao Zhang[1,2], Hao Zhang[2,3], Peijia Zhang[1,2], Zihang Wei[4], Xin Liao[1,2,*]

[1]Department of Operating Room Nursing, West China Second University Hospital, Sichuan University, 610041 Chengdu, Sichuan, China
[2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, 610041 Chengdu, Sichuan, China
[3]Department of Neonatology Nursing, West China Second University Hospital, Sichuan University/West China School of Nursing, Sichuan University, 610041 Chengdu, Sichuan, China
[4]West China School of Nursing, Sichuan University, 610041 Chengdu, Sichuan, China
*Correspondence: sccdhxeytg@163.com (Xin Liao)
Academic Editor: Andrea Tinelli
Submitted: 20 December 2024 Revised: 4 May 2025 Accepted: 9 May 2025 Published: 18 July 2025

Abstract

Objective: Intrauterine adhesions (IUAs) are primarily addressed through hysteroscopic surgery, and the clinical application of self-cross-linked sodium hyaluronate gel has progressively gained traction to prevent postoperative recurrence, alterations in uterine morphology, and menstrual irregularities. Clinicians frequently employ sodium hyaluronate gel in combination with an intrauterine device (IUD) or balloon; however, the precise effectiveness of these combined approaches warrants further investigation. Accordingly, this study aimed to synthesize the outcomes of various treatment modalities reported in existing research and summarize the outcome measures employed, thereby providing valuable insights and references for the field. **Findings in Brief**: Our findings indicate that using self-cross-linked sodium hyaluronate gel alone significantly reduces the severity of adhesions in patients with uterine adhesions, but has no considerable effect on those with mild adhesions. The postoperative recurrence rate of adhesions was significantly lower in patients who received a combined therapy of a gel and a uterine balloon or IUD, compared to those treated with the gel alone. Additionally, the combined gel and electrophysiological techniques enhanced local blood circulation in the pelvic floor and mitigated scar tissue formation in the uterus, reducing IUAs. However, none of the three treatment modalities demonstrated a significant impact on the final pregnancy outcomes of the patients. **Conclusions**: Self-cross-linked sodium hyaluronate gel proves effective in preventing postoperative recurrence in patients with IUAs; however, further research is required to elucidate the impact of these gels on patients with mild versus severe adhesions. Future studies should consider conducting high-quality, large-scale randomized controlled trials to compare the therapeutic efficacy of these approaches, thereby advancing their clinical application.

Keywords: self-cross-linking sodium hyaluronate gel; intrauterine adhesion; endometrium; operative hysteroscopy

1. Introduction and Background

Intrauterine adhesion (IUA) is a pathological condition resulting from various etiological factors that cause damage to the basal layer of the endometrium, leading to uterine wall adhesions [1,2]. The primary causes of IUA include excessive manipulation of uterine instruments, surgical trauma, endometrial curettage following pregnancy, intrauterine infections, abdominal and hysteroscopic myomectomy, genital tuberculosis, and cesarean section [3–5]. In addition, IUA can result in adverse outcomes, such as partial or complete obstruction of the uterine cavity or cervical canal [6], infertility, ectopic pregnancy, recurrent miscarriage, preterm birth, and placental abnormalities. These complications can promote significant clinical and social challenges [7]. While the precise incidence of IUA remains undetermined, studies suggest that approximately 5% of women of reproductive age experience two or more miscarriages, the majority of whom undergo dilation and curettage [8]. Of those who undergo dilation and curettage, 15%–20% develop IUA. Meanwhile, the global number of induced abortions reached 56.3 million annually between 2010 and 2014 [9], which may contribute to more than 10 million cases of IUA each year [10,11]. Furthermore, IUA may present with few or no obvious symptoms, or patients may fail to recognize the significance of their symptoms, resulting in delayed medical attention and diagnoses [12,13]. Consequently, the true incidence of IUA is likely underestimated [7].

The standard treatment for IUA typically involves hysteroscopic adhesion lysis. However, postoperative complications often include increased rates of adhesion recurrence and suboptimal pregnancy outcomes [14]. Presently, physical barriers such as balloon catheters and intrauterine devices (IUDs) are employed to mitigate IUA following hysteroscopic adhesion lysis. However, despite the efficacy of these barriers, concerns remain regarding discomfort associated with foreign bodies, elevated infection risks, and potential uterine perforation [15]. In contrast, semi-solid reagents, specifically self-cross-linking

hyaluronic acid (ACHA) or hyaluronic acid (HA) gels, have emerged as alternatives in recent years, aiming to overcome the limitations of these physical barriers. Sodium hyaluronate, a glucuronic aldehydic acid family member, constitutes a principal constituent in the cellular and intercellular matrix. The primary mechanisms through which sodium hyaluronate mitigates IUA involve forming a disordered mesh structure in an aqueous solution, both a spatial and mechanical barrier [16]. Additionally, the resultant protective film aids in minimizing surgical trauma. Sodium hyaluronate also inhibits the activation and aggregation of inflammatory cells, thus reducing fibroblast aggregation in traumatized tissues and lowering the risk of IUA. Moreover, the lubricating properties of sodium hyaluronate alleviate friction during the healing process [17]. Furthermore, HA gel offers significant advantages such as reduced degradation and high viscosity, and utilizes an automatic cross-linking technology that activates and modifies linear HA molecules into a three-dimensional network structure. This technology is designed to extend the half-life of the gel, prolonging its absorption time (up to 7 to 14 days). Additionally, the material properties of HA gel contribute to enhancing the quality of the endometrium and improving uterine receptivity (Fig. 1). The ability of HA gel to expand ensures continued isolation of the intrauterine cavity after surgery, effectively reducing the risk of re-adhesion [18]. Notably, no adverse events have been reported in studies utilizing sodium hyaluronate gel to prevent IUA [19–21].

