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Original Article

Long-Term Reproductive Outcomes after Hysteroscopic Treatment of Dysmorphic Uteri in Women with Reproductive Failure: An European Multicenter Study

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ABSTRACT **Objective:** To evaluate the long-term reproductive outcomes in patients with dysmorphic uterus treated by hysteroscopic metroplasty with miniaturized instruments.

Design: Retrospective multicenter cohort study.

Setting: Tertiary care university hospitals.

Patients: The study was conducted on 214 women with a dysmorphic uterus (T-shaped, infantilis, or other type of dysmorphic uterus according to the European Society of Human Reproduction and Embryology and the European Society for Gynaecological Endoscopy classification system) with history of primary unexplained infertility (group 1) or repeated (>2) early miscarriages (group 2). Dysmorphic uteri were diagnosed by office hysteroscopy and 3-dimensional transvaginal ultrasound (3D-TVS).

Interventions: All patients underwent in office hysteroscopic metroplasty using a continuous-flow hysteroscope with a 5 Fr operating channel introduced into the uterine cavity using the vaginoscopic approach. Longitudinal incisions were performed on the fibromuscular constriction rings in the isthmic area and in some cases on the other uterine walls with a 5 Fr bipolar electrode or scissors. At the end of the procedure, an antiadhesive gel was applied into the uterine cavity to minimize adhesion formation. Postsurgical assessment of the uterine cavity was carried out through office hysteroscopy and 3D-TVS. All patients were followed for at least 24 months.

Measurements and Main Results: The metroplasty was completed in all cases, resulting in a significant increase of uterine cavity volume (100%) and optimization of uterine morphology in 211 of 214 women (98.6%). After 60 months, the overall clinical pregnancy rate was 72.9% (n = 156/214), and the live birth rate was 80.1% (n = 125/156). Specifically, 74 of 156 women (47.4%) conceived spontaneously (with a median time to pregnancy of 5.5 months), of whom 32.4% had previously failed 1 or more attempts at in vitro fertilization/intracytoplasmic sperm injection.

Conclusion: Our long-term follow-up data demonstrate that the hysteroscopic correction of dysmorphic uteri may result in a high live birth rate in women suffering from unexplained infertility or repeated miscarriages. Journal of Minimally Invasive Gynecology (2019) 00, 1−8. © 2019 AAGL. All rights reserved.

Keywords: Dysmorphic uterus; Office hysteroscopy; Hysteroscopic metroplasty; T-shaped uterus; Infantilis uterus; Clinical pregnancy; Live birth; Infertility; Recurrent miscarriage

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In recent years, several studies have shown that genetically normal embryos may fail to implant if the uterine environment is not permissive for implantation. The anatomic integrity of the uterine cavity is a prerequisite for achieving and maintaining a pregnancy by allowing for proper implantation and placentation [1−4]. Uterine canalization defects may be associated with reproductive issues, such as primary infertility, recurrent miscarriage, and severe obstetric complications (e.g., intrauterine growth restriction, preterm labor) [3,5−7]. Nevertheless, a causal relationship between müllerian anomalies and impaired endometrial receptivity remains unproven.

Dysmorphic uterus is a müllerian anomaly that has been long underestimated (i.e., initially supposed to be associated only with diethylstilbestrol [DES] exposure during organogenesis) and misdiagnosed (i.e., not framed by clear diagnostic criteria) [8−10]. The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) have recently categorized dysmorphic uterus as a class 1 uterine anomaly. This class incorporates 3 different subgroups of anomalies: U1a (T-shaped uterus), U1b (infantilis uterus), and U1c (T-shaped uterus with partial septum) [11] (Fig. 1).

Different studies have demonstrated that a dysmorphic uterus may account for reproductive failure when a surgical correction is not undertaken [3,5,9,12,13]. As early as in 1992, Golan et al [14] demonstrated an association between a T-shaped uterus and a high rate of first-trimester abortion (47%) and a low rate of full-term delivery (21%).

