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Intrauterine Adhesions (IUAs) or Asherman's Syndrome (AS) and the Stem Cells Treatment: A Systemic Review and Meta-Analysis

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Abstract

Background: Intrauterine Adhesions (IUAs) or Asherman's Syndrome (AS) usually contains symptoms such as decreased menstrual flow or even amenorrhea, chronic pelvic pain, recurrent abortion and infertility. The current treatment of IUAs includes hysteroscopic adhesiolysis, oral hormone and biological barriers, but each of them has limitation. Stem cell therapy may be an expanding field seeking for therapy in IUAs. **Objective:** We will discuss current advances in stem cell therapy as a treatment for endometrial pathophysiology. **Materials and Methods:** We search on PubMed, Embase and Cochrane library and select several keywords on researches, then review the cell biology theories and animal experiments, finally do meta-analysis in human clinical trials. **Results:** 77 articles on PubMed, 71 articles on Embase and 17 articles on Cochrane Library, as a result, 37 articles are included under the criteria, which are intrauterine adhesions (IUAs), Asherman's Syndrome (AS), cell therapy, stem cells, bone marrow stem cells, clinical trials, recent 10 years and human or animal experiments. The included criteria: original articles, cohort study, case control study, animal experiments, human clinical trials, high quality, 10 years recent. The excluded articles are case reports, meeting reports, low quality or more than 10 years ago. **Conclusion:** Stem cell may be a new therapeutic schedule for IUAs in the future clinical treatment, but it is necessary to compare it with traditional therapy such as oral hormone, also the development of random clinical tests should proceed. For clinical treatment on IUAs, stem cells could be a new choice.

Keywords

Intrauterine Adhesions IUA, Asherman's Syndrome, Stem Cells, Therapy, Infertility, Meta-Analysis

1. Introduction

Intrauterine Adhesions (IUAs) or Asherman's Syndrome (AS) is common caused by inflammatory or trauma damaging the endometrial basal layer after delivery or surgery [1] [2] [3]. The epidemiology of IUAs is unclear now, however, some researchers have reported that approximately 19% amongst women suffering miscarriage and being prospectively assessed by hysteroscopy within 1 year [4]. In addition, about 70% of patients with severe Asherman's Syndrome had history of instrumentation such as aspirator during the postpartum period [5], whereas approximately 80% - 90% patients with mild Asherman's Syndrome had similar procedures experienced at the first trimester. Furthermore, amongst women surgically treated for retained products of conception and evaluated hysteroscopy afterwards, the overall incidence of IUAs varies widely between 6 and 22% [6] [7].

The typical symptoms of IUAs or AS include decreased menstrual flow or amenorrhea, chronic pelvic pain, recurrent abortion and infertility [2] [8] [9]. However, the exact pathophysiologic origin of IUAs is still unclear. With expanded clinical awareness and availability of diagnostic testing, the frequency of diagnosis of IUAs has increased. Generally, the diagnosis of intrauterine adhesions depends on symptoms like menstruation and fertility and test such as ultrasound, Magnetic Resonance Imaging (MRI), Hysterosalpingography (HSG) and hysteroscopy [3]. Under a few of decades exploring and practice, the clinician recommended hysteroscopy as the golden standard of diagnosis by following the European Society of Gynecological Endoscopy (ESGE) publish the guidelines of diagnosis in 2016 [4].

In addition, the classification of IUAs is various in different areas, but no one is accepted universally, however, each of them is based on the grade of European Society for Hysteroscopy (ESH) in 1989 [4] [9] and American Fertility Society (AFS) in 1988 [1].

