Postoperative Management of Hysteroscopic Metroplasty of Congenital Uterine Anomalies

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Abstract

Background: Successful implantation of the embryo and normal development of pregnancy after hysteroscopic metroplasty in women with congenital uterine anomalies, obtaining a normal endometrium is a necessary condition, which must be achieved by preventing development of postoperative intrauterine adhesions (IUA) and stimulating regeneration of the endometrium. Despite years of studies aimed at evaluating strategies to prevent IUA after operative hysteroscopy, it is still unclear which strategies are most effective.
Aim: The aim of this literature review is to analyze and evaluate advantages and disadvantages of therapeutic means used for prevention of development of IUA after hysteroscopic metroplasty and to stimulate the regeneration of the endometrium
Methods: In order to collect literature data, we used such electronic search databases as PubMed, Medline, Google Scholar and Cochrane Library. Key words used were: congenital uterine anomalies. Hysteroscopy, metroplasty, intrauterine adhesion, anti-adhesion therapy, endometrial regeneration.
Results: From 136 articles retrieved, we selected 62 articles and included them in our review. Analysis of selected literary sources revealed that use of mechanical barriers against IUA in postoperative period does not provide additional positive benefits in terms of reduction of spontaneous abortions, development of spontaneous pregnancy and increase of the rate of live birth. Their role in reducing development of IUA is also controversial. Also, use of mechanical barriers in combination with estrogen therapy did not show reliably high results in terms of improving female reproductive function. Regarding positive therapeutic effect of anti- adhesion gels, by analyzing reviewed literature sources, we obtained contradictory results. As for the effectiveness of using anti-adhesion gels with estrogen therapy after metroplasty, postoperative treatment with similar combination could not be seen in the literature sources. It should be noted that available literature has significant heterogeneity and a high risk of bias, which makes it difficult to draw final conclusions and does not allow for elaboration of optimal postoperative management scheme.
Conclusion: Based on the analysis of literature sources it is clear that more randomized control trials are needed to evaluate effectiveness of different anti-adhesion means both as monotherapy and in combination. **(TCM-GMJ June 2024; 9 (1):P43-P48)**

Keywords: congenital uterine anomalies; hysteroscopy; metroplasty; Intrauterine adhesion, Endometrial regeneration.

Introduction

Congenital uterine anomalies (CUA) are deviations from the normal anatomical landmarks of uterus, which are associated with disorders developed during formation of the female genital tract in the embryo during pregnancy. Prevalence of CUA in the non-selective female population is 5.5%, and in the selective population prevalence of these anomalies is higher, namely in 8.0% (5.3–12%) of infertile women, in 13.3% of women with history of spontaneous abortions, in 24.5% of childless women with spontaneous abortions. [1]. CUAs are directly associated with unfavorable reproductive outcomes, which are mainly manifested by: high rates of female infertility, recurrent pregnancy loss, premature birth, intrauterine fetal development retardation, and fetal malposition during labour [1,2.].

Among separate forms of CUA, which are associated with female reproductive function disorders, the most frequent forms are groups of septate (complete and par-

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tial) and dysmorphic (T-shaped) uteri. Septate uterus accounts for 36%-55% of CUA [4,5,6]. Prevalence of T-shaped uterus ranges from 0.2 to 10% [7].

Despite development of endoscopic surgery, many forms of CUA development due to them anatomical polymorphism is not amenable to or do not require surgical correction. Therefore, currently, in order to improve the female reproductive function, hysteroscopic metroplasty is performed only in the presence of a septate, dysmorphic (T-shaped, Y-shaped) and bicornuate uterus. In other cases, hysteroscopy is performed to clarify the diagnosis or to treat other accompanying gynecological disease (polyp, endometrial hyperplasia, etc.) [8].

Systematic reviews and meta-analysis of the literature has shown that hysteroscopic metroplasty improves reproductive outcomes in women with both septate and T-shaped uteri [9-14]. However, reproductive outcomes are still far from optimal. According to the meta-analysis conducted by Valle et al., the overall pregnancy rate after septoplasty of the septate uterus does not exceed 67.8% and live birth rate does not exceed 53.5% [15], and in women with T-shaped uterus, the overall pregnancy rate after hysteroscopic metroplasty reaches 68.9% and combined live birth rate - 56.2% [16]. The causes of such unsatisfactory reproductive outcomes should be associated with one of the most frequent and undesirable complications after metroplasty - formation of intrauterine adhesions (IUA). IUA have significant negative impact on female reproductive function. In 43% of cases, IUA are the cause of both primary and secondary infertility [17]. The role of IUA in the development of spontaneous abortions should also be mentioned. According to the observational studies review, the prevalence of IUA in women with the history of spontaneous abortions ranges from 5 to 39% [18, 19].