On this basis, various techniques for achieving surgical correction of dysmorphic uterus have been proposed [15,16]. Initial techniques relied on abdominal surgery (i.e., with a laparotomic or laparoscopic approach), with considerable risk of intraoperative complications and high morbidity. The recent development of highly sensitive 3-dimensional (3D) imaging and hysteroscopic surgery has enabled accurate diagnosis and treatment of uterine malformations with a minimally invasive approach, resulting in decreased morbidity [12,17]. Different methods and instruments have been used for the hysteroscopic repair of dysmorphic uterus, including scissors and a resectoscope with a monopolar hook [8,9,12] and bipolar energy [18]. Recent technologic advances, with the introduction of miniaturized mechanical instruments and bipolar energy, have allowed the management of dysmorphic uterus in the outpatient hysteroscopy setting, avoiding more invasive approaches [19−21]. However, there remains a lack of evidence on the impact of outpatient hysteroscopic correction of dysmorphic uterus in women experiencing reproductive failure.

Thus, the aim of the present study was to evaluate the long-term reproductive outcomes of infertile women undergoing outpatient hysteroscopic metroplasty of dysmorphic uteri in 3 tertiary care centers.

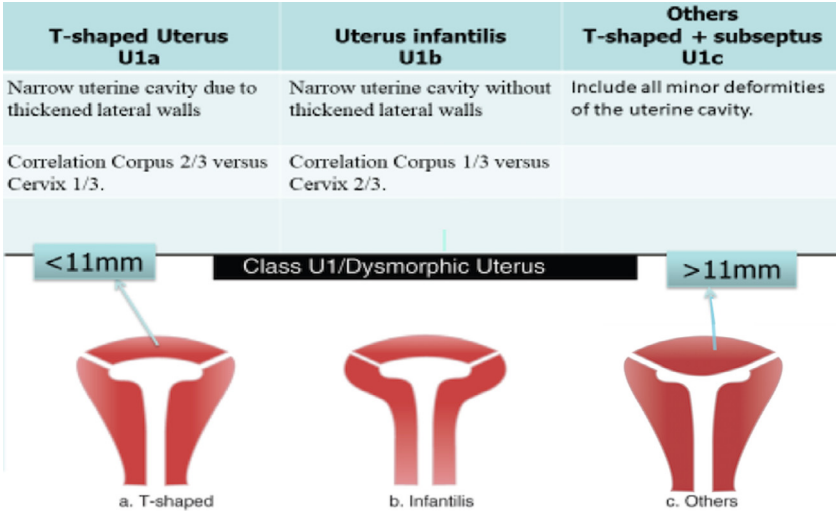
Materials and Methods

Study Design

This retrospective multicenter cohort study was conducted between June 2011 and January 2017 at the hysteroscopy unit,

Fig. 1

Illustration of dysmorphic uteri (class 1 including all cases with a normal external uterine profile but with an altered shape of the uterine cavity) according to European Society of Human Reproduction and Embryology and the European Society for Gynaecological Endoscopy classification of female genital tract congenital anomalies. (A) Class U1a or T-shaped uterus, characterized by a narrow uterine cavity due to thickened lateral walls with a correlation of two-thirds of the uterine corpus and one-third of the cervix. (B) Class U1b or uterus infantilis, characterized also by a narrow uterine cavity without lateral wall thickening and an inverse correlation of one-third of the uterine body and two-thirds of the cervix. (C) Class U1c or others included all minor deformities of the uterine cavity (i.e., T-shaped uterus with partial septum).



Department of Gynecology and Obstetrics of 3 tertiary care university hospitals: University of Naples Federico II (Naples, Italy), Ziekenhuis Oost Limburg (Genk, Belgium), and University of Bari (Bari, Italy).

The study was conducted in accordance with the Declaration of Helsinki (1975) and Good Clinical Practice guidelines. Before enrollment, each patient received detailed information about the study, including its purpose, and provided informed consent. The study was deemed exempt from institutional review board approval because its design was observational (i.e., without any modification of the routine clinical practice in each center), and all data were anonymized before analysis.