Numerous extant studies have explored the utilization of sodium hyaluronate in preventing adhesions among patients following uterine maneuvers, yet conclusive evidence remains lacking. Therefore, this review aimed to synthesize the findings regarding the efficacy of sodium hyaluronate in preventing IUA after intrauterine procedures. Moreover, this review aimed to provide healthcare professionals with a comprehensive summary of existing research and to open new avenues for future investigations.

2. Methods

2.1 Search Strategy and Study Selection

To identify relevant studies, we systematically searched several electronic databases, including PubMed, Web of Science, Cochrane, and EMBASE. The search was restricted to articles published in English up to March 11, 2025, which investigated HA gel interventions for patients with IUAs. A combination of standardized terms and keywords was used, including “intrauterine adhesion”, “uterine adhesion”, “tissue adhesions”, “uterine diseases”, “synechia”, “Asherman syndrome”, along with terms related to intervention (“prevent”, “reduce”, “manage”, “decrease”) and hyaluronic acid derivatives (“hyalobarrier”, “hyaluronan gel”). The characteristics of included articles are presented in Table 1 (Ref. [6,17,19–33]).

2.2 Inclusion Criteria

Studies were included upon meeting the following criteria: Female participants with diagnosed IUAs; studies with at least two groups, one receiving a HA gel or related derivatives and the other a placebo or control group post-intrauterine surgery; adhesion severity classification based on the American Fertility Society (AFS) system as determined by hysteroscopic evaluation; primary outcomes focused on the incidence and severity of the IUA.

2.3 Exclusion Criteria

The following studies were excluded: Abstract-only articles, duplicate publications, and studies that did not report specific, usable data on the outcomes of interest.

3. Review

3.1 Evaluation of the Efficacy of Self-Cross-linking HA Gel as a Standalone Treatment for Managing IUAs

Most studies indicate that using HA gel following intrauterine procedures effectively reduces the incidence of postoperative IUA. In a systematic review, Zheng *et al.* [20] included 952 women of childbearing age who underwent intrauterine surgery. Of these, 455 received HA gel following adhesion separation, while 497 constituted the control group. The findings demonstrated a reduction in the incidence of IUA and IUA severity scores following intrauterine surgery with HA gel administration. Subgroup analysis of this study further revealed that the preventive effect of HA gel on IUA was not influenced by the type of intrauterine surgery or the primary disease. In patients undergoing curettage and hysteroscopy, the application of HA gel significantly prevented IUA ($p < 0.001$). Furthermore, HA gel effectively prevented IUA in patients following a miscarriage and with conditions such as IUA, submucosal uterine fibroids, endometrial polyps, or uterine septum.

Several studies, including those by Acunzo *et al.* [22], Guida *et al.* [23], Sroussi *et al.* [24], and Chen *et al.* [25], reported a significant reduction in IUAs in the experimental group compared to the control group at the 3-month follow-up. Adhesion staging revealed a marked decrease in adhesion severity among patients treated with HA gel, with no reported adverse effects during its usage. In contrast, Zhou *et al.* [26] found no statistically significant differences in IUA recurrence rates, the American Fertility Society (AFS) score, or menstrual patterns between patients treated with HA gel and controls postoperatively at 4 weeks. Similarly, research by Thubert *et al.* [27] indicated that HA gel failed to prevent IUA recurrence or increase pregnancy rates. Nonetheless, the small sample size (90 patients) in the study underscores the need for randomized controlled trials with larger cohorts to explore the efficacy of HA gel further, as emphasized by the authors.

However, the postoperative preventive effect of HA gel in patients with mild IUA remains unclear. A comprehensive review conducted by Liu *et al.* [28] and Liu

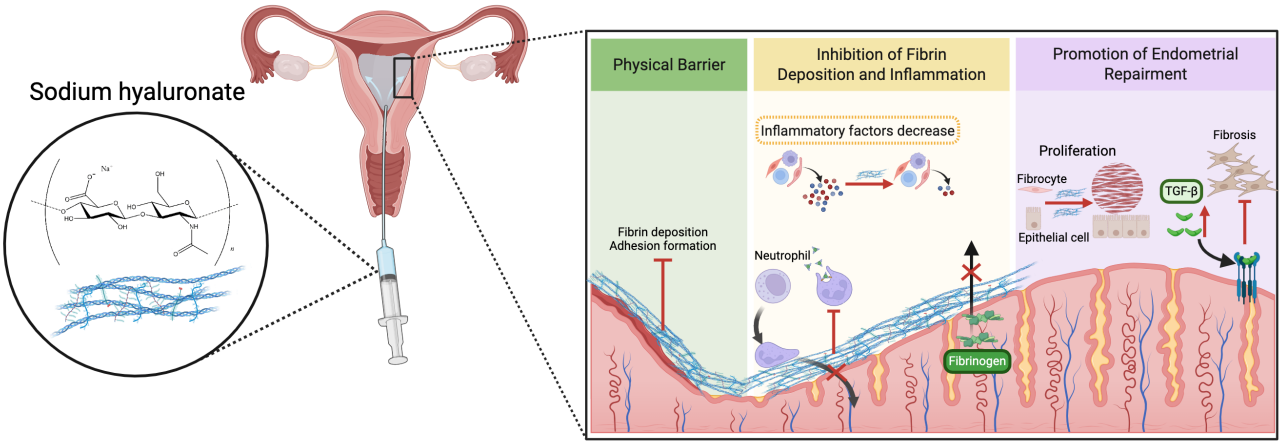

Fig. 1. Mechanism of action of sodium hyaluronate gel in the uterine cavity. TGF-β, Growth factors that promote endometrial repair.