The rate of IUA formation after hysteroscopic metroplasty is not precisely defined and varies in a rather wide range - from 6.7% to 88% [20-25]. In order to improve woman reproductive function in the post-metroplasty period, it is essential to prevent development of IUA and increase the endometrial receptivity. Accordingly, the goal of postoperative management of hysteroscopic metroplasty is to obtain a normal endometrium, which means reducing the risk of IUA formation and promoting endometrial growth. In order to prevent the development of IUA, various types of anti-adhesion agents are used. Depending on their physical properties, the anti-adhesion agents used to perform the mechanical barrier function can be solid, liquid (hydroflotation), or gel [37- 46, 60], which contain polyethylene sodium oxide carboxymethylcellulose and autocrosslinked hyaluronic acid.

Solid mechanical anti-adhesion devices used are: intrauterine device (IUD), intrauterine balloon stents, Foley catheter, Malecot catheters and triangular silicone sheets [26-33, 61]. To stimulate endometrial growth, hormone therapy (estrogen, combined estrogen-gestagen medications), aduvand therapy, platelet-rich plasma, stem cells are used [48-52, 57-59, 62].

Aim: The aim of this literature review is to analyze and evaluate advantages and disadvantages of therapeutic means used for prevention of development of IUA after hysteroscopic metroplasty and to stimulate the regeneration of the endometrium

Methods

In order to collect literature data, we used such electronic search databases as PubMed, Medline, Google Scholar and Cochrane Library. Search terms were: congenital uterine anomalies, hysteroscopy, metroplasty, intrauterine adhesion, anti-adhesion therapy, endometrial regeneration.

Results and discussion

From 136 articles retrieved, we selected 62 articles and included them in our review. According to the literature data, effectiveness of all anti-adhesion agents used in prevention of formation of intrauterine adhesions are mainly evaluated in the period after hysteroscopic treatment of Asherman syndrome. Studies describing and evaluating the effectiveness of anti-adhesion therapy after hysteroscopic metroplasty for congenital uterine anomalies are very few and represent small cohort studies. Based on the pathophysiology of the IUA development, the goal of all anti-adhesion therapy is to mechanically separate front and back walls of the uterus (surfaces of the postoperative wound) and stimulate endometrial regeneration processes.

Therefore, postoperative anti-adhesion strategies used in Asherman syndrome can be considered and applied in the postoperative management of uterine anomalies. Anti-adhesion effect of mechanical barriers is due only to the creation of a physical barrier between opposite walls of the uterine cavity. Based on the above, the form of selected intrauterine anti-adhesion agent is of great importance for performance of anti-adhesion function.

Due to its shape, T-shaped IUD cannot ensure separation of the entire surface of post-metroplasty uterine wound [33]. A cohort study by Tonguc et al. in 2010 examined the efficacy of postoperative use of a T-shaped IUD and estrogen therapy after hysteroscopic septoplasty. Repeated hysteroscopy performed one month after surgery showed that the rate of intrauterine adhesions in the control (untreated) group of patients was 5.3%, in the intrauterine device and estrogen therapy group - 12%, in the intrauterine device group - 10.5%, and no postoperative adhesions were observed in the estrogen therapy group. In the same study, no statistically significant difference between the groups was detected in the rate of spontaneous pregnancy development [29].

In 2016, Yu et al studied the incidence of intrauterine adhesions formation after hysteroscopic septoplasty in 238 patients, who underwent the treatment with postoperative estrogen therapy, IUD, and balloon stent. Repeated hysteroscopy showed that the adhesions formation rate in the patient groups were 22%, 28.8%, 26.7% respectively and 24.1% in the untreated (control) patient group. These data clearly indicate that use of postoperative estrogen therapy, IUD or balloon stent does not significantly reduce the rate of postoperative adhesions [28]. It should also be taken into account that copper-containing T-form intrauterine

contraceptives, on the contrary, provoke an inflammatory reaction in the endometrium and may stimulate the adhesions formation process [32]. A loop-shaped intrauterine contraceptive device (e.g. Lippes loop) can be considered as an optional treatment for the prevention of postoperative adhesions. However, it is no longer available in many countries [18].