Currently, the therapeutic methods of IUAs include hysteroscopic adhesiolysis, oral hormone and biological barriers [10]. Primarily, severe forms may require multiple hysteroscopic adhesiolysis to achieve a satisfactory anatomical and functional result. Unfortunately, the recurrent rate of IUAs after hysteroscopy therapy is high [9] [10]. Then, estrogen supplementation is commonly given postoperatively to stimulate endometrial growth; yet, there is no standard dosage length or regimen or explanation of risk of stimulating breast and ovarian tumor [11] [12]. At last, using intrauterine barriers such as balloons, catheters and other intrauterine devices which may keep the uterine walls apart from

adhesiolysis to reduce adhesion recurrence are frequently employed [13] [14]. Whereas, 2010 American Association of Gynecologic Laparoscopists (AAGL) Practice Guidelines do not support use of antibiotic therapy before, during or after surgical management of IUAs because of increasing risks of infection [4].

In recent year, stem cell therapy [15] is an expanding field that seeks for alleviating numerous diseases involving malignant tumor, fibrosis, wound repair and inflammation. In addition, currently, cell bio-therapeutics for AS employ numerous sources of stromal and hematopoietic cell populations, including menstrual blood derived stromal cells (MenSCs), Umbilical Cord (UC) derived Mesenchymal Stromal Cells (MSCs), Bone Marrow derived Mononuclear Cells (BMMNCs) and peripheral blood derived mobilized populations. Thus, we aim to conclude stem cell therapy and IUAs or AS association in animal models and human clinical trials [16]. However, the problems of stem cells therapy like ethic, immune reaction or even risks of tumorigenesis limit it application in clinic, also, unknown mechanism, like gene regulation, protein modulation or paracrine effects should be explored and confirmed by future and it can be a new irritation for researchers.

In this article, we will discuss current advances in stem cell therapy as a treatment for intrauterine adhesions (IUAs) or Asherman's Syndrome (AS).

2. Materials and Methods

We search on PubMed, Embase and Cochrane library and select several keywords on researches including: intrauterine adhesions (IUAs), Asherman's Syndrome (AS), cell therapy, stem cells, bone marrow stem cells, clinical trials, recent 10 years and human or animal experiments. The included criteria: original articles, cohort study, case control study, animal experiments, human clinical trials, high quality, 10 years recent. In addition, the excluded criteria: case reports, meeting reports, low quality, more than 10 years ago.

Each article abstraction was performed using a standardized form; which included study characteristics such as year, author, area, type of study. Also each study should be scored under the scoring system like NOS (Newcastle-Ottawa quality assessment scale), Jadad, CASPin and iCAHE.

All the researches on human clinical trials are single-arm trials, and the data are extracted from text, tables, or figures. We conclude them and do the meta-analysis, all the differences in continuous outcomes using mean, weight mean difference (WMD) and sample size for each group, meanwhile Binary outcome is expressed as Odds Ratio (OR) and 95% Confidence Interval (CI). Hozo formula was used to convert data expressed as median and range. Statistical analysis was performed using Meta-Analyst.

3. Results

Depending on those search strategies, we found about 77 articles on PubMed, 71 articles on Embase and 17 articles on Cochrane Library. As a result, 37 articles

are included under the criteria, which are in details: clinical treatment 4, molecular 8, guideline 3, review article 7, stem cells application 15 (animal 10, human 5). The search process is below as the Figure 1 and Table 1 illustrates the scores and quality of the articles.

3.1. Molecular Experiments for Stem Cell and IUAs

Multiple studies show that the stem cells may improve the outcomes of injuring diseases [17] [18], but it is still unclear that whether stem cells transplantation can be used as a therapy for IUAs. Nesrine [19] *et al.* Investigated the Transforming Growth Factors-β (TGF-β), Tumor Necrosis Factor-α (TNF-α) and Vascular Endothelial Growth Factor (VEGF) are significant decreased in extracellular vesicles derived from human umbilical cord mesenchymal stem cells (UCMSCs-EVs) alone or combined with estrogen therapeutic groups. Also, they reported that mesenchymal stem cells (MSCs) play a significant role in repairing injured tissues, which through the secretion of a wide range of paracrine factors. In addition, bone marrow stem cells (BMSCs) have been hypothesized to be important for endometrial regeneration and repair. In addition, a great deal of studies reported that endometrial stem cells could contribute to endometrial repairing physiologically, which may be crucial for the treatment of IUAs. An increasing number of evidences have proposed that stem cells play a key role in developing the therapeutic strategies for IUAs, although the molecular mechanism has not been acknowledged.

