

# Retrospective cohort study of the risk factors for secondary infertility following hysteroscopic metroplasty of the uterine septum in women with recurrent pregnancy loss

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## Abstract

**Purpose:** A hysteroscopic metroplasty was performed for women with recurrent pregnancy loss owing to a uterine septum, following which some women became infertile. The aim of this study was to elucidate the risk factors of secondary infertility 1 year after hysteroscopic metroplasty for a uterine septum.

**Methods:** A retrospective, single-center, cohort study included women with a history of at least two miscarriages that had been attributed to a uterine septum who underwent a hysteroscopic metroplasty. The patients' background data were compared between the patients who conceived and those who remained infertile at 1 year postoperatively. The data were analyzed by using the Mann-Whitney U-test and multivariate analyses.

**Results:** The postoperative live birth rate was 83.9% ( $n = 26$ ), with persistent infertility in five women at 1 year. When comparing the pregnancy group with the infertile group, the women in the postoperative infertility group were significantly older than those in the postoperative pregnancy group. The multivariate analysis showed that age was an independent risk factor for persistent infertility.

**Conclusion:** Age was identified as an independent risk factor for postoperative secondary infertility. Therefore, surgery as early as possible is recommended.

## KEYWORDS

a uterine septum, hysteroscopic metroplasty, miscarriage, recurrent pregnancy loss, secondary infertility

## 1 | INTRODUCTION

Many studies have reported that abnormalities of the uterine septum are associated with miscarriage, recurrent pregnancy loss, and premature delivery. The frequency of uterine malformations in patients with recurrent pregnancy loss is reportedly 13.3%, with septate uteri reported to be the most frequent, at an incidence of 5.3%.<sup>1</sup> Several

studies have indicated that the surgical correction of uterine abnormalities can improve the live birth rate in women with a history of recurrent pregnancy loss.<sup>2-4</sup> However, these findings have not been confirmed in a prospective, randomized, controlled trial (RCT) comparing the treatment of the uterine septum with no treatment. Although many authors have recommended further prospective RCTs to compare surgical treatment with no treatment, such studies are becoming

increasingly difficult to perform in Japan because the age of women at first pregnancy has increased significantly.

The surgical treatment of malformations of the uterine septum has been performed by the transabdominal approach, but a hysteroscopic approach is currently more widely used for metroplasty because the former is associated with an increased risk of complications, including intra-abdominal adhesions, tubal occlusion, and bleeding. In addition, a laparotomy requires a longer recovery period, resulting in longer hospital stays, and transabdominal metroplasty requires a longer postoperative interval before conception. Therefore, the less invasive hysteroscopic metroplasty is replacing the transabdominal procedure.

The authors introduced hysteroscopic metroplasty for the correction of a uterine septum in 2010. Although the pregnancy outcomes mostly were improved as a result, some patients remained infertile at 1 year postoperatively. The aim of this study was to elucidate the risk factors for secondary infertility after hysteroscopic metroplasty for a uterine septum.

## 2 | MATERIALS AND METHODS

### 2.1 | Design and patient selection

Patients with a uterine septum who underwent hysteroscopic metroplasty at the authors' department from January, 2011 to December, 2015 were retrospectively evaluated. During the study period, hysteroscopic metroplasty was performed on 38 patients, but complete postoperative follow-up data were available for only 31 of those patients (Figure 1). All the patients had a history of at least two miscarriages before their hysteroscopic metroplasty and underwent examinations in order to elucidate the etiology of the pregnancy loss, including uterine diagnostic imaging, chromosome analysis of both partners, determination of antiphospholipid antibodies (aPL), and blood tests for thyroid dysfunction, diabetes mellitus, and thrombophilia. The patients' background data, including their age, number of

