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A prospective, randomized, controlled trial comparing two doses of oestrogen therapy after hysteroscopic adhesiolysis to prevent intrauterine adhesion recurrence

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KEY MESSAGE

This is the first RCT to compare the efficacy of two different doses of post-operative oestradiol therapy in the prevention of adhesion re-formation after hysteroscopic adhesiolysis. The findings do not support the use of high-dose oestrogen therapy after hysteroscopic adhesiolysis.

A B S T R A C T

The aim of this prospective, randomized, controlled trial was to evaluate the efficacy of different doses of oestrogen treatment (2 mg and 6 mg daily) after hysteroscopic adhesiolysis in patients with moderate to severe adhesion according to the American Fertility Society (AFS) classification of intrauterine adhesions. A total of 121 patients were included in the final analysis. Fifty-nine patients received 2 mg oestrogen daily (low-dose group), and 62 received 6 mg oestrogen daily (high-dose group) for three cycles after surgery. Second- and third-look outpatient hysteroscopy was performed 4 and 8 weeks after the initial surgery. There was no difference in the menstrual pattern and AFS scores before and after surgery between the two groups, and AFS scores at the second- and third-look hysteroscopy were found to be significantly lower than the scores before surgery in both groups (both $P < 0.01$). While this study did not address the fundamental question of whether oestrogen adjuvant therapy prevents the recurrence of intrauterine adhesions, the findings do not support the use of high-dose oestrogen therapy after hysteroscopic adhesiolysis.

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http://dx.doi.org/10.1016/j.rbmo.2017.07.011
1472-6483/© 2017 Published by Elsevier Ltd on behalf of Reproductive Healthcare Ltd.

Please cite this article in press as: Jun Guo, et al., A prospective, randomized, controlled trial comparing two doses of oestrogen therapy after hysteroscopic adhesiolysis to prevent intrauterine adhesion recurrence, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.07.011

Introduction

Asherman's Syndrome is a condition characterized by the presence of intrauterine adhesions (IUA) and/or fibrosis due to trauma to the basal layer of the endometrium. It may manifest as hypomenorrhoea, amenorrhoea, dysmenorrhoea, cyclical pelvic pain, infertility or recurrent miscarriage. In the vast majority of cases, the condition is caused by dilation and curettage (D and C) in the pregnant state (Panayotidis et al., 2009; Yu et al., 2008). Hysteroscopic adhesiolysis is a safe and effective means to treat this condition, by dividing the adhesions and reconstructing the uterine cavity to normal (Al-Inany, 2001; Pabuccu et al., 1997, 2008; Thomason et al., 2007). However, the most challenging problem in the management of moderate and severe IUA is the recurrence of adhesion, which on average ranges from 3 to 24% (Pabuccu et al., 1997; Preutthipan and Linasmita, 2000; Valle and Sciarra, 1988) and in those with severe adhesion the reformation rate was even higher and in some series reached 60% (Capella-Allouc et al., 1999; Pabuccu et al., 1997; Preutthipan and Linasmita, 2000; Valle and Sciarra, 1988).

Post-operative oestrogen therapy has been widely used by many investigators to prevent recurrence of the adhesions (Chen et al., 1997; Fernandez et al., 2006; Liu et al., 2016; March and Israel, 1976; Pabuccu et al., 2008; Robinson et al., 2008; Roy et al., 2010; Takai et al., 2015; Thomason et al., 2007). The AAGL Practice Guideline recommended post-operative hormone therapy with oestrogen (Grade B evidence) but did not specify the dose of oestrogen to be used (AAGL, 2010). Review of the literature suggests that the dose of oestrogen used varied considerably, ranging from oestradiol 2 mg daily or its equivalent (Roy et al., 2010) to oestradiol 12 mg daily (Orhue et al., 2003). Currently, there is no agreement on the optimal dose of oestrogen to be used, primarily because there is little literature data comparing the efficacy of different doses of oestrogen.

To the best of our knowledge, there has never been a randomized controlled trial (RCT) to verify whether high- or low-dose oestrogen therapy is more beneficial. We therefore conducted a prospective RCT to compare the efficacy of two different doses (2 mg and 6 mg daily) of post-operative oestradiol therapy in the prevention of adhesion reformation after hysteroscopic adhesiolysis.

