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Do the types of treatments after hysteroscopic resection of septate uterus cause different results?

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Summary

Background: Two protocols are generally performed after the following hysteroscopic resection of septate uterus to prevent Asherman's syndrome in Iran. The aim of this study was to assess and compare the postoperative complication rate by alternate and constant therapy following hysteroscopic septum resection procedure. *Materials and Methods:* The authors conducted a retrospective interventional study on secondary data obtained from the medical records of 106 infertile women with septate uterus who underwent a hysteroscopic resection between April 2005 and February 2014. After septum resection, 71 patients received alternate hormonal therapy and 35 patients received constant hormonal therapy. All the women were followed-up postoperatively with interview and physical examination for more than six months. *Results:* Of the 71 women who received alternate hormonal therapy, 16 (22.5%) had spotting. While in the constant protocol therapy group, the rate of the spotting during the follow-up period was reported in 13 (37.1%) patients. There was no significant difference between the two groups in terms of spotting complication after the septum resection. Self-reported breast tenderness as complications of hormonal therapy after septum resection in constant protocol was greater than in alternate protocol group (21.1% *vs.* 60.0%) ($p < 0.0001$). *Conclusion:* The result of this study indicated that hormonal therapy complications following hysteroscopic resection of septate uterus in both protocols was the same.

Key words: Resection of septate uterine; Treatment protocols; Hysteroscopy; Spotting.

Introduction

Septate uterus refers to the congenital Müllerian anomaly; it is likely that to cause infertility and abortion. Fortunately, many cases of uterine septum with infertility are treatable through hysteroscopic resection [1-3]. However there is controversy regarding treatment following hysteroscopic resection of septate uterine to prevent Asherman's syndrome. Several studies have shown that intrauterine device (IUD) insertion with concurrent estrogen and terminal progesterone or without hormone replacement therapy (HRT) may decrease complications after hyseroscopic resection of septate uterus. Therapies following hysteroscopy with and without IUD and HRT were studied, but did not investigate on type of HRT. There is no conclusive evidence that treatments following hysteroscopy works better than no treatment follow ups [4-12]. Most authors considered HRT after hystroscopic resection of septate uterus over the past years [13-22] versus other investigators not suggesting HRT after hystroscopic resection of septate uterus [8, 23-27]; however the present authors performed HRT and IUD therapy for all patients after hysteroscopic resection of uterine septum in their infertility center with two different HRT protocols.

The current study aimed to assess and compare the effect(s) of the two protocols, on postoperative complication rate following hysteroscopic septum resection procedure.

Materials and Methods

The study design was a retrospective interventional study on secondary data obtained from the medical records of 106 infertile women with uterine septum who underwent a hysteroscopic septum resection between April 2005 and February 2014. The study protocol was approved by the Ethics Committee of Babol University of Medical Science and written informed consents were also obtained from the participants prior to the implementation of the study. The infertile women with uterine septum who underwent hysteroscopic septum resection in the infertility center by investigator and received two treatment protocols after the procedure were included. Based on inclusion criteria, a total of 106 patients were reviewed. The infertile women with septate uterus were detected in the infertility center during hysterosalpingography for initial diagnosis of intrauterine septum according the American Fertility Society classification of Müllerian duct anomalies by septate uterus and variable lengths (class Va: complete; class Vb: partial was done) [28] and confirmed using laparoscopy in early proliferative phase. Miso-

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Table 1. — *Demographic and clinical characteristics of 106 participants.*

Variables	Total (n=106) n (%)	Alternate protocol 71 (67.0%)	Constant protocol 35 (33.0%)	*p*-value
Age (years)				0.022
< 30	47 (44.3)	37 (52.1)	10 (28.6)	
≥ 30	59 (55.7)	34 (47.9)	25 (71.4)	
Menarche age (years)				0.166
< 13	33 (31.1)	19 (26.8)	14 (40.0)	
≥ 13	73 (68.9)	52 (73.2)	21 (60.0)	
BMI (kg/m^2)				0.587
< 25	34 (32.1)	24 (33.8)	10 (28.6)	
≥ 25	72 (67.9)	47 (66.2)	25 (71.4)	
Occupation				0.854
Housewife	93 (87.7)	62 (87.3)	31 (88.6)	
Work	13 (12.3)	9 (12.7)	4 (11.4)	
Duration of infertility (years)				0.134
< 2	65 (61.3)	40 (56.3)	25 (71.4)	
≥ 2	41 (38.7)	31 (43.7)	10 (28.6)	
Infertility type				0.720
Primary	61 (57.5)	40 (56.3)	21 (60.0)	
Secondary	45 (42.5)	31 (43.7)	14 (40.0)	
Hysteroscopy type				0.228
Operative	83 (78.3)	58 (81.7)	25 (71.4)	
Both	23 (21.7)	13 (18.3)	10 (28.6)	
Male infertility				0.465
Yes	29(27.4)	21(29.6)	8(22.9)	
No	77(72.6)	50(70.4)	27(77.1)	