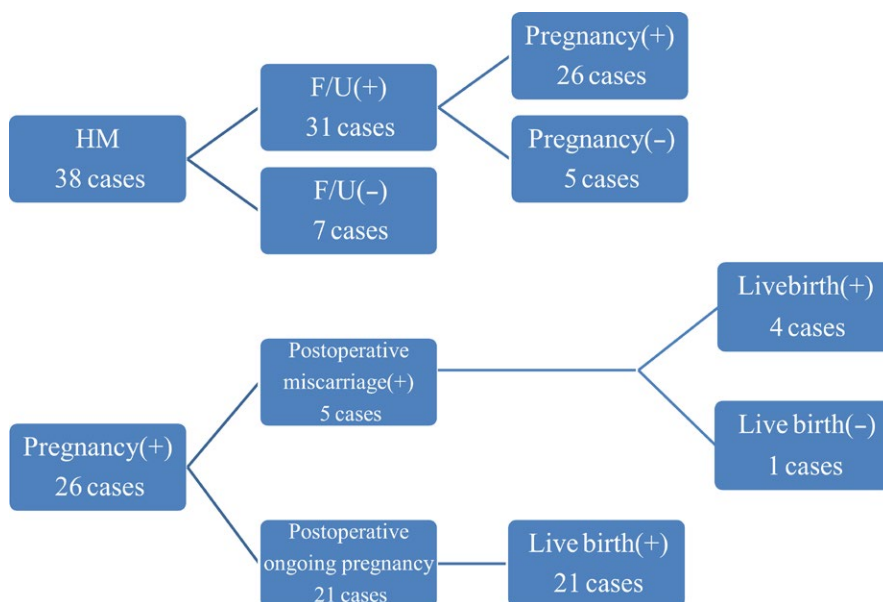
previous miscarriages, other risk factors for miscarriage, history of infertility treatment, the depth of the preoperative septum, and the postoperative thickness of the residual septum were compared between the patients who conceived and those who remained infertile at 1 year after their hysteroscopic metroplasty. As an additional study, the complications during pregnancy and delivery after hysteroscopic metroplasty were compared in 902 patients who gave birth at the authors' hospital in the same period.

### 2.2 | Diagnosis and assessment of septate uteri

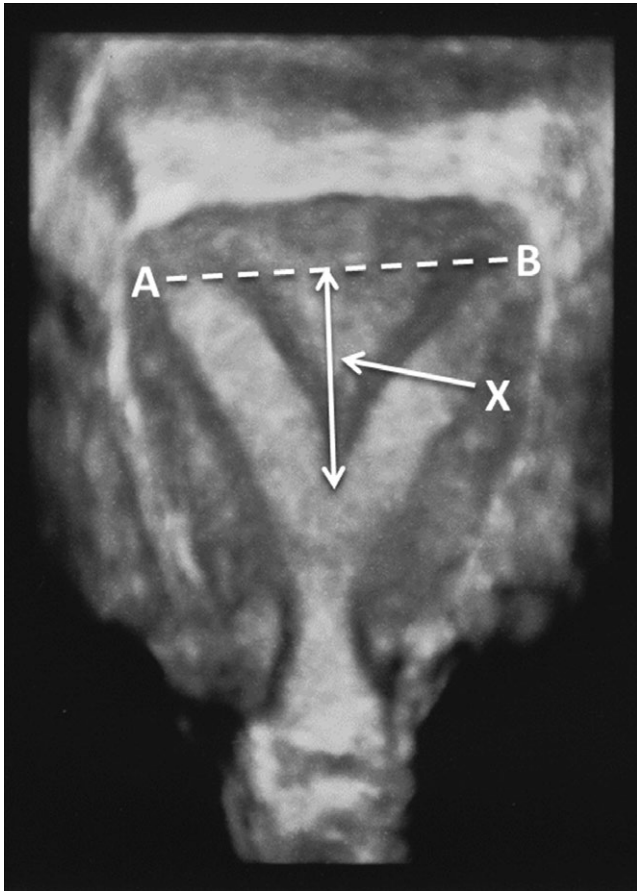
The diagnosis of a uterine septum was based on the American Fertility Society's classification<sup>5,6</sup> by using magnetic resonance imaging (MRI) and three-dimensional ultrasonography (3DUS). Also performed were a hysteroscopy and hysterosalpingography (HSG) as an auxiliary diagnosis. The depth of the preoperative septum was determined on images that had been acquired by preoperative 3DUS and MRI. As shown in Figure 2, point A is the right utero-tubal junction and point B is the left utero-tubal junction. A distance of >1.5 cm from the interstitial line to the apex of the indentation was considered to indicate a uterine septum.

