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Fgf is required to regulate anterior-posterior patterning in the Xenopus lateral plate mesoderm

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Fertility and pregnancy outcomes following resectoscopic septum division with and without intrauterine balloon stenting: a randomized pilot study

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BACKGROUND AND OBJECTIVES: Although uterine stenting is performed routinely following hysteroscopic metroplasty, we were unable to find any evidence documenting its value with regards to septum reformation and/or obstetrical performance. To evaluate the benefits of intrauterine Foley catheter/balloon splinting after resectoscopic septum division on septum reformation, fertility, and pregnancy outcomes.

DESIGN AND SETTING: Prospective, randomized controlled pilot study (Canadian Task Force Classification I) conducted in university affiliated teaching hospital.

PATIENTS AND METHODS: Twenty-eight women with infertility and/or adverse pregnancy outcomes diagnosed with intrauterine septum were randomized into having a No. 14 pediatric Foley catheter/balloon for 5 days (n=13) vs. no balloon (n=15) following resectoscopic septum division. None of the patients received preoperative endometrial thinning, antibiotic prophylaxis or adjuvant postoperative hormone therapy. All uterine septa were divided under general anaesthesia using a 26 F (9 mm) resectoscope with a monopolar electrical knife using glycine irrigant solution (1.5%) and 120 watts of power of low voltage (cut) waveform.

RESULTS: The median age (range) was 29 years (23-38) and 32 years (22-40), respectively ($P=.59$). The groups were comparable by age, past obstetrical performance and comorbidities including endometriosis stage I-IV in 3 and 4 women, in the catheter/balloon and balloon group, respectively, and one in each group of polycystic ovarian syndrome and Crohn disease and one case of tubal obstruction in the balloon group. There were no intra- or postoperative complications. At 3 months, a hysterosalpingogram was done in 10 (77%) and 13 (87%) women, respectively, the results of which were normal. At 12-18 months, 1 woman in the balloon and 3 in the control group were not trying to conceive and 1 in each group had not conceived. Of the remaining women, 11 (92%) in each group had conceived and pregnancy outcomes included spontaneous abortion 3 (25%) and 4 (33.3%), ectopic pregnancy 0 and 1, second trimester loss 1 (8.3%) and 0 and term pregnancy 8 (66.6%) in both groups. Conception through assisted reproductive technology occurred in 2 and 1 woman, respectively.

CONCLUSIONS: Following resectoscopic septum division with monopolar knife electrode, splinting the uterine cavity with Foley catheter provided no advantage in septum reformation, clinical pregnancy rate, and pregnancy outcomes.

A systematic review up to March 2011 of 94 observational studies comprising 89,861 women, reported a prevalence of congenital uterine anomalies of 5.5% (95% CI, 3.5%-8.5%) in the unselected population, 8.0% (95% CI, 5.3%-12.0%) in infertile women, 13.3% (95% CI, 8.9%-20.0%) in those with a history of miscarriages, and 24.5% (95% CI, 18.3%-32.8%) in those with a history of miscarriages and infertility. Arcuate uterus is the most common anomaly in the unselected population (3.9%; 95% CI, 2.1%-7.1%) and its prevalence is not increased in high-risk groups. In contrast, septate uterus is the most common anomaly in high-risk populations¹ with a prevalence of 1.1% in the general/fertile population and 3.9% in women with infertility.²

Septate uterus, resulting from failure of apoptotic resorption of the medial segment of the Müllerian ducts, is the most common congenital uterine anomaly, accounting for approximately 35% of all uterine anomalies,³ and is associated with the highest incidence of reproductive failure and adverse obstetrical complications when compared with other uterine anomalies. As a rule, septate uterus affects reproductive health by impairing fertility, and increasing spontaneous abortions and adverse pregnancy outcomes.^{4,5} Adverse pregnancy outcomes include recurrent abortions of the first and second trimester, intrauterine growth restriction, abnormal placentation, fetal malpresentation, premature delivery, and an increased risk of Caesarian delivery.⁶