Table 2. — *Complications during postoperative treatment of hysteroscopic septum resection (n=106).*

Variables	Total (n=106) n (%)	Alternate protocol 71 (67.0%)	Constant protocol 35 (33.0%)	*p*-Value
Complication during treatment	29 (27.4)	16 (22.5)	13 (37.1)	0.113
Spotting	29 (27.4)	16 (22.5)	13 (37.1)	0.113
Severity of spotting				0.266
Mild	21 (19.8)	12 (16.9)	9 (25.7)	
Moderate	8 (7.5)	4 (5.6)	4 (11.4)	
Duration spotting				0. 259
1-5 days	19 (17.9)	11 (15.5)	8 (22.9)	
> 5 days	10 (9.4)	5 (7.0)	5 (14.3)	
Headache	14 (13.2)	7 (9.9)	7 (20.0)	0.147
Breast tenderness	36 (34.0)	15 (21.1)	21 (60.0)	0.000

prostol suppository for cervical dilation was placed in the posterior vaginal fornix prior night of surgery. Cervical dilator (10–10.5 cm) for dilatation of cervical OS was used for endoscopy. A 3.5-mm mini-hysteroscope was administered; normal saline was used for distending. An endoscopic vaginal exploration explored the presence of one uterine cervix at the open vaginal side and the uterine distention pressure was set at 150 mm Hg. An electro resectoscope was inserted to corroborate the location, range and size of the septum. Then the septum by needle electrode was incised, and for monitoring during the operation, completely ultrasonography was applied [1]. Postoperatively, IUD was inserted in operating room and two protocols were administrated in order to decrease the formation of intrauterine adhesion after hysteroscopy. Antibiotic treatment was not given to the patients. All patients after receiving hormone therapy instruction and consciousness were discharged. Alternate hormone therapy (first protocol) after septum resection was performed in 71 (67%) women in the form of conjugated estrogens (1.25 mg) daily for 25 days after surgery with ten mg medroxyprogesterone acetate twice per day from day 16 of this time in combination with the conjugated estrogens until 25th of the cycle. After menstruation, the patients received this treatment process for two months. Constant hormonal therapy (second protocol) was performed in 35 patients (33%) in form of 1.25 mg conjugated estrogen twice daily for 50 days. Ten mg medroxyprogesterone acetate for the last ten days of this time was performed twice daily in combination with the conjugated estrogen [5, 29].

During both postoperative hormonal therapies following hystroscopic septum resection, spotting (mild, moderate, and sever), bleeding, headache, and breast tenderness complication of patient with duration of and severity problem were checked and assessed. After hormonal therapy duration and withdrawal of bleeding at second day of menstruation, the IUD was removed. Follow-up of pregnancy and delivery was done for 12 months. If pregnancy spontaneously di not occur after six-month therapy, according to surgeon's indications, ART procedure started

The data obtained were statistically analyzed using the Statistical Package for Social Sciences0 (SPSS) software version 18. Chi-square and *t*-test were also used to compare the values within two treatment protocols groups. *P* value of ≤ 0.5 was considered significant.

Results

Of the 127 participants, a total of 106 patients were selected for the propose this study, from which 21 were excluded from this study, 71 used alternate hormonal therapy after septum resection, and constant hormonal therapy was also performed in 35 patients. Table 1 shows some demographic and clinical characteristics of the patients. There was no difference between age, menarche age, occupation of women, BMI, male infertility, infertility type, duration infertility, and hysteroscopy type in two treatment protocols following hystroscopic septum resection. The total complications during postoperative treatment were 27.4%. The present results showed no significant differences between total complications after hysteroscopic septum resection in two postoperative treatment groups (Table 2). Also, there were no significant differences in spotting, severity of spotting, duration spotting, and headaches between two postoperative treatments. However there was a statistically significant difference in self-reported breast tenderness with two postoperative treatments after hystroscopic septum resection ($p = 0.0001$).

Discussion

Numerous researchers have accepted hysteroscopic septum resection as modality for uterine septum removal in infertile women. However, ways of preventing postsurgical adhesions

are still lacking certainly [7, 11].