### 2.3 | Hysteroscopic metroplasty procedure

Presently, Dienogest (2 mg/day) is administered to thin the endometrium before performing a hysteroscopy for septum incision. Hysteroscopic metroplasty of a uterine septum was performed in the operating room under general anesthesia with propofol and sevoflurane. In order to ensure sufficient dilatation for a safe hysteroscopic metroplasty and placement of a 27 French gage resectoscope into the uterine cavity, the uterine cervix was dilated by using a medium-sized laminaria tent on the day before surgery. A 5 mm laparoscopic trocar was inserted into the umbilicus to access the abdominal cavity for observation of the fundus of the uterus before and after surgery. It is



**FIGURE 1** Total hysteroscopic metroplasty (HM) (38 cases). The HM was performed on 38 patients, but complete postoperative follow-up data were available for only 31 patients. Of the 26 patients who became pregnant, 21 achieved a live birth. Five patients miscarried in the first pregnancy after the HM and four achieved a live birth in the second pregnancy. Five patients remained infertile even at 1 year after the HM. F/U, follow-up (-, without; +, with)



**FIGURE 2** Morphological evaluation of the uterine cavity by three-dimensional ultrasonography (3DUS). Point A is the right utero-tubal junction and point B is the left utero-tubal junction. A length of >1.5 cm from the interstitial line to the apex of the indentation by preoperative 3DUS indicates a uterine septum

possible to confirm the presence of uterine perforation and muscular layer thinning. The 3DUS was used to determine the presence of a residual septum. Hysteroscopic metroplasty was performed by using a resectoscope that was equipped with a cutting knife electrode, with the cutting current set at 70 W. The uterine cavity then was distended by using a UROMATIC® device (Baxter International, Inc., Deerfield, IL, USA). Postoperatively, an intrauterine device (IUD) was inserted and hormonal treatment was given for 3 months.

The IUD was FD-1 (P-70) (FUJI LATEX, Tokyo, Japan), with a shape similar to that of a fish bone made of plastic. After 2-3 months from surgery, hysteroscopic re-examination was performed to observe the postoperative intrauterine conditions and to check whether the cavity shape had returned to normal. Afterward, pregnancy was allowed. Provided there was neither thinning of the uterine myometrium nor uterine perforation, vaginal delivery was the recommended mode of delivery.

## 2.4 | Statistical analysis

The results of this retrospective study are expressed as the mean  $\pm$  standard deviation. The continuous data were analyzed by

using the Mann-Whitney U-test and multivariate analysis. JMP software (SAS Institute, Cary, NC, USA) was used for all the analyses. A *P*-value of <.05 was considered to be statistically significant.

## 3 | RESULTS

The characteristics of the study's participants are shown in Table 1. No patient had chromosomal abnormalities, thyroid dysfunction, or disorders of carbohydrate metabolism. Of the 31 patients who were followed up, there were 26 pregnancies, which resulted in 21 live births. Five patients miscarried in the first pregnancy after metroplasty and four patients achieved a delivery in the second pregnancy. Five patients remained infertile even at 1 year after metroplasty (Figure 1). The postoperative pregnancy rate was 83.9% (26/31), the total live birth rate per operation was 80.6% (25/31), and the cumulative live birth rate per pregnancy was 96.2% (25/26) (Figure 1).

A comparison of the pregnant (26) and infertile (five) women after hysteroscopic metroplasty revealed no significant difference in the number of previous miscarriages, history of infertility treatments, aPL positivity, thrombophilia, depth of the preoperative septum, or the presence of a residual postoperative septum between the two groups (Table 2). However, the women in the postoperative infertility group were significantly older than those in the postoperative pregnancy group. The multivariate analysis that was used to identify the independent risk factors confirmed that age was an independent risk factor for postoperative secondary infertility (Table 3).

Regarding the obstetric outcomes, there was no uterine rupture during pregnancy or labor and heavy hemorrhage at delivery. There was one case of placental abruption. There was no case of placental previa or a low-lying placenta. The mean birthweight was  $2969.0 \pm 434.2$  g (1820-3736 g), the mean number of gestational weeks at delivery was 38 weeks and 5 days (30 weeks and 1 day-41 weeks and 4 days), the cesarean section rate was 60.0% (15/25), and the breech presentation rate was 20.0% (5/25). Of the 15 cesarean sections, one case was a previous cesarean section and one case was after myomectomy; therefore, cesarean section was selected. There was a significant difference in the cesarean section rate and breech presentation rate and there was no significant difference in the placental abruption rates, placental previa, and low-lying placenta rates, compared with primiparous women without a history of uterine surgery who gave birth (902 patients) in the authors' hospital during the same period (cesarean section rate: 28.0% [253/902]; breech presentation rate: 7.2% [65/902]; placental abruption rate: 0.9% [8/902]; placental previa rate or low-lying placenta: 2.9% [26/902]).