The mechanism by which a uterine septum causes these adverse effects remains speculative. Theories include an excessive amount of fibroelastic tissue and a decreased blood supply to the septum which may adversely affect placentation,⁷⁻¹⁰ but these findings remain controversial.¹¹ The diagnosis of septate uterus is made by a variety of imaging techniques or by direct endoscopic visualization. Hysterosalpingography (HSG) and/or two dimensional ultrasound (2D US) may be used as initial screening tools,¹² but contrast infusion sonography (saline infusion sonography or gel infusion sonography) and 3D US are more accurate for a definitive diagnosis.¹²⁻¹⁵ MRI has been reported to detect 100% of septate uteri, but because it is time consuming and expensive, its routine use in clinical practice remains controversial.^{12,13,16} Combined laparoscopic and hysteroscopic examination is considered the gold standard for assessing congenital uterine anomalies, establishing a correct diagnosis and possibly applying the principle of 'see and treat'.¹³ Laparoscopy is recommended to complete the evaluation of patients with infertility, including assessment and possible concomitant treatment of tubal disease and/or other conditions in-

cluding endometriosis. Laparoscopy also differentiates between a septate and a bicornuate uterus and may be of value in aspirating excessive intra-abdominal irrigant fluid and be more safe during hysteroscopic metroplasty. The only situation in which it may be unnecessary is when the patient has undergone a previous laparoscopic evaluation. The main indications to treat a septate uterus are recurrent pregnancy loss and unexplained infertility in the presence of a uterine septum. Hysteroscopic metroplasty (septum incision) over laparotomic transfundal correction is presently considered the standard of care.^{6,17-19}

This minimally invasive approach offers many advantages, including outpatient surgery with or without anaesthesia/analgesia,²⁰ a reduced risk of intra- and postoperative morbidity, no risk of postoperative pelvic adhesions, and an increased rate of vaginal delivery.²¹ Following hysteroscopic metroplasty, by any method, the incidence of a residual septum (>1 cm) was reported between 0% and 36%.²²⁻²⁴ To minimize the risk of septum recurrence, it was standard practice to splint the uterine cavity with an intrauterine device (IUD) for one month or a Foley catheter, and even shaped balloons, for 72 hours postoperatively hoping to prevent the incised septum edges from fusing; then start the patient on estrogen to stimulate endometrial lining growth over the denuded incised septum area. Although we had adopted and used all of the above measures including antibiotic prophylaxis, intrauterine Foley balloon, and postoperative estrogen,²⁵ this standard practice is not supported by evidence. We have found no studies describing their benefit on septum reformation and/or obstetrical performance. Therefore, the objective of this study was to evaluate the value of an intrauterine Foley catheter alone following resectoscopic uterine septum division on the rate of septum reformation, fertility, and pregnancy outcomes.

PATIENTS AND METHODS

Women with infertility and/or adverse pregnancy outcomes diagnosed with intrauterine septum by HSG, sonohysterography and/or hysteroscopy, were evaluated by the senior author (GAV) and invited to participate in the study. After ethics approval and informed consent, 28 women were randomized in the operating room into having a No. 14 pediatric Foley catheter/balloon for 5 days (n=13) versus no catheter/balloon (n=15) following resectoscopic septum division. The Foley balloon was inflated with 5 mL of normal saline solution. Randomization was based on a computer generated list of numbers (unconcealed). None of the patients received preoperative endometrial thin-

ning, antibiotic prophylaxis or adjuvant postoperative hormone therapy. All patients had general anaesthesia and concomitant laparoscopy and treatment of pelvic pathology including adhesiolysis and/or reduction/excision of endometriosis when indicated using a CO₂ laser and/or electrosurgery. The cervix was dilated to 10 mm and all uterine septa were divided using a 26 French (9 mm diameter) resectoscope and 300 lens (Karl Storz, Tuttlingen, Germany) with a monopolar electrode utilizing (1.5%) glycine irrigant solution via an electronic fluid-management system (Endomat, Karl Storz, Tuttlingen, Germany) and 120 watts of low voltage (cut) waveform delivered by an ICC 350 Erbe electrosurgical unit (Erbe, Tuttlingen, Germany). There was no specific timing to perform the surgery with regards to the menstrual cycle.

