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Review Article

Efficacy of Estrogen Therapy in Patients With Intrauterine Adhesions: Systematic Review

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ABSTRACT Hysteroscopic adhesiolysis has become the preferred option for management of intrauterine adhesions (IUA). Use of estrogen as perioperative adjuvant therapy has been suggested for preventing recurrent adhesions. The primary objective of this article was to review the literature for evidence of the efficacy of estrogen therapy in the management of IUA. All eligible studies were identified using computerized databases (PubMed, Scopus. and Web of Science) from their earliest publication date to July 2013. Additional relevant articles were identified from citations in these publications. Twenty-six studies were identified that reported use of hormone therapy as ancillary treatment after adhesiolysis. Of these studies, 19 used at least one of the following methods: intrauterine device, Foley catheter, hyaluronic acid gel, or amnion graft, in addition to hormone therapy as ancillary treatment. In 7 studies, hormone therapy was used as a single ancillary treatment. In 2 studies, no adjunctive therapy was used after adhesiolysis. Meta-analysis could not be performed because of the differences in treatment methods in these articles. There was a wide range of reported menstrual and fertility outcomes. Better menstrual and fertility outcomes were associated with use of estrogen in combination with other methods of ancillary treatment. At present, hormone therapy, in particular estrogen therapy, is beneficial in patients with IUA, regardless of stage of adhesions. However, estrogen therapy needs to be combined with ancillary treatment to obtain maximal outcomes, in particular in patients with moderate to severe IUA. Journal of Minimally Invasive Gynecology (2014) 21, 44–54 © 2014 AAGL. All rights reserved.

Keywords: Endometrium; Estrogen therapy; Hysteroscopy; Intrauterine adhesions; Repeat adhesions

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Asherman syndrome, or intrauterine adhesions (IUA), is characterized by adhesions and/or fibrosis within the uterine cavity due to trauma of the basalis layer of the endometrium, primarily from dilation and curettage (D&C) [1,2], and produces a partial or complete obliteration in the uterine cavity, possibly affecting the cervical canal. This may result in hypomenorrhea, amenorrhea, dysmenorrhea, and infertility or recurrent miscarriages. Depending on the severity of the adhesions, the entire cavity can be occluded due to scar formation after the trauma (Fig. 1, A and B). Even with relatively little scarring, the endometrium may become dysfunctional and may fail to respond to estrogen [1].

The primary objective of management of IUA is to restore the uterine cavity to its normal size and shape, stimulate regeneration of the destroyed endometrium, prevent re-formation of adhesions, and restore normal menstruation and reproductive function. Hysteroscopic adhesiolysis is a safe and effective method for dividing adhesions and reducing trauma to adjacent normal endometrium [3,4].

Although use of hormones for perioperative adjuvant therapy is needed in the management of IUA, this treatment remains empirically based. In previous studies of IUA, various protocols of hormone therapy have been used in terms

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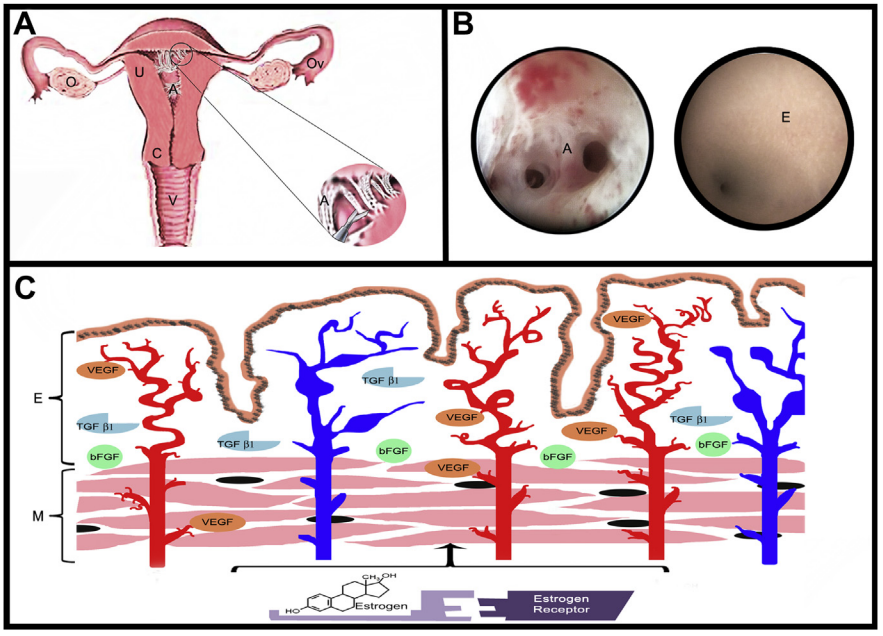
Fig. 1

(**A**) Illustration of intrauterine adhesions, characterized by adhesion and/or fibrosis within the uterine cavity. A = adhesion; C = cervix; O = ovary; Ov = oviduct; U = uterus; V = vagina. (**B**) Typical hysteroscopic finding of intrauterine adhesion includes a dense adhesion (A) inside the uterine cavity and thin endometrial layer (E), with hypodense glands. (**C**) The role of estrogen in preventing recurrent adhesions is achieved via endometrial tissue remodeling and regeneration. Estrogen escalates vascularization and proliferation of glandular epithelial and stroma cells in the endometrium by up-regulating expression and increasing secretion of angiogenic growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta 1 (TGF-β1).



of regimen, dosage, route of administration, duration of course, and combination of hormones. The primary objective of the present article was to review the literature for evidence of the efficacy of estrogen therapy in the management of IUA.

Methods

Search Strategy

All eligible studies were identified on computerized databases (PubMed, Scopus, and Web of Science), using the keywords "Asherman syndrome," "Asherman's syndrome," "Fritsch syndrome," "gynatresia," "intrauterine adhesions," "intrauterine synechiae," "synechia uteri," and "uterine synechiae." The search included studies from the earliest publication date to July 2013. Additional relevant articles were identified from citations within these publications.

Study Characteristics

Because of the lack of randomized control trials (RCT), observational studies (prospective/retrospective cohort and case-control studies) were included for review. Studies that could not be assessed in full text and non-English references were excluded. Reviews and case reports were also excluded from this systematic review. The steps involved in literature inclusion were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 2).

Of 28 studies, 19 used multiple ancillary treatment methods to prevent recurrent adhesions in the management of IUA. To our knowledge, no study focused solely on comparing the efficacy of estrogen as an adjunctive therapy in patients with IUA after adhesiolysis. Therefore, all studies that examined outcomes after various adhesiolysis methods, with or without post-procedural estrogen therapy, were considered eligible for this systematic review. A meta-analysis was not performed because of the heterogeneity of the included studies. There was a wide range of clinical diversity in terms of the adhesion staging system, the methods used for adhesiolysis, and ancillary treatments, which confounded our attempt at meta-analysis.

From each study, data extracted included first author, year of publication, number of participants, mean age, stage of adhesion, adhesiolysis technique, ancillary treatment used (hormone therapy, intrauterine device [IUD], Foley catheter, hyaluronic acid gel, and amnion graft), and complications. The primary outcomes of interest included clinical outcome (improvement in menstrual flow) and fertility (pregnancy and live birth rates).