Materials and methods

Subjects

This RCT was conducted in 2016 at the Hysteroscopic Centre, Fuxing Hospital, Capital Medical University, a national training centre for hysteroscopy in China. The centre has carried out ~150 cases of hysteroscopic surgery monthly over the last 3 years. Ethical approval was obtained from the Institutional Review Board of Fuxing Hospital on 23 October 2015 (IRB Review Approval Notice Number: 2015FXHEC-KY101). The study was registered in the ClinicalTrials.gov Protocol Registration System (ClinicalTrials.gov identifier: NCT02726971). The inclusion criteria for patient participation included: (i) women aged 25–45 years; (ii) moderate and severe IUA according to the AFS IUA scoring system (AFS 1988 version) (The American Fertility Society, 1988) as shown in **Table 1** (AFS score ≥5); (iii) scheduled for hysteroscopic adhesiolysis; (iv) agreed to have two follow-up hysteroscopies; and (v) written informed consent obtained. The exclusion criteria included: (i) received oestrogen therapy within 3 months of enrolment; (ii) suffering from leiomyoma, polyps, cancer or polycystic ovary syndrome (PCOS); (iii) history of genital tuberculosis; and (iv) contraindication for oestrogen therapy.

Table 1 – The American Fertility Society (AFS) classification of intrauterine adhesions, 1988.

Affected area	*<1/3*	*1/3 to 2/3*	*>2/3*
	1	2	4
Adhesions	Filmy	Filmy and dense	Dense
	1	2	4
Menstrual pattern	Normal	Hypomenorrhoea	Amenorrhoea
	0	2	4
Stage of adhesion			
Stage I (mild)	1–4		
Stage II (moderate)	5–8		
Stage III (severe)	9–12		

Source: The American Fertility Society classification of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies Mullerian anomalies and intrauterine adhesions. Fertil Steril 1988;49:944–55.

Sample size calculation

Assuming that the adhesion recurrence rate was 40% in women receiving 2 mg oestradiol and the adhesion recurrence rate in women receiving 6 mg oestradiol was 15%, and accepting a type 1 error (α) of 0.05, and a type 2 error (β) of 0.10, the number of subjects required in each arm was 62. Assuming a drop-out rate of 15%, the total number of subjects required to be recruited was 146.

Randomization

At the conclusion of the hysteroscopic surgery, subjects who fulfilled the inclusion criteria and who gave prior consent to participate in the study were randomized into the 2 mg or 6 mg oestrogen groups in a 1:1 ratio using a computer-generated randomization list and sealed opaque envelopes prepared by the first author. The patients were not blinded to the dose of oestrogen used but the surgeons performing the second- and third-look hysteroscopies were.

In considering the daily doses of oestradiol to be used in this RCT, we reviewed previous publications and found that among 15 papers published on the use of oestradiol, the majority (Capella-Allouc et al., 1999; Dawood et al., 2010; Farhi et al., 1993; Fernandez et al., 2006; Malhotra et al., 2012; Myers and Hurst, 2012; Roy et al., 2010; Salma et al., 2011; Xiao et al., 2014; Yu et al., 2008; Zikopoulos et al., 2004) used a daily dose between 2 mg and 6 mg, with only four studies using a daily dose greater than 6 mg oestradiol (Liu et al., 2012, 2016; Meng, 2015; Orhue et al., 2003). Consequently, we chose to compare 2 mg and 6 mg daily doses. We did not consider using higher doses because of concerns about side effects and compliance, especially in a Chinese population with a considerably lower body mass and BMI (mean = 21 in our study) than a Caucasian population (see **Table 2**).

Group 1 were given 2 mg oral oestradiol (Femoston; Abbott Biologicals BV) daily for 21 days, followed by 20 mg dydrogesterone daily for the last 10 days of hormone treatment. Group 2 were given 6 mg oral oestradiol (Femoston; Abbott Biologicals BV) daily for 21 days, followed by 20 mg dydrogesterone daily for the last 10 days of hormone treatment. All subjects received the hormone treatment for three cycles.

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