Resectoscopic metroplasty was carried out using a Collin (Karl Storz, Tuttlingen, Germany) monopolar knife electrode at 90 degrees. After visualization of both uterine cavities and tubal ostia, the division was started at the apex of the septum and continued towards the fundus with a progressive horizontal incision in the midline, equidistant from the anterior and posterior wall. Septum division was terminated when both tubal ostia could be viewed simultaneously, the resectoscope could be moved freely from one cornual recess to the other without intervening obstruction, or when significant bleeding was observed signifying that the incision had reached normal myometrium, even when anatomic perfection had not been achieved. All procedures were carried out by the two senior authors (BA, GAV) and all metroplasties were completed within 5 to 10 minutes. All patients were discharged the same day and the patients with the Foley catheter/balloon were instructed to cut with scissors the end of the catheter at 5 days at home and remove the catheter themselves. They were also instructed to avoid pregnancy until their first assessment in 3 months by HSG and they were reassessed at 6 and 12 to 18 months for pregnancy outcomes.

Data were analyzed using SAS software (SAS Institute, Inc., Cary, NC), with the *t* test or Wilcoxon signed-rank test for interval data and chi-square analysis for comparison of nominal data. A *P* value of <.05 was considered statistically significant.

RESULTS

The median (range) of the patient demographics, obstetrical history and comorbidities are shown in **Table 1**, while the intraoperative estimation of the relative septal length is shown in **Table 2**. Both tables indicate that the two groups were comparable. There were no complica-

Table 1. Median and (range) of patient demographics, obstetrical history and comorbidities randomized into Foley balloon versus no balloon.

Parameter	Balloon (n=13)	No balloon (n=15)	<i>P</i>
Age (years)	29 (23 - 38)	32 (22-40)	.59
Parity			
Term delivery	2	2	.94
Preterm delivery	1	3	.33
Second trimester loss	1	1	.96
First trimester loss			
One	2	3	.69
Two	4	5	.79
Three	2	2	.94
> Three	0	2	.16
Infertility	3	2	.69
Comorbidities			
Endometriosis			
Stage 1	1	2	NS
Stage 2	0	0	NS
Stage 3	1	0	NS
Stage 4	1	2	NS
Crohn's disease	1	0	NS
PCOS	1	1	NS
Tubal blockage	1	0	NS

PCOS: Polycystic ovary syndrome

Table 2. Intraoperative estimation of the relative septal length among the two groups.

From fundus	Foley balloon (n=13)	No balloon (n=15)	<i>P</i>
1/3	4	4	.91
1/2	2	2	.94
2/3	4	3	.6
Complete	3	6	.29

tions intraoperatively or in the immediate postoperative period. Results of HSG three months post-metroplasty are shown in **Table 3**. We could not be certain that the <1 cm septum, reported by the radiologist, in the balloon group was a recurrence or incomplete division at the time of metroplasty but in the intention-to-treat

Table 3. Hysterosalpingogram 3 months following metroplasty (intention to treat analysis).

	Balloon (n=13)	No balloon (n=15)	P
Not done (refused)	3	2	NS
Normal	9 (69%)	13 (87%)	NS
Septum <1 cm	1	0	NS

Table 4. Pregnancy outcome 12 months following metroplasty.

	Balloon (n=13)	No balloon (n=15)	P
First trimester loss	3	4	NS
Second trimester loss	1	0	NS
Preterm delivery	0	0	NS
Term delivery	8	8	NS
Ectopic	0	1	NS
Currently pregnant	0	3 2 at 8 weeks 1 at 22 weeks	
Not trying	1	3	
No conception	1	1	
Conceived with ART	2	1	

ART: Assisted reproductive technology

(ITT) analysis we considered this cavity as normal. The patient did conceive and had a term delivery. The rates of normal uterine cavity by ITT analysis were 77% and 87% in the Foley balloon and no balloon groups respectively (NS), and 100% in both groups if only the known HSG are included. Fertility and pregnancy outcome at 12 to 18 months postmetroplasty are shown in **Table 4**. The rates of first trimester loss in the balloon versus no balloon group were 25% and 33%, respectively, while the term delivery rate was 66.7% in both groups (NS).