Recently, some researchers [20] [21] devote to explore the hypothesis and evidence of stem cells repairing in IUAs. Typically, Estrogen Receptor α (ERα) is able to effectively promote BMSC proliferation and migration via Stromal Derived Factor/Chemokine Receptor type 4 (SDF-1/CXCR-4) according to Zhou *et al.* [22]. They point out that the upregulation of anti-inflammatory cytokines (base Fibroblast Growth Factor, bFGF and Interleukin, IL6) and the droppedregulation of pro-inflammatory cytokines after BMSCs transplantation may stimulate proliferation endometrial cell and exert an inhibitory action on endometrial

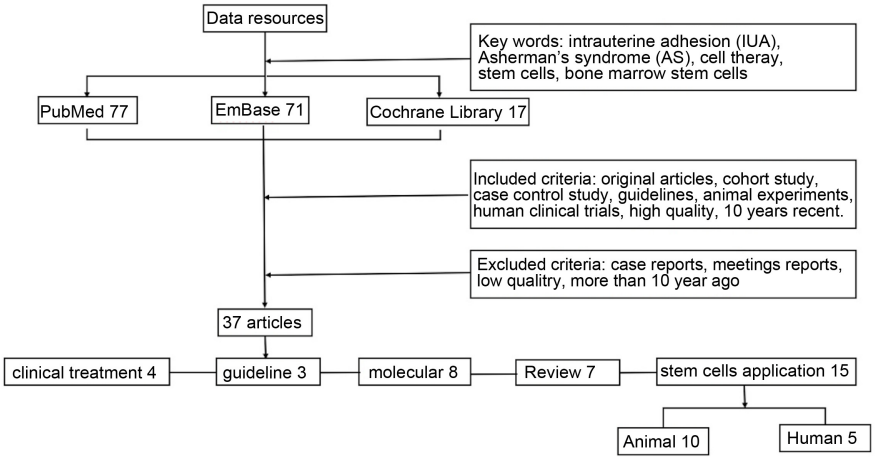

Figure 1. Research process.

Table 1. Summary of researches.

No.	Title	Author	Year	Type	Tools	Scores	Quality
1	Effectiveness of estrogen treatment before transcervical resection of adhesions on moderate and severe uterine adhesion patients	Ai-Zhen Liu	2016	case-cohort	NOS	7	high
2	Prevalence of intrauterine adhesions after the application of hyaluronic acid gel after dilatation and curettage in women with at least one previous curettage: short-term outcomes of a multicenter, prospective randomized controlled trial	Angelo B. Hooker, M.D	2017	RCT	Jadad	5	high
3	The incidence of post-operative adhesion following transection of uterine septum: a cohort study comparing three different adjuvant therapies	Xiao Yu	2016	cohort	NOS	6	high
4	The management of Asherman syndrome: a review of literature	Alessandro Conforti	2013	review	CASPin	7	moderate
5	Transdermal estrogen gel and oral aspirin combination therapy improves fertility prognosis via the promotion of endometrial receptivity in moderate to severe intrauterine adhesion	Yuguang Chi	2017	RCT	Jadad	5	high
6	AAGL Practice Report: Practice Guidelines for Management of Intrauterine Synechiae	AAGL	2009	clinical practical guideline	iCAHE guideline quality checklist	11	high
7	AAGL Practice Report: Practice Guidelines on Intrauterine Adhesions Developed in Collaboration With the European Society of Gynaecological Endoscopy (ESGE)	AAGL	2016	clinical practical guideline	iCAHE guideline quality checklist	11	high
8	Review of Intrauterine Adhesions	Rebecca Deans	2010	review	CASPin	8	high
9	Abnormal expression of fibrosis markers, estrogen receptor α and stromal derived factor-1/chemokine (C-X-C motif) receptor-4 axis in intrauterine adhesions	QIN ZHOU	2018	basic research	ARRIVE	15	moderate
10	Elevated NF-κB signaling in Asherman syndrome patients and animal models	Xiangzhen Wang	2017	basic research	ARRIVE	16	moderate
11	Molecular implication of ADAM-15 and 17 in intrauterine adhesions	Dan Liu	2013	basic research	ARRIVE	17	high
12	Role of Transforming Growth Factor-β1 and Smads Signaling Pathway in Intrauterine Adhesion	Umme Salma	2016	basicl research	ARRIVE	18	high
13	The Overexpression of TGF-β and CCN2 in Intrauterine Adhesions Involves the NF-κB Signaling Pathway	Xiang Xue	2015	basicl research	ARRIVE	17	high