Schrager *et al.* reported abnormal uterine bleeding as a common but rarely dangerous side effect of hormonal contraception. However, the discontinuation of hormonal contraception is a major cause. They also suggested although hormonal contraception is a common cause of abnormal uterine bleeding, other causes also need to be considered [30]. In addition, a study also concluded that oral contraceptives can be given continuously, but be withdrawn every three to four months (same as alternate therapy) which is needed to allow endometrial shedding and avoid irregular bleeding [31].

The present findings are in agreement with a study that showed breast tenderness in patients with the continuous-combined hormonal therapy after surgery that reported it to be higher than in the group of the patients with raloxifene therapy [32]. In addition, a recent research has shown that conjugated equine estrogens with medroxyprogesterone acetate doubled the risk of invasive breast cancer among women with baseline breast tenderness, but had a smaller effect among women without baseline breast tenderness. New-onset breast tenderness was associated with a higher risk of breast cancer among women assigned to conjugated equine estrogens with medroxyprogesterone acetate [33].

The present findings showed that self-reported breast tenderness during postoperative treatment of hystroscopic septum resection should be carefully evaluate by surgeons; therefore, it is suggested that postoperative hormone therapies using estrogen and terminal progesterone can be prescribed and personalized according to patient situation and surgeon indication because their efficacy has not been demonstrated in well-designed, accurate randomized, and precise prospective studies.

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References

[1] Abu R.B., Vilos G.A., Oraif A.M., Power S.G., Cains J.H., Vilos A.G.: "Fertility and pregnancy outcomes following resectoscopic septum division with and without intrauterine balloon stenting: a randomized pilot study". *Ann. Saudi Med.*, 2012, *33*, 34.

[2] Hadibroto B.R.: "Hysteroscopy for metroplasty of uterine septa and hypoplastic uterus". *Bersama Kita Maju,* 2009, *114.*

[3] Wang S., Shi X., Hua X., Gu X., Yang D.: "Hysteroscopic transcervical resection of uterine septum". *J. Soc. Laparoendosc. Surg.*, 2013, *17*, 517.

[4] Assaf A.: "Value of postoperative treatment after cutting of a broad base intrauterine septum". *Int. J. Gynaecol. Obstet.*, 1999, *64*, 315.

[5] Esmaeilzadeh S., Delavar M.A., Andarieh M.G.: "Reproductive outcome following hysteroscopic treatment of uterine septum". *Mater. Sociomed.*, 2014, *26*, 366.

[6] Vercellini P., Fedele L., Arcaini L., Rognoni M., Candiani G.: "Value of intrauterine device insertion and estrogen administration after hysteroscopic metroplasty". *J. Reprod. Med.*, 1989, *34*, 447.

[7] Tonguc E.A., Var T., Yilmaz N., Batioglu S.: "Intrauterine device or estrogen treatment after hysteroscopic uterine septum resection". *Int. J. Gynaecol. Obstet.*, 2010, *109*, 226.

[8] Nouri K., Ott J., Huber J.C., Fischer E.M., Stögbauer L., Tempfer C.B.: "Review Reproductive outcome after hysteroscopic septoplasty in patients with septate uterus-a retrospective cohort study and systematic review of the literature". *Reprod. Biol. Endocrinol.*, 2010, *8*, 1.

[9] Nawroth F., Schmidt T., Freise C., Foth D., Römer T.: "Is it possible to recommend an 'optimal'postoperative management after hysteroscopic metroplasty? A retrospective study with 52 infertile patients showing a septate uterus". *Acta Obstet. Gynecol. Scand.*, 2002, *81*, 55.

[10] Dabirashrafi H., Mohammad K., Moghadami-Tabrizi N., Zandinejad K., Moghadami-Tabrizi M.: "Is estrogen necessary after hysteroscopic incision of the uterine septum?" *J. Am. Assoc. Gynecol. Laparosc.*, 1996, *3*, 623.

[11] Roy K.K., Negi N., Subbaiah M., Kumar S., Sharma J.B., Singh N.: "Effectiveness of estrogen in the prevention of intrauterine adhesions after hysteroscopic septal resection: A prospective, randomized study". *J. Obstet. Gynaecol. Res.*, 2014, *40*, 1085.

[12] Amer M.I., Nadim A.E., Karim H.: "The role of intrauterine balloon after operative hysteroscopy in the prevention of intrauterine adhesions: a prospective controlled study". *Middle East Fertil. Soc. J.*, 2005, *10*, 125.

[13] Yang J., Yin T.U., Xu W.M., Xia L.G., Li A.B., Hu J.: "Reproductive outcome of septate uterus after hysteroscopic treatment with neodymium: YAG laser". *Photomed Laser Surg.*, 2006, *24*, 625.