DISCUSSION

There is limited evidence and a lack of consensus on the postoperative management of hysteroscopic septum division. For example, there no evidence to support routine preoperative endometrial thinning. One study randomized women into receiving danazol 600 mg/d for 2 to 4 weeks (n=15) or luprolide acetate depot 3.75 mg for 2 months (n=15) prior to hysteroscopic metroplasty. Metroplasty was simpler overall in the dan-

azol group and also faster in introducing the resectoscope. The authors concluded that short preoperative preparation with danazol results in favorable operating conditions at limited costs with minimal side effects.²⁶ However, most authors do not consider it essential and recommend that hysteroscopic metroplasty be scheduled in the early proliferative phase of the cycle. Two circumstances that may merit preoperative endometrial thinning to facilitate visualization include a complete or a wide septum with narrow uterine cavities.

Many surgeons practice and advocate routine use of antibiotic prophylaxis during hysteroscopic metroplasty. However, a beneficial role for routine antibiotic therapy during hysteroscopy has not been firmly established. In one study of 2116 hysteroscopic surgical procedures over a 10-year period, where urinary catheters and antibiotics were not used, there were 30 (1.4%) infections, 18 endometritis and 10 of the urinary tract. There were no infections in 90 women who had septum division.²⁷ Furthermore, in a study of 631 women who underwent routine diagnostic hysteroscopy, antibiotic prophylaxis was prescribed to 266 women while 365 women underwent the procedure without prophylaxis, only one infection, adnexitis, that occurred among the 266 (0.38%) who had taken antibiotics.²⁸ Both studies indicate that during hysteroscopy, antibiotic prophylaxis was not indicated.

Following hysteroscopic septum division, the incidence of a residual septum (>1 cm) is 0-36% and may impair fertility and pregnancy outcomes,²²⁻²⁴ but a residual uterine septum of less than 1 cm after hysteroscopic metroplasty does not impair reproductive outcome.²⁹ Septum division leaves significant mirror image areas of denuded myometrium in the anterior and posterior walls, which are eventually epithelialized. One study reported on hysteroscopy with multiple biopsies at different intervals after hysteroscopic septal incision in 19 women. Seven days after surgery the sectioned areas were very evident and not epithelialized. At 14 days, the incised zone was depressed with scattered epithelialization and at one month, the sectioned surfaces were still depressed and uniformly covered by thin endometrium. At two months, the uterine cavity was almost normal with a minimal tendency to central fundal adhesions. The authors concluded that there is probably no reason to delay attempts at pregnancy for longer than two cycles after surgery.³⁰

Attempts to epithelialize the denuded septal surface more rapidly have been made with the use of exogenous estrogen. One study in the 1980s recommended estrogen but no IUDs after hysteroscopic metroplasty.³¹ However, a prospective randomized trial that evaluated

with HSG, one month postoperatively, the use of estrogen alone (n=23) versus no estrogen (n=23) concluded that estrogen has no apparent role after hysteroscopic incision of the septum.³²

In the natural state of a collapsed uterine cavity, the opposing areas of a divided septum touch each other, raising the concern of agglutination and reformation of the septum or intrauterine adhesions resulting in Asherman syndrome. To prevent this, many surgeons have advocated the use of temporary splints such as IUDs³³⁻³⁷ to maintain the uterine cavity distended and/or estrogen to epithelialize the denuded endometrial cavity rapidly.^{5,35-37} The role of IUD plus conjugated estrogen for 30 days (n=10) was compared to no postoperative treatment (n=10). The authors concluded that IUD insertion and hormonal therapy after hysteroscopic metroplasty do not seem to be needed to prevent septal fusion.^{33,38} A retrospective review of 17 patients also concluded that neither an IUD nor estrogen treatment had any effect on intrauterine adhesion formation.³⁹

Another retrospective study reported term delivery rates, at 21 months post-hysteroscopic metroplasty of 53.3%, 64.4%, and 88.9% in infertile women who had received estrogen plus IUD (n=22), estrogen alone (n=13), and no treatment (n=17), respectively. The authors concluded that a postoperative 3-month estrogen plus IUD insertion or estrogen alone after hysteroscopic metroplasty are not necessary.³⁵