et al. [29] on the use of HA gel in patients undergoing intrauterine surgery demonstrated a significant reduction in the incidence of moderate to severe IUA following the application of HA gel; however, it had no observed effects on mild IUAs. Similarly, Fei *et al.* [30] found that HA gel significantly reduced post-abortion IUA scores, markedly decreasing the occurrence of moderate-to-severe post-abortion IUA ($p < 0.001$), albeit without impacting mild uterine adhesions ($p = 0.19$). Therefore, the efficacy of HA gel in patients with varying degrees of IUAs requires further investigation. Future studies should focus on stratifying the population to implement targeted intervention strategies.

3.2 The Therapeutic Efficacy of Using Sodium Hyaluronate Gel in Conjunction With Either a Balloon Catheter or an Intrauterine Device (IUD)

In addition to the standalone use of HA gel to prevent postoperative IUA, it is also clinically utilized in combination with intrauterine balloons or contraceptive devices in patients following adhesion separation surgery. This combined approach has been shown to reduce postoperative adhesions to some extent. Specifically, in patients presenting with IUA, a Foley balloon catheter was inserted into the uterine cavity, followed by injection of 3 mL self-cross-linking HA gel, after adhesion separation. At the 3-month postoperative evaluation, the treatment group showed a significantly greater reduction in adhesions, with 76% and 48% efficacy rates, compared to the control group [31]. Furthermore, total AFS scores were notably lower in the treatment cohort, with significant improvements in adhesion type and menstrual patterns.

Most research suggests that the combined application of HA gel with intrauterine balloons or contraceptive devices is more effective in preventing adhesions than using HA gel alone. Trinh *et al.* [32] identified distinct treatment categories for patients with IUA, including HA gel treatment alone, IUD treatment alone, and HA gel and IUD treatment. Notably, the recurrence rates and AFS scores were significantly lower in women treated with HA gel and IUD than those treated with HA gel alone. However, no significant difference in pregnancy rate was observed. A comprehensive systematic review by Vitale *et al.* [34] incorporating data from 1596 women highlighted the substantial effect of combining HA gel with an IUD on mean adhesion scores, with the greatest improvement observed in this group. Noteworthy trends were identified in postoperative adhesion severity, with the HA gel and IUD combination exhibiting the largest cumulative area under the ranking curve (49.9%), followed by IUD alone (30.8%). A similar approach was employed by Xiao *et al.* [31], who introduced a Foley balloon catheter into the uterine cavity post-adhesion separation, followed by HA gel injection to prevent postoperative re-adhesion. The treatment group showed a significant reduction in re-adhesion rates at the 3-month follow-up, accompanied by improvements in adhesion type and menstrual patterns.

However, most studies have primarily focused on comparing the effects of single use versus combined use of HA gel, without differentiating between the efficacy of HA gel combined with an intrauterine balloon versus HA gel combined with an IUD. Future research should explore and compare the effectiveness of these two intervention strategies in greater detail.

3.3 Efficacy of Sodium Hyaluronate Gel Combined With Bioelectrical Stimulation To Prevent Intrauterine Adhesions

Pelvic floor bioelectrical stimulation has gained traction recently as a complementary treatment modality to using balloons and IUDs combined with HA gel to prevent IUAs. Pelvic floor neuromuscular electrical stimulation (NMES) is designed to enhance the strength and function of the pelvic floor muscles, promoting tissue healing and reducing scar tissue formation by stimulating these muscles and improving local blood circulation [35]. This non-inva-

Table 1. Characteristics of the studies included in this review.

Name of first author and year [Ref. number]	Study design	Participants	Intervention	Outcomes
Cheng M *et al*., 2020 [6]	Meta-analysis	Hysteroscopic surgeries for fibroids, polyps, and septum (n = 242).	Intervention: PEO-NaCMC or ACHA gel.	ACHA gel significantly reduced new IUAs in postoperative patients.
Sun Y *et al*., 2024 [17]	Randomized controlled	Termination of pregnancy and abortion. Intervention group: n = 70 Control group: n = 70	Intervention: the sodium hyaluronate injection and pelvic floor NMES treatment. Control: a single 5 mL injection of sodium hyaluronate.	Combination therapy promoted significant advantages in preventing and reducing IUA after abortion.
Wang YQ *et al*., 2020 [19]	Randomized controlled	Patients after intrauterine adhesion lysis. Group A: n = 30 Group B: n = 24 Group C: n = 35	Group A: 3 mL of the HA gel was placed into the uterine cavity. Group B: 3 mL of the HA gel and an IUD were placed into the uterine cavity. Group C: only an IUD was placed into the uterine cavity.	HA gel has an advantage over an IUD in reducing IUA recurrence and decreasing adhesions.
Zheng F *et al*., 2020 [20]	Meta-analysis	Patients after intrauterine adhesion lysis (n = 952).	Intervention: HA gel. Control: No HA gel.	The HA gel reduced the incidence of IUA after intrauterine surgery and increased the postoperative pregnancy rate.
Tafti SZG *et al*., 2021 [21]	Randomized controlled	Women undergoing uterine septum resection. Group A: n = 34 Group B: n = 31	Intervention: 1 cc of HA gel was injected into the uterine cavity. Control: 1 cc normal saline solution as a placebo was injected into the uterine cavity.	The HA gel exhibited a capacity to reduce the risk of IUA in women with endometrial damage following a septal resection surgery.
Acunzo G *et al*., 2003 [22]	Prospective, randomized, controlled study	Intrauterine adhesions referred to the hysteroscopic. Group A: n = 46 Group B: n = 46	Intervention: hysteroscopic adhesiolysis plus intrauterine application of ACP gel (10 mL). Control: operative hysteroscopy alone.	The ACP gel significantly reduced the development of IUA postoperatively and its use is likely to be associated with a reduction in severe adhesions.
Guida M *et al*., 2004 [23]	Prospective, randomized, controlled study	A single surgically remediable intrauterine lesion (myomas, polyps and uterine septa). Group A: n = 66 Group B: n = 66	Intervention: hysteroscopic surgery plus intrauterine application of ACP gel (10 mL). Control: hysteroscopic surgery alone.	ACP gel significantly reduces the incidence and severity of the *de novo* formation of intrauterine adhesions after hysteroscopic surgery.