Patients

Consecutive patients age <40 years with hysteroscopic and 3D transvaginal ultrasonography (3D-TVS)−confirmed diagnosis of dysmorphic uterus (class U1a, U1b, or U1c according to the ESHRE/ESGE classification system) (Fig. 1) with the following inclusion criteria were enrolled: history of primary unexplained infertility, defined by World Health Organization (WHO) as failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, "unexplained" after the exclusion of common causes of infertility using standard fertility investigations, including semen analysis, assessment of ovulation, and tubal patency test, with or without previous failed in vitro fertilization (IVF), and history of repeated early miscarriages (2 or more consecutive pregnancy losses before 24 weeks of gestation). Exclusion criteria included abnormal karyotype (including partner evaluation), hereditary or acquired thrombophilic conditions (e.g., factor V Leyden, prothrombin mutation, antiphospholipid syndrome), decreased ovarian reserve (i.e., follicle-stimulating hormone >10 mUI/mL on day 3, antral follicle count ≤5−7, or anti-Mullerian hormone ≤0.5−1.1 ng/mL), age >40 years, severe endometriosis (American Society for Reproductive Medicine stage III−IV), body mass index >30 kg/m^2, positive pregnancy test, previous pregnancy ending in live birth, uterovaginal prolapse and urinary symptoms, malignancy, presence of other gynecologic pathology (i.e., polyps, myomas, or intrauterine adhesions), other severe intercurrent conditions (i.e., coagulative disorders, systemic disease, or severe cardiac disease), and recent hysteroscopic surgery (within the 12 months preceding the referral to our unit).

The patients were divided into 2 groups according to their reproductive history: group 1, with a history of primary unexplained infertility, and group 2, with a history of repeated early miscarriages.

Presurgical Assessment of Uterine Cavity

Preoperative evaluation was focused on the volume and morphology of the uterine cavity, evaluated by diagnostic hysteroscopy and 3D-TVS. On hysteroscopic evaluation (performed on days 6−10 of the menstrual cycle, as calculated based on the patient's last reported menstrual period), a suspicion of dysmorphic uterus was raised in the presence of an increased distance between the tubal ostia, a narrow uterine cavity, or an abnormally elongated cervical canal. Interostial distance (i.e., distance between the 2 tubal ostia [IO]) and transverse diameter at the level of isthmus were evaluated using the opening of the jaws of the 5 Fr grasping forceps (6 mm) as reference measure.

The diagnosis of dysmorphic uterus was confirmed by 3D-TVS. To obtain better visualization of the morphology of the uterine cavity, the 3D-TVS examination was performed during the luteal phase of the cycle (days 21−25, when the endometrium usually appears thick and echogenic). The uterus was visualized in the longitudinal plane, and 3D volume was obtained using the automatic sweep of the mechanical transducer. Uterine volume was analyzed using the technique of planar reformatted sections. This technique captures a coronal view of the uterus, which usually lies perpendicular to the ultrasound beam. Evaluation of uterine architecture was carried out in a standardized plane using the interstitial portions of the fallopian tubes as reference points. A coronal view of the uterus was obtained and the distance between the 2 IO, the transversal diameter at the isthmus (I), the I/IO ratio, and the thickness of the uterine side walls and depth of the healthy myometrium up to the serosa were also measured. In the presence of associated subseptum, the length of the endocavitary development of the septum was obtained and categorized according to the ESHRE/ESGE classification system.

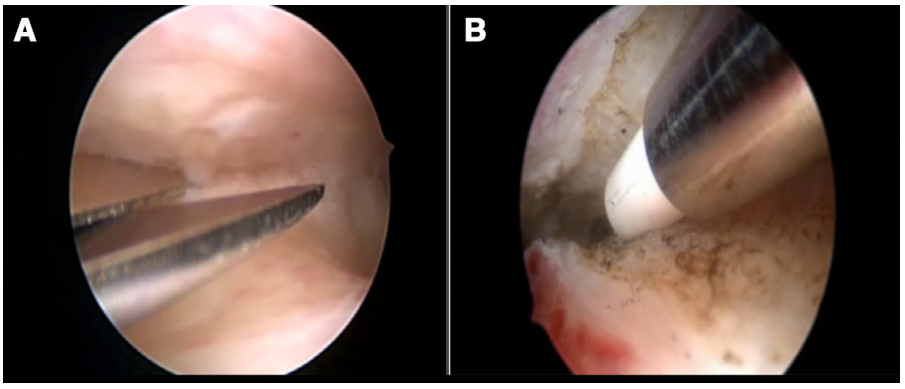
Surgical Procedure

All patients underwent hysteroscopic metroplasty in an ambulatory setting under conscious sedation (as achieved with i.v. midazolam 10 mg and fentanyl 100 g) during the follicular phase immediately after the menstrual phase (days 6−10) of a spontaneous cycle. No pharmacologic preparation of the endometrium was provided.