Finally, a recent study allocated 100 women undergoing hysteroscopic metroplasty into receiving no treatment (n=25), IUD (Cu 250, n=25), estrogen + progestin (2 mg estradiol valerate + 0.5mg norgestrel for 2 weeks, n=25), IUD + estrogen (n=25). All patients were given antibiotic prophylaxis. At second-look hysteroscopy, adhesions were noted in 1/19 (5.3%) of the untreated, 3/25 (12%) of IUD + hormones, 2/19 (10.5%) of IUD only, and 0% in the hormone only group. The authors concluded that neither IUD placement, nor estrogen treatment, nor both, were found to prevent adhesions or facilitate pregnancy after hysteroscopic uterine septum resection.³⁶

Originally then, both measures were thought necessary to prevent fusion of the fresh divided septum and intrauterine adhesion formation or septum reformation.^{31,37} However, current literature suggests that splints and hormonal therapy are not necessary.^{32,36-38}

Although the use of intrauterine balloons for 5 to 7 days has been advocated, we found no studies to describe a risk-benefit analysis. To our knowledge, this is the first randomized comparison of a Foley balloon versus no balloon following hysteroscopic metroplasty.

Since we found no benefits, and since there may be potential adverse events associated with routine use of Foley intrauterine balloons, at this time, we cannot recommend its routine use in clinical practice. Potentially, uterine rupture can occur because of intrauterine expansion of Foley balloon after hysteroscopic metroplasty. Indeed a case of uterine rupture and intraperitoneal bleeding presumably related to the pressure of the intrauterine Foley balloon five hours after hysteroscopic lysis of adhesions has been reported.⁴⁰

Routine second look hysteroscopy and break down of adhesions has been advocated by some investigators.⁵ This practice however remains controversial in view of the failure in detecting adhesions in a series of 29 patients undergoing diagnostic hysteroscopy 2 months after surgery.³⁴

Table 1 indicates that pelvic pathology may co-exist in women with infertility and uterine septum. For this reason, in women with septate uterus who had no laparoscopy as part of their routine evaluation of infertility, we advocate concomitant laparoscopy at the time of metroplasty. At least two studies reported significantly higher prevalence of endometriosis in patients with Müllerian anomalies compared to controls, but no difference between non-obstructive anomalies and controls.⁴¹⁻⁴² Furthermore, a retrospective evaluation of 120 women with septate uterus compared to 486 consecutive infertile women with non-septate uterus found endometriosis in 25.8% and 15.2% of women, respectively ($P < .006$).⁴³

The underlying mechanism by which the presence of septi impairs fertility remains speculative. Using scanning electron microscopy, a study demonstrated significant ultrastructural alterations in septal endometrium compared with endometrium from the lateral uterine wall in samples obtained during the preovulatory phase.⁴⁴ These ultrastructural changes may result in impaired sensitivity or receptivity associated with alterations of homeobox cluster A (HOXA-10) implantation genes decreasing sensitivity or receptivity of the endometrium covering the septum. This mechanism may be similar to that exerted by the presence of submucosal/intramural myomas⁴⁵ and/or endometrial polyps⁴⁶ in impairing implantation. Recent evidence indicates that in the presence of submucous and intramural myomas there is a global reduction in endometrial HOX gene expression which may impair receptivity of the entire endometrium.^{45,46}

The strength of our study is that it is a randomized controlled trial comparing a single variable, the use of Foley balloon on septum reformation, determined by an objective method, HSG, and clinical outcomes in-

cluding fertility and pregnancy outcomes. Limitations of the study include heterogeneity and small number of enrolled subjects with insufficient power to determine significant differences between the two groups.

Following resectoscopic septum division with monopolar knife electrode, splinting the uterine cavity with a Foley catheter provided no advantage in septum reformation, clinical pregnancy rate, and pregnancy

outcomes. Our results on clinical outcomes, including fertility and reproduction, are in keeping with those reported by previous observational studies; a reduction in miscarriage rate from 88% to 14% and an increase in live birth rate from 3% to 80% after metroplasty.^{5,13,47} However, the need remains for larger randomized controlled trials to address the effectiveness and safety of adjunct therapy with hysteroscopic metroplasty.

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