Table 1. Continued.

Name of first author and year [Ref. number]	Study design	Participants	Intervention	Outcomes
Sroussi J *et al*., 2022 [24]	Multicentric randomized controlled trial	Patients who had a miscarriage between weeks 7 and 14 of gestation, required dilation and curettage, and wanted another pregnancy. Group A: n = 171 Group B: n = 172	Intervention: surgery with intrauterine instillation of HA gel. Control: surgery alone.	Intrauterine instillation of HA gel reduces the rate of IUAs in women treated with dilation and curettage for miscarriage.
Chen H *et al*., 2022 [25]	Multi-center randomized controlled trial	Patients undergoing hysteroscopic electrosurgical resection. Group A: n = 82 Group B: n = 82	Intervention: received an intrauterine infusion of ACP gel after hysteroscopic electrosurgical resection. Control: nothing after hysteroscopic electrosurgical resection.	The ACP gel appeared to reduce IUAs and trended toward AFS scores and improved subsequent pregnancy rates after hysteroscopic electrosurgical resection.
Zhou Q *et al*., 2021 [26]	Randomized controlled trial	Patients with moderate-to-severe (American Fertility Society (AFS) score $\geq$5) IUAs underwent hysteroscopic adhesiolysis. Treatment group: n = 122 Control group: n = 123	Intervention: auto-cross-linked hyaluronic acid gel after surgery. Control: standard care only.	ACP gel did not seem to improve IUA recurrence after hysteroscopic adhesiolysis.
Thubert T *et al*., 2015 [27]	Observational retrospective study	Patients who underwent hysteroscopic removal of IUAs. Treatment group: n = 32 Control group: n = 58	Intervention: received ACP gel during hysteroscopic removal of IUAs. Control: did not receive ACP gel.	Application of ACP gel did not prevent recurrence of IUAs and was not associated with an increased pregnancy rate.
Liu YR *et al*., 2022 [28]	Meta-analysis	Patients after hysteroscopic surgery	Intervention: HA gel after hysteroscopy.	HA gel reduced severe IUAs, but had no significant effect on mild adhesions.
Liu H *et al*., 2018 [29]	Meta-analysis	Patients after hysteroscopic surgery	Intervention: HA gel after hysteroscopy.	HA gel prevented IUAs, particularly those with moderate severity and a lower adhesion score.
Fei Z *et al*., 2019 [30]	Meta-analysis	Women with miscarriage	Intervention: HA gel therapy after miscarriage.	HA gel significantly reduced the incidence of moderate and severe IUAs and significantly improved the pregnancy rate after miscarriage.
Xiao S *et al*., 2015 [31]	Prospective, randomized, Controlled clinical study	Women with moderate to severe IUA. Treatment group: n = 60 Control group: n = 60	Intervention: a Foley balloon catheter was first introduced into the uterine cavity and then 3 mL of auto-cross-linked HA gel. Control: only received Foley balloon catheter.	ACP gel could reduce IUAs and decrease adhesion severity.

Table 1. Continued.

Name of first author and year [Ref. number]	Study design	Participants	Intervention	Outcomes
Trinh TT *et al*., 2022 [32]	Retrospective study	Women who underwent hysteroscopic adhesiolysis. Group A: n = 121 Group B: n = 59 Group C: n = 20	Intervention: Group A: HA gel alone. Group B: IUDs alone. Group C: HA gel + IUD.	A combination of HA gel and IUD provided greater prevention of recurrent IUAs and could decrease post-treatment AFS scores.
Shabiti Y *et al*., 2023 [33]	Prospective observational study	Patients with infertility and a thin endometrium. Group A: n = 60 Group B: n = 60	Intervention: Femoston combined with biomimetic electrical stimulation. Control: Femoston alone.	Biomimetic electrical stimulation combined with Femoston could improve endometrial type and thickness in patients with infertility and thin endometrium compared with Femoston alone.