The procedures were performed by 3 skilled surgeons (Drs. Di Spiezio Sardo, Campo, and Bettocchi), with similar experience and expertise in hysteroscopic metroplasty (approximately 3000 surgical procedures each). Metroplasty was performed using a vaginoscopic approach and 2 compact 30-degree rigid continuous-flow 4- to 5-mm hysteroscopes (Trophy and Integrated Office operative hysteroscopes; Karl Storz, Tüttlingen, Germany). Longitudinal lateral incisions were performed on the fibromuscular constriction rings in the isthmic area, and in the presence of a tubular cavity also on the anterior and posterior uterine walls, with a 5 Fr bipolar electrode or scissors (Fig. 2). In patients with diagnosis of dysmorphic uterus subtype U1c, resection of the subseptum with the same instruments was performed as well.

Fig. 2

Longitudinal lateral incisions performed on the fibromuscular constriction rings with hysteroscopic scissors (A) or a 5 Fr bipolar electrode (B).



At the end of the procedure, 10 to 15 mL of an antiadhesive gel (polyethylene oxide sodium carboxy methylcellulose gel or cross-linked hyaluronic acid gel) was applied inside the uterine cavity under hysteroscopic visualization through the inflow channel of the hysteroscope. The operator gradually moved the hysteroscope from the fundus of the uterus back to the external cervical os, releasing the gel throughout the uterine cavity and the endocervical canal. The procedure was considered complete when under hysteroscopic visualization, the gel seemed to have replaced all the distention media and the cavity appeared completely filled with the antiadhesive gel from the tubal ostium up to the external cervical os [7].

Postsurgical Evaluation of Uterine Cavity Volume and Morphology

Postsurgical evaluation was assessed by second-look hysteroscopy and 3D-TVS. During the luteal phase of the menstrual cycle following surgery, 3D-TVS was performed to compare the postsurgical measurements with those obtained at enrollment. The primary parameter evaluated was the increase of the volume of uterine cavity. The secondary parameters were IO and I diameters, I/IO ratio, and the possible presence of residual septum or intrauterine adhesions (Fig. 3).

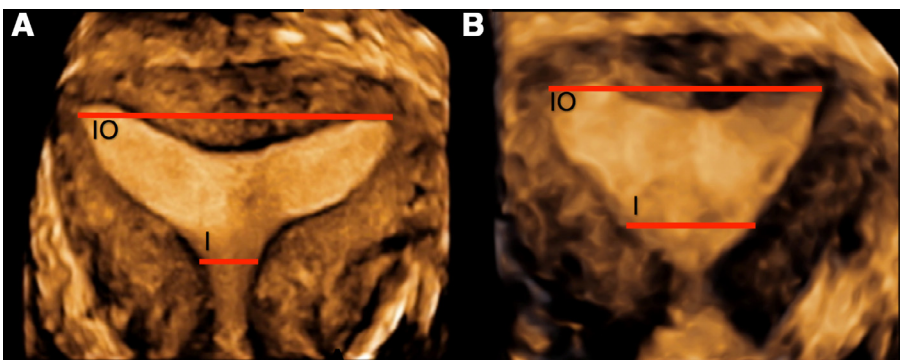
After 3D-TVS, office hysteroscopy was performed in the early proliferative phase of the next menstrual cycle. The postoperative results in terms of uterine volume increase and morphology improvement were assessed using the opening of the jaws of the 5-Fr grasping forceps as a reference measure. Any postsurgical intrauterine synechiae detected were documented and cut using 5 Fr sharp- or blunt-tip scissors.

Data Collection and Reproductive Follow-Up

Drs. Zizolfi and Santangelo at the Naples and Bari sites and Drs. Meier Furst and Di Cesare at the Genk site retrospectively collected all data from the patients' clinical charts (recorded at time of metroplasty). Inclusion and exclusion criteria were evaluated, and in cases of missing data, the same authors contacted the patients by telephone to retrieve the missing information. Subsequently, all

Fig. 3

3D-TVS showing the increased volume and improvement of the morphology of T-shaped uteri before (A) and after (B) hysteroscopic metroplasty. An increase in the ratio I/IO was detected; IO: distance between the 2 internal tubal ostia ; I : uterine cavity width at the corpus-isthmic level .



patients were followed for reproductive outcomes for at least 24 months from the day of hysteroscopic metroplasty. Information was collected clinically during gynecologic office visits and by periodic phone interviews (every 6 months). In cases of ongoing pregnancy at the time of interviews, patients were followed to document the pregnancy outcome.