[14] Valle R.F., Sciarra J.J.: "Hysteroscopic treatment of the septate uterus". *Obstet. Gynecol.*, 1986, *67*, 253.

[15] Cararach M., Penella J., Ubeda A., Labastida R.: "Hysteroscopic incision of the septate uterus: scissors versus resectoscope". *Hum. Reprod.*, 1994, *9*, 87.

[16] March C.M., Israel R.: "Hysteroscopic management of recurrent abortion caused by septate uterus". *Am. J. Obstet. Gynecol.*, 1987, *156*, 834.

[17] Daly D.C., Maier D., Soto-Albors C.: "Hysteroscopic metroplasty: six years' experience". *Obstet. Gynecol.*, 1989, *73*, 201.

[18] Fedele L., Arcaini L., Parazzini F., Vercellini P., Di Nola G.: "Reproductive prognosis after hysteroscopic metroplasty in 102 women: life-table analysis". *Fertil. Steril.*, 1993, *59*, 768.

[19] Valle R.F.: "Hysteroscopic treatment of partial and complete uterine septum". *Int. J. Fertil. Menopausal. Stud.*, 1995, *41*, 310.

[20] Marabini A., Gubbini G., Stagnozzi R., Stefanetti M., Filoni M., Bovicelli A.: "Hysteroscopic metroplasty". *ANYAS*, 1994, *734*, 488.

[21] Grimbizis G., Camus M., Clasen K., Tournaye H., De Munck L., Devroey P.: "Hysteroscopic septum resection in patients with recurrent abortions or infertility". *Hum. Reprod.*, 1998, *13*, 1188.

[22] Hollett-Caines J., Vilos G.A., Abu-Rafea B., Ahmad R.: "Fertility and pregnancy outcomes following hysteroscopic septum division". *J. Obstet. Gynaecol. Can.*, 2006, *28*, 156.

[23] Tonguc E.A., Var T., Batioglu S.: "Hysteroscopic metroplasty in patients with a uterine septum and otherwise unexplained infertility". *Int. J. Gynaecol. Obstet.*, 2011, *113*, 128.

[24] Zlopaša G., Škrablin S., Kalafatić D., Banović V., Lešin J.: "Uterine anomalies and pregnancy outcome following resectoscope metroplasty". *Int. J. Gynaecol. Obstet.*, 2007, *98*, 129.

[25] Colacurci N., De Franciscis P., Mollo A., Litta P., Perino A., Cobellis L., *et al.*: "Small-diameter hysteroscopy with Versapoint versus resectoscopy with a unipolar knife for the treatment of septate uterus: a prospective randomized study". *J. Minim. Invasive Gynecol.*, 2007, *14*, 622.

[26] Litta P., Spiller E., Saccardi C., Ambrosini G., Caserta D., Cosmi E.: "Resectoscope or Versapoint for hysteroscopic metroplasty". *Int. J. Gynaecol. Obstet.*, 2008, *101*, 39.

[27] Mollo A., De Franciscis P., Colacurci N., Cobellis L., Perino A., Venezia R., *et al.*: "Hysteroscopic resection of the septum improves

the pregnancy rate of women with unexplained infertility: a prospective controlled trial". *Fertil. Steril.*, 2009, *91*, 2628.
[28] Buttram V., Gomel V., Siegler A., DeCherney A., Gibbons W., March C.: "The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions". *Fertil. Steril.*, 1988, *49*, 944.
[29] Freud A., Harlev A., Weintraub A.Y., Ohana E., Sheiner E.: "Reproductive outcomes following uterine septum resection". *J. Matern. Fetal. Neonatal Med.*, 2015, 28, 2141.
[30] Schrager S.: "Abnormal uterine bleeding associated with hormonal contraception". *Am. Fam. Physician*, 2002, *65*, 2073.
[31] Ely J.W., Kennedy C.M., Clark E.C., Bowdler N.C.: "Abnormal uterine bleeding: a management algorithm". *J. Am. Board Fam. Med.*, 2006, *19*, 590.
[32] Jackson V.P., San Martin J.A., Secrest R.J., McNabb M., Carranza-Lira S., Figueroa-Casas P., *et al.*: "Comparison of the effect of raloxifene and continuous-combined hormone therapy on mammographic breast density and breast tenderness in postmenopausal women". *Am. J. Obstet. Gynecol.*, 2003, *188*, 389.
[33] Crandall C.J., Aragaki A.K., Cauley J.A., McTiernan A., Manson J.E., Anderson G., *et al.*: "Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone women's health initiative clinical trials". *Breast Cancer Res. Treat.*, 2012, *132*, 275.

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