In 2014, Salma et al. conducted a systematic review of cohort studies evaluating the efficacy of loop-shaped IUDs against formation of adhesions following hysteroscopic synechiolysis. In the five studies reviewed by the authors, high rate of postoperative adhesions was observed; Spontaneous pregnancy and live birth rates were not statistically significantly increased, and three studies showed decrease in intrauterine adhesions and statistically significantly increased live birth rate. The authors concluded that the loop-shaped IUD may be useful for anti-adhesion therapy, but for maximum results in patients with moderate to severe intrauterine adhesions, it needs to be combined with other treatments [30].

In 2023, Zhuang et al. compared anti-adhesion efficacy of intrauterine device and intrauterine balloon stent after hysteroscopic synechiolysis. According to the results obtained by the authors, patients in the balloon stent group had significantly better reproductive outcomes compared with the intrauterine device group. At the same time, in order to prevent readhesion and increase the frequency of spontaneous pregnancy, the authors recommend that it is preferable to perform synechiolysis using a cold knife and to prescribe estrogen therapy and an adequate course of antibiotic therapy together with the placement of a balloon stent after the surgery, since they have additional positive effects [31].

In order to prevent intrauterine adhesions, several authors have used the Foley catheter as a mechanical anti-adhesion device [33-36]. In 2003, Orhue et al. conducted non-randomized study evaluating the effectiveness of anti-adhesion therapy of Foley catheter. Postoperatively, after 10 days of exposure to a pediatric Foley catheter in the uterine cavity, the rate of adhesion development was assessed by hysterosalpingography. Lower adhesion rate was found in the Foley catheter group compared to the control group, although the fertility rate was very low in both groups [36].

In addition to the unfavorable therapeutic effect, the use of mechanical anti-adhesion agents is accompanied by a number of adverse effects, such as: longer bleeding after surgery, discomfort or circling pain in the small pelvis, higher risk of ascending infections (especially with the use of a Foley catheter and balloon stent), expulsion of the Foley catheter and intrauterine contraceptives from the uterine cavity, as well as the need for repeated medical interventions for patients to remove the Foley catheter and intrauterine contraceptive device [26,27].

Barrier gels, which are the most convenient and comfortable for practical use, have been proposed for the prevention of post-operative intrauterine adhesions. Currently, there are many anti-adhesion barrier gels on the pharmaceutical market. Most of them are made on the basis of hyaluronic acid and contain various polysaccharides (sodium D-glucuronate and N-acetyl-glucosamine) as additives. Autocross-linked hyaluronic acid (ACHA) and polyethylene oxide-sodium carboxymethylcellulose (PEO-NaCMC) gels are also actively used [37-41].

Exact mechanisms by which biodegradable gels can reduce the development of intrauterine adhesions are not known. Their anti-adhesion action may be related to the hydroflotation or siliconizing effects by which anti-adhesion gels provide mechanical separation of adjacent wound surfaces [42].

In 2003, Acunzo et al studied anti-adhesion efficacy of autocross-linked hyaluronic acid gel following hysteroscopic synechiolysis; Postoperative ultrasound studies showed that in the anti-adhesion barrier gels the uterine walls remained separated for at least 72 hours. Repeated hysteroscopy, performed 3 months after surgery showed that compared to the control group, intrauterine adhesions were significantly reduced in women receiving the adhesive barrier gel (6/43 [14%] vs 13/41 [32%]; p - 0.05). Fertility data were not considered in this study [43].

In 2014, Jan Bosteels et al. conducted systematic review and meta-analysis to evaluate the effectiveness of using anti-adhesion barrier gels after operative hysteroscopy for the treatment of infertility associated with uterine anomalies. According to their data, use of any barrier gel reduces the rate of formation of postoperative intrauterine adhesions. However, there is no reliable evidence of higher rates of spontaneous pregnancy or live births, and no data on reductions in spontaneous abortion rates. According to their recommendation, after operative hysteroscopy in infertile women, gynecologists may use any barrier gel to reduce adhesion formation [42].

In 2023, Lee et al. conducted meta-analysis of randomized controlled trials evaluating the role of hyaluronic acid and its derivative gels in preventing postoperative intrauterine adhesions and improving pregnancy rates. According to the authors' conclusion, hyaluronic acid gel prevents development of intrauterine adhesions and reduces their severity. In addition, hyaluronic acid gel can increase the pregnancy rate after hysteroscopic treatment of intrauterine pathologies. However, these findings should be interpreted with caution due to inadequate quality of some studies (small number of patients and high heterogeneity) [44].