Continued

14	The expression of marker for endometrial stem cell and fibrosis was increased in intrauterine adhesious	Jianguo Hu	2015	basic research	ARRIVE	17	high
15	A 10-year Review of the Clinical Presentation and Treatment Outcome of Asherman's Syndrome at a Center with Limited Resources	IU Takai	2015	review	CASPin	8	high
16	Systemic administration of bone marrow-derived cells leads to better uterine engraftment than use of uterine-derived cells or local injection	Ying Liu	2017	review	CASPin	7	moderate
17	A comprehensive review of Asherman's syndrome: causes, symptoms and treatment options	Christina A. Salazar	2017	review	CASPin	9	high
18	Cellular therapies for the endometrium	Suzanna Queckbörner	2018	review	CASPin	6	moderate
19	Efficacy and Safety of Hyaluronic Acid Gel for the Prevention of Intrauterine Adhesion: A Meta-Analysis of Randomized Clinical Trials	Huafang Liu	2017	review	CASPin	10	high
20	Intrauterine adhesion prevention after hysteroscopy: a systematic review and meta-analysis	Mae Wu Healy	2016	review	CASPin	8	high
21	Meta-analysis of the use of amniotic membrane to prevent recurrence of intrauterine adhesion after hysteroscopic adhesiolysis	Fei Zheng	2018	review	CASPin	8	high
22	Endometrial reconstruction from stem cells	Caroline E. Gargett, Ph.D	2012	review	CASPin	6	moderate
23	CXCL12 Promotes Stem Cell Recruitment and Uterine Repair after Injury in Asherman's Syndrome	Gulcin Sahin Ersoy	2017	animal research	ARRIVE	17	high
24	Application of Bone Marrow-Derived Mesenchymal Stem Cells in the Treatment of Intrauterine Adhesions in Rats	Jianmei Wang	2016	animal research	ARRIVE	16	moderate
25	Feasibility analysis of treating severe intrauterine adhesions by transplanting menstrual blood-derived stem cells	SHEN-XIA ZHENG	2016	animal research	ARRIVE	18	high
26	Human amniotic mesenchymal stromal cell transplantation improves endometrial regeneration in rodent models of intrauterine adhesions	LU GAN	2017	animal research	ARRIVE	17	high
27	Human mesenchymal stem cell-derived extracellular vesicles/estrogen combined therapy safely ameliorates experimentally induced intrauterine adhesions in a female rat model	Nesrine Ebrahim	2018	animal research	ARRIVE	17	high