PEO–NaCMC, polyethylene oxide–sodium carboxy methylcellulose; ACHA, auto-cross-linked hyaluronic acid; ACP, auto-cross-linked hyaluronic acid; IUA, intrauterine adhesions; IUD, intrauterine device; HA, hyaluronic acid; AFS, American Fertility Society; NMES, neuromuscular electrical stimulation.

sive technique targets uterine cavity scarring resulting from endometrial injury. The bioelectrical stimulation of pelvic muscles enhances uterine healing, inhibits excessive scar tissue formation, and supports overall recovery. Recent studies have explored the combination of electrical stimulation with HA gel to prevent adhesions following uterine surgery. A study by Sun *et al*. [17] examined the efficacy of combining NMES with HA gel to prevent IUAs in a post-abortion experimental group, with the control group solely receiving HA gel injected into the uterine cavity (5 mL). The results indicated a significantly lower incidence of IUAs in the combined treatment group. Furthermore, this combined approach effectively enhanced endometrial thickness and reduced the pulsatility index (PI) and resistance index (RI) in the endometrial spiral arteries.

In a separate study, Shabiti *et al*. [33] investigated the effects of bionic electrical stimulation combined with Femoston on pregnancy outcomes and endometrial characteristics (including thickness and type) in patients with infertility and thin endometrium. Although the combination therapy resulted in higher endometrial thickness than Femoston alone, no significant improvement was observed in pregnancy rates.

While studies in this field remain limited, the promising potential of combining bioelectrical stimulation with HA gel in patients with IUAs warrants further investigation. Future research should aim to improve elucidation of the therapeutic benefits of this combination treatment and the impacts on uterine cavity healing, adhesion prevention, and pregnancy outcomes.

3.4 Outcome Indicators

Primary short-term outcome indicators for follow-up typically include the incidence of IUAs, which is assessed via repeat hysteroscopy at the 3-month postoperative mark. Secondary outcome indicators commonly encompass the degree of uterine cavity involvement, adhesion type, menstrual pattern, and endometrial thickness. Most studies have reported improvements in these parameters, with sodium hyaluronate gel demonstrating no significant adverse effects throughout the study period. Uterine cavity involvement is generally reassessed by hysteroscopy, usually scheduled 3 to 6 months after surgery, using the AFS adhesion extent, adhesion type score, and menstrual pattern for grading adhesions.

Secondary outcome indicators, such as endometrial thickness, uterine artery PI, and RI, have received less attention. Increased endometrial thickness is critical for improving conception rates, particularly relevant for patients undergoing *in vitro* fertilization (IVF) and women of reproductive age [36]. Additionally, lower values of spiral uterine artery PI and RI indicate enhanced uterine blood flow, which promotes tissue repair and endothelial growth [37]. Future studies should consider incorporating these parameters as additional outcome measures, with long-term follow-up concentrating on sustained pregnancy outcomes, thus broadening the research scope in this field.

Several studies have also explored the ultimate pregnancy outcome following uterine manipulation. Research by Fei *et al*. [38], Fuchs *et al*. [39], Tsapanos *et al*. [40], Liu *et al*. [28], and Fei *et al*. [30] exhibited higher conception rates in the experimental groups receiving self-cross-linked sodium hyaluronate after adhesion separation, compared to the control groups. A meta-analysis by Zheng *et al*. [20] revealed a pregnancy rate of 77.7% among patients treated with HA gel, significantly higher than the 60.0% rate observed in patients treated with IUD. Additionally, Huberlant *et al*. [41] conducted uterine curettage on 20 New Zealand white rabbits at 10-day intervals, randomly assigning them into two groups. The experimental group received intrauterine anti-adhesion gel drops post-curettage and underwent mating after a recovery period. The experimental group showed a significantly higher number of fetuses than the control group, suggesting the beneficial impact of sodium hyaluronate gel on fertility following curettage.

However, certain studies have reported no significant impact of postoperative sodium HA gel use on pregnancy outcome, highlighting the need for further investigation [32]. A more comprehensive evaluation of the efficacy of HA gel in preventing postoperative IUA requires larger sample sizes, longer follow-up periods, and rigorously designed randomized, controlled clinical studies.

3.5 Clinical Application of Sodium Hyaluronate Acid Gel

HA is a highly polymerized disaccharide chain and a mucopolysaccharide. Meanwhile, due to the irregular coiled structure and unique physicochemical properties of HA [42], it has important physiological functions in the body, including joint lubrication, regulation of vascular wall permeability, modulation of protein and electrolyte diffusion and transport, and promotion of wound healing [43]. Currently, sodium HA gel is widely utilized across various medical fields. In cosmetic surgery, sodium HA gel is a filler for procedures such as rhinoplasty, chin augmentation, nasolabial fold correction, and tear trough treatment, demonstrating effectiveness and stability in facial contouring and rejuvenation [44]. Meanwhile, HA gel is used in dentistry to treat conditions such as dry sockets and chronic periodontitis.

HA is frequently combined with other biopolymers, such as proteins or peptides, through esterification, cross-linking, and other chemical modifications. This has led to the development of various related compounds, such as hyaluronic acid–carboxymethylcellulose gels, which are widely employed to prevent tissue adhesions following surgical procedures [45]. HA gel has garnered significant attention recently for its role in preventing IUAs. Indeed, studies investigating the use of HA gel for this purpose have consistently demonstrated a significant ability for HA gel to reduce the incidence of postoperative IUAs [41,46]. Fur-

thermore, the safety of HA gel has been confirmed in relevant animal model studies, with no gel-related complications, such as perforation, bleeding, or other injuries, reported in clinical applications [20]. Clinicians can choose different treatment plans for patients with varying degrees of adhesion. For instance, patients with severe adhesions may benefit from a combination of HA gel and an intrauterine balloon or IUD to more effectively prevent the recurrence of adhesions. In contrast, patients with mild to moderate adhesions may require fewer intensive interventions. Additionally, treatment decisions should consider factors such as the patient's economic situation, insurance coverage, and other relevant considerations to ensure the most appropriate and accessible care.