**TABLE 1** Patient characteristics

Variable	Mean $\pm$ SD or median
Age (y)	34.80 $\pm$ 3.80 (28.0-41.0)
Number of abortions	2.60 $\pm$ 1.30 (2.0-6.0)
Preoperative septum (mm)	21.50 $\pm$ 7.20 (15.0-46.8)
Antiphospholipid positivity (%)	38.7% (12/31)

SD, standard deviation.

Variable	Postoperative pregnancy group (n = 26)	Postoperative infertility group (n = 5)	P-value
Age (y)	34.2 ± 0.7	38.0 ± 1.6	.0373
Number of abortions	2.6 ± 0.3	2.4 ± 0.6	.7081
History of infertility treatments: N (%)	3/26 (11.5%)	1/5 (20%)	.6235 <sup>a</sup>
Depth of preoperative septum (mm)	21.7 ± 1.4	19.9 ± 3.3	.6153
Postoperative residual septum (mm)	9.1 ± 0.5	8.8 ± 1.1	.8118
aPL-positive and/or thrombophilia: N (%)	10/26 (38.5%)	2/5 (40%)	.9485 <sup>a</sup>

Comparisons by the Mann-Whitney U-test. The data are presented as the mean ± standard deviation or as N (%).

<sup>a</sup>Fisher's exact probability. aPL, antiphospholipid.

**TABLE 3** Multivariate analysis of the risk factors for postoperative infertility

Factor	OR	95% CI	P-value
Age	1.51	1.08-2.49	.0122
Postoperative residual septum	0.79	0.33-1.33	.4161

CI, confidence interval; OR, odds ratio.

## 4 | DISCUSSION

It has been suggested that malformations of the uterine septum are associated with an increased risk of adverse pregnancy outcomes, such as pregnancy loss, preterm labor, malpresentation, intrauterine growth restriction, placental abruption, and perinatal mortality.<sup>7</sup> The sensitivity of the endometrium to preovulatory hormonal changes in the septal tissue of malformed uteri is known to be lower than that in the lateral septal wall and normal uterine tissue.<sup>8</sup> Indeed, one study reported that the number of transmembrane receptors for vascular endothelial growth factor (VEGF) is significantly reduced in the endometrium of the septum, as compared with that of the lateral walls and the normal uterus.<sup>9</sup> Septate uteri therefore have been implicated in pregnancy loss and poor obstetric outcomes.

Furthermore, a uterine septum is believed to be predominantly comprised of fibrous tissue and to be composed primarily of muscle fibers, with less connective tissue.<sup>10</sup> It is thought that narrowing of the uterus and reduced uterine extensibility have a negative impact on pregnancy. In this study, although five patients miscarried in the first pregnancy after metroplasty, 96.2% (25/26) of patients achieved a live birth. The authors believe that hysteroscopic metroplasty for malformation of the uterine septum can effectively improve the pregnancy outcomes of women with recurrent pregnancy loss. Not unreasonably, therefore, one might assume that widening the uterine cavity, which would involve removing the septum that contains relatively few VEGF receptors and is composed of mainly fibrous tissue, would improve pregnancy outcomes.

**TABLE 2** Postoperative pregnancy group compared to postoperative infertility group

With regard to the length of the resection, one study found that a residual septum of >1 cm could worsen reproductive outcomes,<sup>11</sup> as also mentioned by the American Society of Reproductive Medicine. In another study that compared patients with residual septa measuring 0.5-1 cm and those with no residual septa or a septum of <.5 cm, there was no significant difference in reproductive outcomes.<sup>12</sup> Although an excessive septal incision will increase the risk of uterine wall perforation and therefore subsequent pregnancy-related uterine rupture, sufficient excision of the septum is required to improve reproductive outcomes. In the authors' hospital, 3DUS is performed during surgery when making an incision in order to view the residual septum and the thickness of the uterine muscle layer.