At present, anti-adhesion gels of various compositions and modifications are available in clinical practice [38-41]. Several studies have been conducted to compare the anti-adhesion effect of different types of gels [28,45]. There were differences between the type and rate of postoperative intrauterine adhesions formation [46,47]. No significant advantage was found in terms of spontaneous pregnancy and live birth rates [37].

Development of intrauterine adhesions development can be prevented by stimulating regenerative function of the endometrium. For this purpose, in 1964 by Wood J and Pena G. used exogenous estrogen in the postoperative

period for the first time [48]. Although exogenous estradiol is widely used to stimulate endometrial growth, exact pathophysiological mechanisms of posttraumatic endometrial regeneration are still unclear. It is known that the number of estrogen receptors in the endometrium and their functional status determine the biological effects of exogenously administered estrogen [49].

Studies conducted by Ge J. et al (2021) showed that estrogen receptors are quantitatively more presented in the endometrium of patients with intrauterine adhesions compared to patients with normal endometrium. However, estrogen receptors are functionally deficient, and as a result, estradiol receptor binding is reduced, leading to inappropriate angiogenesis and delayed endometrial regeneration [50]. In the current literature, the daily dose of estradiol used to accelerate endometrial regeneration ranges from 2 mg to 12 mg daily [51,52,53].

In clinical observation, the use of high-dose estradiol valerate in the postoperative period did not show significantly better positive endometrial results in terms of endometrial recovery [51,52]. But on the contrary, compared to the pharmacological dose of estradiol valerate (2mg/day) [53], use of higher doses (e.g. 4 mg, 6 mg and 8 mg) led to disruption of transformation of the endometrium in the secretory phase and contributed to the development of endometrial hyperplasia. In addition, experimental animal study by Chen F et al. showed that use of supraphysiological doses of estradiol increased production of adhesion-promoting factors (transforming growth factor-β and basic fibroblast growth factor), which are likely to cause exacerbation of fibrosis [55].

Accordingly, use of estradiol 2 mg/day after hysteroscopic metroplasty can be considered the most effective daily dose to accelerate endometrial regeneration and prevent development of postoperative adhesions, which also avoids the side effects of estrogen therapy [54,56]. During estrogen therapy, it is necessary to prescribe progesterone medications in the second phase of the menstrual cycle to prevent disruption of the transformation of the endometrium in the secretory phase. [53] As for the duration of estrogen therapy in the postoperative period, two months of treatment is considered the most optimal period, rarely for 3 months or more [56].

In 2014, Roy et al. in a retrospective cohort study, evaluated the efficacy of estrogen therapy after uterine septal resection in terms of preventing development of adhesions and improving fertility compared with a control group. Repeated hysteroscopy performed 2 months after the surgery did not reveal intrauterine adhesions in the estrogen therapy group (45 women). In the control group (45 women) intrauterine adhesions developed in 6.9%. However, this percentage difference was not statistically significant (p=0.24). There was no significantly reliable difference in the development of pregnancy either [57].

2014 systematic review of 26 studies by Johary J et al. noted that estrogen therapy in combination with other therapies (e.g. intrauterine contraceptives, bladder catheters) for prevention of postoperative adhesions was found to be beneficial in several studies, but the range of results was wide and meta-analysis was not performed due to variations in study design [64].

2017 meta-analysis conducted by Bosteels J et al. evaluating the effect of estrogen versus placebo reported no difference in pregnancy rates between groups [42]. Analysis of the literature data reviewed by us revealed that use of mechanical barrier means intended against intrauterine adhesions in the postoperative period does not provide additional positive benefits in terms of reducing spontaneous abortions, developing spontaneous pregnancy and increasing the rate of live birth. Also controversial is their role in reducing development of intrauterine adhesions. Use of mechanical barriers in combination with estrogen therapy also did not show reliably high results in terms of improving female reproductive function. Regarding positive therapeutic effect of anti-adhesion gels when used in isolation, analysis of the reviewed literature sources yielded conflicting results; As for effectiveness of using anti-adhesion gels in combination with estrogen therapy after metroplasty, no post-operative treatment with a similar combination was found in the reviewed literary sources. It should be noted that available literature has significant heterogeneity and a high risk of bias, which complicates making final conclusions and does not allow for elaboration of optimal postoperative management scheme.

Conclusion

Based on the analysis of literature sources it is clear that more randomized control trials are needed to evaluate effectiveness of different anti-adhesion therapies both as monotherapy and in combination.

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