4. Limitations

Due to the inconsistencies and heterogeneity in treatment methods, including variations in the amount of gel injected into the uterine cavity, baseline patient conditions, follow-up durations, and other factors across the studies, this article adopted a literature review approach. As a result, this review may lack systematic rigor and have no quantitative analysis of objective data. Future studies should aim to narrow the research focus, establish clear inclusion and exclusion criteria, and employ systematic evaluations to improve the synthesis of the available evidence.

5. Conclusions

In conclusion, existing studies have shown that using HA gel alone and combined with other interventions effectively prevents IUAs. However, the precise effects of HA gel on patients with mild, moderate, and severe IUAs still require further investigation. Additionally, this review provides a comprehensive summary of the outcome measures commonly used in related research, offering valuable guidance for selecting appropriate indicators in future studies.

Author Contributions

MJZ and HZ conducted the literature review, performed literature research, and drafted and revised the manuscript content. PJZ and ZHW contributed to the study's drafted and revised the manuscript content, and literature review. XL served as drafted the manuscript or reviewing it critically for important intellectual content and developed the study protocol. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was supported by Self-crosslinking hyaluronic acid gel for fertility protection in patients undergoing clearance surgery (West China Second University Hospital, Sichuan University) 22H0722.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Liao Z, Liu C, Wang L, Sui C, Zhang H. Therapeutic Role of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Female Reproductive Diseases. Frontiers in Endocrinology. 2021; 12: 665645. https://doi.org/10.3389/fendo.2021.665645.

[2] Manchanda R, Rathore A, Carugno J, Della Corte L, Tesarik J, Török P, *et al*. Classification systems of Asherman's syndrome. An old problem with new directions. Minimally Invasive Therapy & Allied Technologies: MITAT: Official Journal of the Society for Minimally Invasive Therapy. 2021; 30: 304–310. https://doi.org/10.1080/13645706.2021.1893190.

[3] Cao C, Zhou Q, Hu Z, Shu C, Chen M, Yang X. A retrospective study of estrogen in the pretreatment for medical management of early pregnancy loss and the inference from intrauterine adhesion. European Journal of Medical Research. 2022; 27: 129. https://doi.org/10.1186/s40001-022-00767-z.

[4] Yang L, Tian T, Yang X, Guo Y, Huang X, Xia E, *et al*. A comparison of the treatment outcome of Asherman's syndrome which developed within and outside the puerperal period: A matched cohort study. Acta Obstetricia et Gynecologica Scandinavica. 2025; 104: 774–780. https://doi.org/10.1111/aogs.15057.

[5] Zhang X, Liu W, Zhou Y, Qiu J, Sun Y, Li M, *et al*. Comparison of therapeutic efficacy of three methods to prevent readhesion after hysteroscopic intrauterine adhesion separation: a parallel, randomized and single-center trial. Annals of Palliative Medicine. 2021; 10: 6804–6823. https://doi.org/10.21037/apm-21-1296.

[6] Cheng M, Chang WH, Yang ST, Huang HY, Tsui KH, Chang CP, *et al*. Efficacy of Applying Hyaluronic Acid Gels in the Primary Prevention of Intrauterine Adhesion after Hysteroscopic Myomectomy: A Meta-Analysis of Randomized Controlled Trials. Life (Basel, Switzerland). 2020; 10: 285. https://doi.org/10.3390/life10110285.

[7] Lee WL, Liu CH, Cheng M, Chang WH, Liu WM, Wang PH. Focus on the Primary Prevention of Intrauterine Adhesions: Current Concept and Vision. International Journal of Molecular Sciences. 2021; 22: 5175. https://doi.org/10.3390/ijms22105175.

[8] Hooker AB, de Leeuw RA, Twisk JWR, Brölmann HAM, Huirne JAF. 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. Human Reproduction (Oxford, England). 2021; 36: 70–81. https://doi.org/10.1093/humrep/deaa289.

[9] Sedgh G, Bearak J, Singh S, Bankole A, Popinchalk A, Ganatra B, *et al*. Abortion incidence between 1990 and 2014: global, regional, and subregional levels and trends. Lancet (London, England). 2016; 388: 258–267. https://doi.org/10.1016/S0140-6736(16)30380-4.

[10] Gilman AR, Dewar KM, Rhone SA, Fluker MR. Intrauterine Adhesions Following Miscarriage: Look and Learn. Journal of Obstetrics and Gynaecology Canada: JOGC = Journal D'obstetrique et Gynecologie du Canada: JOGC. 2016; 38: 453–457. https://doi.org/10.1016/j.jogc.2016.03.003.

[11] Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brölmann HAM, *et al*. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Human Reproduction Update. 2014; 20: 262–278. https://doi.org/10.1093/humupd/dmt045.

[12] Dreisler E, Kjer JJ. Asherman's syndrome: current perspectives on diagnosis and management. International Journal of Women's Health. 2019; 11: 191–198. https://doi.org/10.2147/IJWH.S165474.

[13] Doroftei B, Dabuleanu AM, Ilie OD, Maftei R, Anton E, Simionescu G, *et al*. Mini-Review of the New Therapeutic Possibilities in Asherman Syndrome-Where Are We after One Hundred and Twenty-Six Years? Diagnostics (Basel, Switzerland). 2020; 10: 706. https://doi.org/10.3390/diagnostics10090706.