The overall median length of the postoperative residual septa was 9.04 ± 2.47 mm (range: 5.4-14.16 mm) in this study. There was no significant difference in the median length of the postoperative residual septum between the postoperative pregnancy group and the infertility group (Table 2). In the five women who were infertile postoperatively, the median length of the preoperative residual septum was 8.80 mm (range: 8.0-9.8 mm).

In this study, at 1 year postoperatively, five women remained infertile. The patient characteristics of the postoperative infertility group are shown in Table 4. The multivariate analysis confirmed that age was an independent risk factor for postoperative secondary infertility. Although two of these women underwent assisted reproductive therapy, neither became pregnant, which might have been related to an age-related decrease in ovarian function. Therefore, this finding implies that the appropriate choice of management of a small septate uterus with a high average age includes in vitro fertilization or intracytoplasmic sperm injection for frozen transfer before surgical intervention.

Hysterosalpingography, hysteroscopy, and 3DUS were used for postoperative evaluation, which confirmed no case of adhesion in the uterine cavity with hysteroscopic metroplasty. There is insufficient evidence to make a recommendation either for or against a specific prophylactic treatment for adhesions. However, the placement of an IUD can cause an intrauterine local inflammatory response and an increased probability of the occurrence of uterus and fallopian tube infection. Thus, the placement of an IUD and administration of hormonal

**TABLE 4** Patient characteristics of the postoperative infertility group

Case	Age (y)	AMH (ng/mL)	d3FSH (mIU/mL)	d3E2 (pg/mL)	AFC (N)
Case 1	39	—	—	—	—
Case 2	32	8.35	6.9	20.2	20
Case 3	40	0.16	27.3	8.4	2
Case 4	41	1.42	13.8	38.7	5
Case 5	38	3.82	5.6	34.1	7

These items were not measured in Case 1. Cases 3 and 4 underwent assisted reproductive therapy. AFC, antral follicle count; AMH, anti-Müllerian hormone; d3E2, d3E2 is serum level of estrogen on day 3 of menstrual cycle; d3FSH, d3FSH is serum level of follicle stimulation hormone on day 3 of menstrual cycle.

therapy might have been important in the prevention of postoperative adhesions in this study. Indeed, previous studies reported that the uterine cavity typically heals by 2 months,<sup>13,14</sup> which supports the use of postoperative treatment (IUD and hormonal therapy) for 3 months.

Also, there was no significant difference in the number of miscarriages postoperatively between groups. Although an analysis was not performed, the endometrial thickness was thought to affect the thinning of the endometrium by repeated dilation and curettage.

The multivariate analysis showed that age was a significant risk factor for postoperative secondary infertility. The influences of social advances and later marriage mean that most women who attend the authors' hospital for investigation of recurrent pregnancy loss are older than previously. This study had a small sample size and was a retrospective cohort study; hence, it provides limited data. Therefore, randomized controlled trials need to be performed in order to confirm this study's findings. Early surgery and the sufficient excision of any uterine septum in order to improve the chances of postoperative fertility are recommended.

Regarding obstetric outcomes, the cesarean section rate is high in the hysteroscopic metroplasty group. The explanation can be found in a report on the influence of the residual septum on breech presentation.<sup>15</sup> Furthermore, in the authors' hospital, cesarean sections increased because of the significantly high breech presentation rate. As for other causes, cesarean section is selectively performed at the hospital to transfer, despite the authors' recommendation for vaginal delivery. This is to ensure the birth of the baby as this group has infertility or has experienced several miscarriages.

In conclusion, although the efficacy of surgical treatment for a uterine septum is unclear, the postoperative live birth rate remains high. As this study's data indicate that the surgery itself does not affect the postoperative secondary infertility and that age can increase the likelihood of postoperative infertility, the authors conclude that early surgery and sufficient excision must be ensured in order to achieve the desired results for fertility.

## DISCLOSURES

**Conflict of interest:** The authors declare no conflict of interest. **Human and Animal Rights:** This study was approved by the ethics committee of Nippon Medical School, Tokyo, Japan, and informed consent was

obtained from all the patients. This article does not contain any study with animal participants that was performed by any of the authors.

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