Continued

28	Neupogen and mesenchymal stem cells are the novel therapeutic agents in regeneration of induced endometrial fibrosis in experimental rats	Dina Sabry	2017	animal research	ARRIVE	16	moderate
29	Vitamin C plus hydrogel facilitates bone marrow stromal cell-mediated endometrium regeneration in rats	Huan Yang	2017	animal research	ARRIVE	17	high
30	Bone Marrow-Derived Stem Cell (BMDSC) Transplantation Improves Fertility in a Murine Model of Asherman's Syndrome	Feryal Alawadhi	2014	animal research	ARRIVE	18	high
31	Effect of stem cell application on Asherman syndrome, an experimental rat model	Sevtap Kilic	2014	animal research	ARRIVE	17	high
32	Platelet-rich plasma improves therapeutic effects of menstrual blood-derived stromal cells in rat model of intrauterine adhesion	Siwen Zhang	2019	animal research	ARRIVE	15	moderate
33	Autologous menstrual blood-derived stromal cells transplantation for severe Asherman's syndrome	Jichun Tan	2016	cohort	NOS	8	high
34	Autologous stem cell transplantation in refractory Asherman's syndrome: A novel cell based therapy	Neeta Singh	2014	cohort	NOS	8	high
35	Autologous cell therapy with CD1331 bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: a pilot cohort study	Xavier Santamaria	2016	cohort	NOS	9	high
36	Transplantation of collagen scaffold with autologous bone marrow mononuclear cells promotes functional endometrium reconstruction via down regulating ΔNp63 expressionin Asherman's syndrome	Guangfeng Zhao	2017	cohort	NOS	8	high
37	Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial	Yun Cao	2018	cohort	NOS	8	high

NOS: Newcastle-Ottawa quality assessment scale, RCT: Random Clinical Trails, iCAHE: The International Center for Allied Health Evidence, ARRIVE: Animal Research: Reporting in Vivo Experiments

cell [20] [23].

3.2. Animal Experiments Results

There were more than ten researches illustrated that stem cells could repair uterine endometrium in animal models during the recent 10 years [24]. Here, we conclude four typical articles among them to illustrate the stem cells application for animal models.

According to Sevtap and Beril [25], they have designed the experiment to evaluate the effects of stem cells to induce endometrial proliferation and angi-

ogenesis on Asherman's Syndrome. This research resulted that the amount of fibrosis, vascularisation, inflammation and immune histochemical staining with vascular endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA) and Ki-67 were evaluated in the uterine tissues. After mesenchymal stem cells (MSCs) therapy; fibrosis in mice uterine decreased but vascularisation and immune histochemical staining increased in the experimental side. This study also concluded that stem cells and estrogen were an extremely useful choose to induce regeneration of endometrium in Asherman Syndrome therapy. Similarly, Feryal Alawadhi *et al.* [26] Jianmei Wang *et al.* [27] and Yang *et al.* [28] conducted research that bone marrow-derived mesenchymal stem cells (BMSCs) were injected to adult female albino rats with uterine damage. They were observed that BMSCs transplantation was an original treatment for Asherman's Syndrome and may also be helpful to prevent Asherman's Syndrome after uterine injury.

The other researchers completed the animal experiments on rat model of IUAs and stem cell therapy for them, which reported that stem cells transplantation was a potential novel treatment for Asherman's Syndrome and may also be useful to prevent Asherman's Syndrome after uterine injury syndrome [15] [29] [30] [31].

3.3. Stem Cell Application in Human IUAs: Meta-Analysis

In recent ten years, there are several articles focusing on stem cells therapy in intrauterine adhesions and we have found five articles of human which are single arm studies focusing on this objection. Thus, we do the meta-analysis depending on them by software of meta-analyst [32] [33] [34] [35] [36].

Figure 2 shows the forest plots of age in the five studies which use random effect model because of P = 0.012. The figure results that the weight mean difference is 33.765% and 95% Confidence Interval (95% CI) is 33.330 to 34.201.

Figure 3 shows that the endometrial thickness before stem cells treatment in these studies. And the weight mean difference (WMD) is 3.66 and 95% CI is 2.599 to 4.620, which results from random effect model by P < 0.001. **Figure 4**

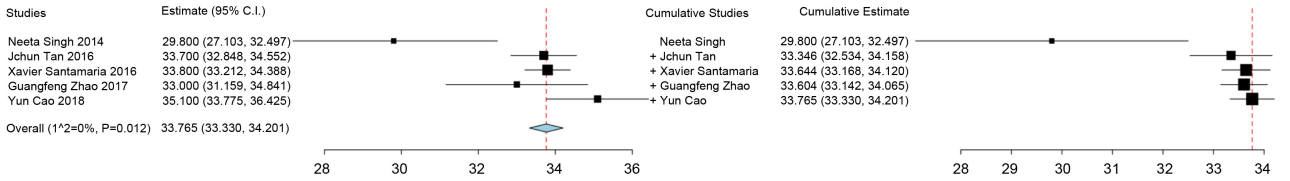

Figure 2. Forest plot of age.