[14] Carbonnel M, Pirtea P, de Ziegler D, Ayoubi JM. Uterine factors in recurrent pregnancy losses. Fertility and Sterility. 2021; 115: 538–545. https://doi.org/10.1016/j.fertnstert.2020.12.003.

[15] Sun Y, Chen X, Qian Z, Cao L, Zhan S, Huang L. Estradiol and intrauterine device treatment for moderate and severe intrauterine adhesions after transcervical resection. BMC Women's Health. 2022; 22: 357. https://doi.org/10.1186/s12905-022-01940-6.

[16] Xin L, Wei C, Tong X, Dai Y, Huang D, Chen J, *et al*. In situ delivery of apoptotic bodies derived from mesenchymal stem cells via a hyaluronic acid hydrogel: A therapy for intrauterine adhesions. Bioactive Materials. 2022; 12: 107–119. https://doi.org/10.1016/j.bioactmat.2021.10.025.

[17] Sun Y, Zhang W, Cai Y, Li H. Preventive effects of sodium hyaluronate combined with pelvic floor neuromuscular electrical stimulation on the intrauterine adhesions in women after abortion. Biomolecules & Biomedicine. 2024; 24: 153–158. https://doi.org/10.17305/bb.2023.9467.

[18] Fan J, Xie J, Liao Y, Lai B, Zhou G, Lian W, *et al*. Human umbilical cord-derived mesenchymal stem cells and auto-crosslinked hyaluronic acid gel complex for treatment of intrauterine adhesion. Aging. 2024; 16: 6273–6289. https://doi.org/10.18632/aging.205704.

[19] Wang YQ, Song XH, Wu SL, Huang YZ, Yan L, Li CZ. Comparison of Autocross-Linked Hyaluronic Acid Gel and Intrauterine Device for Preventing Intrauterine Adhesions in Infertile Patients: A Randomized Clinical Trial. Gynecology and Minimally Invasive Therapy. 2020; 9: 74–80. https://doi.org/10.4103/GMIT.GMIT_103_19.

[20] Zheng F, Xin X, He F, Liu J, Cui Y. Meta-analysis on the use of hyaluronic acid gel to prevent intrauterine adhesion after intrauterine operations. Experimental and Therapeutic Medicine. 2020; 19: 2672–2678. https://doi.org/10.3892/etm.2020.8483.

[21] Tafti SZG, Javaheri A, Firoozabadi RD, Ashkezar SK, Abarghouei HF. Role of hyaluronic acid intrauterine injection in the prevention of Asherman's syndrome in women undergoing uterine septum resection: An RCT. International Journal of Reproductive Biomedicine. 2021; 19: 339–346. https://doi.org/10.18502/ijrm.v19i4.9060.

[22] Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, *et al*. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. Human Reproduction (Oxford, England). 2003; 18: 1918–1921. https://doi.org/10.1093/humrep/deg368.

[23] Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M, *et al*. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. Human Reproduction (Oxford, England). 2004; 19: 1461–1464. https://doi.org/10.1093/humrep/deh238.

[24] Sroussi J, Bourret A, Pourcelot AG, Thubert T, Lesavre M, Legendre G, *et al*. Does hyaluronic acid gel reduce intrauterine adhesions after dilation and curettage in women with miscarriage? A Multicentric randomized controlled trial (HYFACO Study). American Journal of Obstetrics and Gynecology. 2022; 227: 597.e1–597.e8. https://doi.org/10.1016/j.ajog.2022.05.064.

[25] Chen H, Xiong W, Zeng Y, Du H, Ye L, Chen L, *et al*. Efficacy and safety of auto-cross-linked hyaluronic gel to prevent intrauterine adhesion after hysteroscopic electrosurgical resection: a multi-center randomized controlled trial. Annals of Translational Medicine. 2022; 10: 1217. https://doi.org/10.21037/atm-22-4988.

[26] Zhou Q, Shi X, Saravelos S, Huang X, Zhao Y, Huang R, *et al*. Auto-Cross-Linked Hyaluronic Acid Gel for Prevention of Intrauterine Adhesions after Hysteroscopic Adhesiolysis: A Randomized Controlled Trial. Journal of Minimally Invasive Gynecology. 2021; 28: 307–313. https://doi.org/10.1016/j.jmig.2020.06.030.

[27] Thubert T, Dussaux C, Demoulin G, Rivain AL, Trichot C, Deffieux X. Influence of auto-cross-linked hyaluronic acid gel on pregnancy rate and hysteroscopic outcomes following surgical removal of intra-uterine adhesions. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2015; 193: 65–69. https://doi.org/10.1016/j.ejogrb.2015.06.025.

[28] Liu YR, Liu B, Yang BP, Lan Y, Chi YG. Efficacy of hyaluronic acid on the prevention of intrauterine adhesion and the improvement of fertility: A meta-analysis of randomized trials. Complementary Therapies in Clinical Practice. 2022; 47: 101575. https://doi.org/10.1016/j.ctcp.2022.101575.

[29] Liu H, Xu Y, Yi N, Yi W. Efficacy and Safety of Hyaluronic Acid Gel for the Prevention of Intrauterine Adhesion: A Meta-Analysis of Randomized Clinical Trials. Gynecologic and Obstetric Investigation. 2018; 83: 227–233. https://doi.org/10.1159/000486674.

[30] Fei Z, Xin X, Fei H, Yuechong C. Meta-analysis of the use of hyaluronic acid gel to prevent intrauterine adhesions after miscarriage. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2019; 244: 1–4. https://doi.org/10.1016/j.ejogrb.2019.10.018.