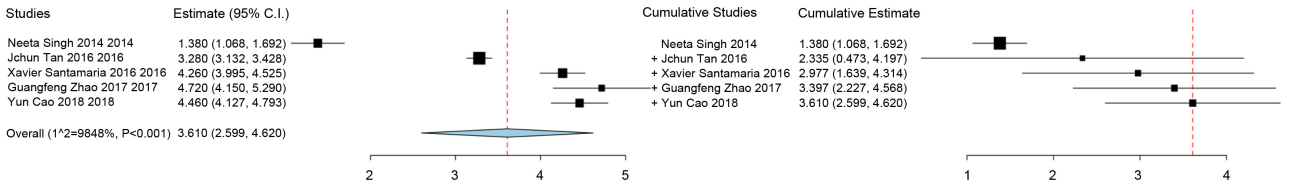

Figure 3. Forest plots of the endometrial thickness before stem cells treatment.

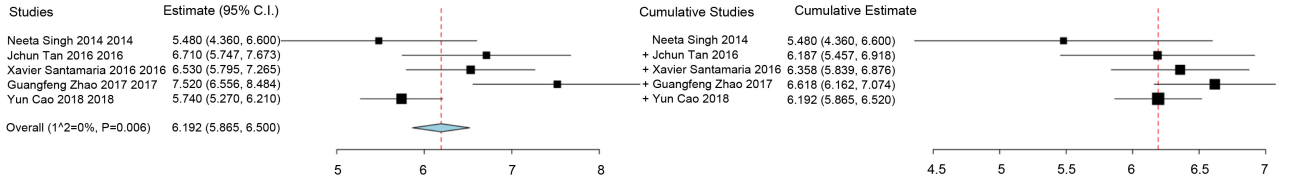

Figure 4. Forest plots of the endometrial thickness after stem cells treatment.

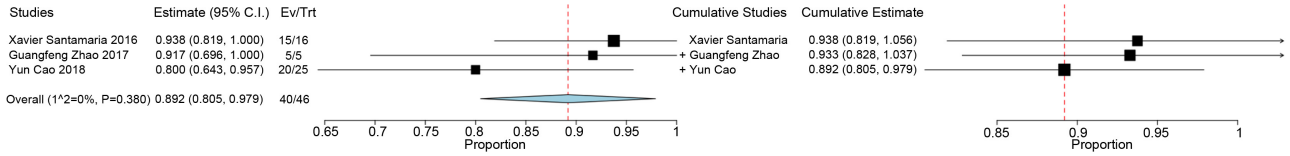

Figure 5. Forest plots of the improvement under hysteroscopy after stem cell therapy.

shows that the endometrial thickness after stem cells treatment. In which, the WMD is 6.192 and 95% CI is 5.865 to 6.520, which also results from random effect model by P = 0.006. Figure 5 illustrates that the improvement under hysteroscopy after stem cell therapy, but only three studies undergo it. And the forest plot shows that the estimated odd ratio is 0.892 (95% CI: 0.805, 0.907) resulting from fixed effect model by P = 0.3800.