[31] Xiao S, Wan Y, Zou F, Ye M, Deng H, Ma J, *et al*. Prevention of intrauterine adhesion with auto-crosslinked hyaluronic acid gel: a prospective, randomized, controlled clinical study. Zhonghua Fu Chan Ke Za Zhi. 2015; 50: 32–36.

[32] Trinh TT, Nguyen KD, Pham HV, Ho TV, Nguyen HT, O'Leary S, *et al*. Effectiveness of Hyaluronic Acid Gel and Intrauterine Devices in Prevention of Intrauterine Adhesions after Hysteroscopic Adhesiolysis in Infertile Women. Journal of Minimally Invasive Gynecology. 2022; 29: 284–290. https://doi.org/10.1016/j.jmig.2021.08.010.

[33] Shabiti Y, Wufuer S, Tuohuti R, Yun T, Lu J. Impact of biomimetic electrical stimulation combined with Femoston on pregnancy rate and endometrium characteristics in infertility patients with thin endometrium: a prospective observational study. Gynecological Endocrinology: the Official Journal of the International Society of Gynecological Endocrinology. 2023; 39: 2214629. https://doi.org/10.1080/09513590.2023.2214629.

[34] Vitale SG, Riemma G, Carugno J, Perez-Medina T, Alonso Pacheco L, Haimovich S, *et al*. Postsurgical barrier strategies to avoid the recurrence of intrauterine adhesion formation after hysteroscopic adhesiolysis: a network meta-analysis of randomized controlled trials. American Journal of Obstetrics and Gynecology. 2022; 226: 487–498.e8. https://doi.org/10.1016/j.ajog.2021.09.015.

[35] Allon EF. The role of neuromuscular electrical stimulation in the rehabilitation of the pelvic floor muscles. British Journal of Nursing (Mark Allen Publishing). 2019; 28: 968–974. https://do

i.org/10.12968/bjon.2019.28.15.968.

[36] Kou L, Jiang X, Xiao S, Zhao YZ, Yao Q, Chen R. Therapeutic options and drug delivery strategies for the prevention of intrauterine adhesions. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2020; 318: 25–37. https://doi.org/10.1016/j.jconrel.2019.12.007.

[37] Li LN, Li XD, Du J. The effect of aspirin on uterine arterial blood flow and endometrium in moderate and severe intrauterine adhesion after transcervical resection of adhesion: a systematic review and meta-analysis. The Journal of Maternal-fetal & Neonatal Medicine: the Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians. 2023; 36: 2209818. https://doi.org/10.1080/14767058.2023.2209818.

[38] Fei Z, Bin Z, Xin X, Fei H, Yuechong C. Meta-analysis on the use of hyaluronic acid gel to prevent recurrence of intrauterine adhesion after hysteroscopic adhesiolysis. Taiwanese Journal of Obstetrics & Gynecology. 2019; 58: 731–736. https://doi.org/10.1016/j.tjog.2019.09.002.

[39] Fuchs N, Smorgick N, Ben Ami I, Vaknin Z, Tovbin Y, Halperin R, *et al*. Intercoat (Oxiplex/AP gel) for preventing intrauterine adhesions after operative hysteroscopy for suspected retained products of conception: double-blind, prospective, randomized pilot study. Journal of Minimally Invasive Gynecology. 2014; 21: 126–130. https://doi.org/10.1016/j.jmig.2013.07.019.

[40] Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae. Journal of Biomedical Materials Research. 2002; 63: 10–14. https://doi.org/10.1002/jbm.10040.

[41] Huberlant S, Fernandez H, Vieille P, Khrouf M, Ulrich D, de-Tayrac R, *et al*. Application of a hyaluronic acid gel after intrauterine surgery may improve spontaneous fertility: a randomized controlled trial in New Zealand White rabbits. PloS One. 2015; 10: e0125610. https://doi.org/10.1371/journal.pone.0125610.

[42] Wang M, Liu C, Xiao W. Intra-articular injection of hyaluronic acid for the reduction in joint adhesion formation in a rabbit model of knee injury. Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA. 2014; 22: 1536–1540. https://doi.org/10.1007/s00167-013-2547-3.

[43] Itano N. Simple primary structure, complex turnover regulation and multiple roles of hyaluronan. Journal of Biochemistry. 2008; 144: 131–137. https://doi.org/10.1093/jb/mvn046.

[44] Zhang HJ, Yu B, Niu F, Liu JF, Chen Y, Jin Q. Clinical application and observation of injectable modified sodium hyaluronate gel filler for facial cosmetic surgery. Zhonghua kou qiang yi xue za zhi = Zhonghua Kouqiang Yixue Zazhi = Chinese Journal of Stomatology. 2017; 52: 194–197. https://doi.org/10.3760/cma.j.issn.1002-0098.2017.03.013.

[45] Knopf-Marques H, Pravda M, Wolfova L, Velebny V, Schaaf P, Vrana NE, *et al*. Hyaluronic Acid and Its Derivatives in Coating and Delivery Systems: Applications in Tissue Engineering, Regenerative Medicine and Immunomodulation. Advanced Healthcare Materials. 2016; 5: 2841–2855. https://doi.org/10.1002/adhm.201600316.

[46] Wang L, Yu C, Chang T, Zhang M, Song S, Xiong C, *et al*. In situ repair abilities of human umbilical cord-derived mesenchymal stem cells and autocrosslinked hyaluronic acid gel complex in rhesus monkeys with intrauterine adhesion. Science Advances. 2020; 6: eaba6357. https://doi.org/10.1126/sciadv.aba6357.