4. Discussion

Along with development and progression of IUAs, fibrotic tissues gradually covered or replaced the normal endometrium and promoted the formation of IUAs. And inflammatory factor TGF-β has demonstrated to be a central mediator of the fibrotic response. Currently, Smad3 protein proves to an important signal transduction molecule that induces the activation of TGF-β and the binding of TGF with receptors to the signal transduce from the cytoplasm to the nucleus. Through the TGF/Smad3 pathway, collagen synthesis and extracellular matrix precipitates are increased, promoting the formation of tissue fiber scar [23]. Activation and abnormal expression of TGF-β1 can inhibit the expression of Matrix Metalloproteinase-9 (MMP-9), promote the expression of Tissue Inhibitor of Matrix Metalloproteinases-1 (TIMP-1), reduce the activity of proteolytic enzyme, then promote the formation of Extracellular Matrix (ECM) but not easy to be degraded, leading to the transformation of fibroblasts into myofibroblasts, and promote wound contraction [19]. The process of the pathogenesis of IUAs is complicated, other studies showed that the expression of MMP-9 and Nuclear Factor-κB (NF-κB) miRNA are also significantly higher in the endometrial sample from intrauterine adhesion compared to normal endometrial controls. Furthermore, the specific mechanism needs to be investigated [37] [38].

Although a couple of experiments have demonstrated the safety of stem cells transplantation as a therapeutic strategy for IUAs, the capability of self-renew of stem cell and the up-regulation of anti-inflammatory may induce uncontrolled cell growth and tumorigenesis.

As human clinical experiments result, we found that the age of IUAs under

stem cells is about 33 years in four studies but one research which was written by Neeta Singh, included patients much younger than others (29.8). However, this study just integrated 6 cases that could not change the results significantly because of less weight. Thus, the bias of age is less. In addition, the endometrial thickness (3.61 mm) under ultrasound before treatment is rather thinner than normal ones (more than 5 mm), which may be the main reason for amenorrhea and infertility. Then, after stem cell therapy including intrauterine injection and vein injection, the thickness of endometrial (6.192 mm) is improved significantly. However, the ultrasound could not be the best standard for evaluating the effectiveness of therapy depending on the guideline. Three of them finish hysteroscopy after stem cell therapy and 40 amongst 46 patients in these studies get improved from severe IUAs to normal endometrial or moderate IUAs. Also, the improving symptoms could be the evaluation like normal menstruation, pregnancy and delivery. Depending on Xavier Santamaria study more than 50% patient pregnant and 16% patients got babies in full-term, as well as, 4 patients and 1 patient in study from Zhao *et al.* are reported to full-term and premature labor in 28 weeks(twins) respectively. Thus, in clinical trial reports, we conclude that stem cell could be a new therapeutic schedule for IUAs.

However, all these researches are single-arm studies without control groups for comparison because it may be difficult for clinic to finish comparing with other therapy. Furthermore, we can develop the stem cell therapy treating IUAs for more patients and implement multi-center clinical study and Random Clinical Tests (RCTs).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

IUAs = Intrauterine Adhesions.
AS = Asherman's Syndrome.
MRI = Magnetic Resonance Imaging.
HSG = Hysterosalpingography.
ESGE = European Society of Gynecological Endoscopy.
ESH = European Society for Hysteroscopy.
AFS = American Fertility Society.
AAGL = American Association of Gynecologic Laparoscopists.
MenSCs = Menstrual blood derived Stromal Cells.
UC = Umbilical Cord.
MSCs = Mesenchymal Stromal Cells.
BMMNCs = Bone Marrow derived Mononuclear Cells.
NOS = Newcastle-Ottawa quality assessment scale.
WMD = Weight Mean Difference.
OR = Odds Ratio.
CI = Confidence Interval.
TGF-β = Transforming Growth Factors-β.
TNF-α = Tumor Necrosis Factor-α.
VEGF = Vascular Endothelial Growth Factor.
UCMSCs-EVs = Extracellular Vesicles derived from human Umbilical Cord Mesenchymal Stem Cells.
ERα = Estrogen Receptor α.
SDF-1/CXCR-4 = Stromal Derived Factor/Chemokine Receptor type 4.
bFGF = Fibroblast Growth Factor.
IL = Interleukin.
VEGF = Vascular Endothelial Growth Factor.
PCNA = Proliferating Cell Nuclear Antigen.
MMP-9 = Matrix Metalloproteinase-9.
TIMP-1 = Tissue Inhibitor of Matrix Metalloproteinases-1.
ECM = Extracellular Matrix.
NF-κB = Nuclear Factor-κB.
RCTs = Random Clinical Tests.