The primary endpoint was an evaluation of the pregnancy rate (per woman) after hysteroscopic metroplasty. Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonography visualization of 1 or more gestational sacs; spontaneous abortion, as the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation; and live birth, as delivery of a live fetus after 20 completed weeks of gestational age. This outcome was expressed in a dual manner (i.e., per women and per pregnancy) to highlight 2 potential types of benefits inherent to the intervention: the percentage of women achieving a live birth after the metroplasty and the percentage of pregnancies that ended with a live birth.

The secondary endpoints were full-term delivery rate, conception time, mode of conception (i.e., spontaneous or after assisted reproductive technology [ART]: IVF or intracytoplasmic sperm injection [ICSI]), mode of delivery, occurrence of preterm delivery, and other obstetric complications.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 (IBM, Armonk, NY). Data are shown as mean ± SD or as number (percentage). Comparisons between repeated measures were performed with the use of dependent *t* test and expressed as mean difference with 95% confidence interval (CI). A p value <.05 was considered to indicate statistical significance.

Results

A total of 214 patients with dysmorphic uterus were enrolled. The main baseline characteristics of these patients are summarized in Table 1. Among the 214 women, 166 (77.6%) had a diagnosis of primary unexplained infertility (group 1) and 48 (22.4%) had a history of repeated early spontaneous abortion (group 2).

Anatomic Results

The surgical procedures were completed without intraoperative complications in all cases, with a mean duration of the procedure of 9.7 ± 2.4 minutes. At the 3D-TVS post-operative evaluation, the volume of the uterine cavity was significantly improved after surgery in all cases (from 1.42 ± 0.07 cm^3 to 2.09 ± 0.10 cm^3; mean difference, 0.67; 95% CI, 0.65−0.69; p < .0001); improved morphology of the uterine cavity was observed in all but 3 women (1.4%), in whom the uterine dysmorphism persisted.

Table 1

Baseline patient characteristics (n = 214)

Characteristic	Value
Age, yr, mean ± SD	36 ± 3.7
Caucasian ethnicity, n (%)	214 (100)
Body mass index, kg/m^2, mean ± SD	23.7 ± 5.4
Indications for surgery n (%)	
Primary infertility	166 (77.6)
Repeated spontaneous abortions (>2)	48 (22.4)
Subtypes of dysmorphic uteri n (%)	
T-shaped uterus	124 (57.9)
Tubular-shaped (infantilis uterus)	39 (18.3)
T-shaped with subseptum uterus	51 (23.8)

No patients with a history of DES exposure or acquired T-shaped malformation were included.

At the hysteroscopic follow-up, mild intrauterine adherences were detected in the isthmic area in 36 patients out of 214 (16.8%) and were easily cut with 5 Fr sharp scissors.

Reproductive Outcomes

The mean duration of follow-up was 60 months (range, 24−96 months). The main reproductive outcomes are presented in Table 2. The clinical pregnancy rate was 72.9%, the term-delivery rate was 86.4%, the live birth rate per women was 58.4%, and the live birth rate per pregnancy was 80.1%. A miscarriage occurred in 19.9% of clinical pregnancies, and a single case of fetal intrauterine death (due to thrombosis of the umbilical cord at 36^0 weeks) was recorded. Among the 156 pregnant women, 74 (47.4%) conceived spontaneously, with a median time to pregnancy of 5.5 months (range, 1.5−9.5 months), and 24 (32.4%) of these women had previously undergone 1 or more attempts at IVF or ICSI. No cases of cervical incompetence or uterine rupture occurred after surgery. Eight cases of retained placenta (i.e., 1 hysterectomy, 4 manual removal and 3 with hysteroscopic removal) were observed and treated.

Discussion

Main Findings

In this retrospective cohort study, the increase in uterine volume and optimization of uterine morphology following the hysteroscopic metroplasty of dysmorphic uteri resulted in a high rate of clinical pregnancies and live births in women with a history of reproductive failure. These results are in line with the findings of our previous pilot study [19] but are considerably more robust, being derived from a larger number of patients (214 vs 30) and longer follow-up after surgery (60 months vs 15 months).

Specifically, in the present study, we evaluated patients with dysmorphic uterus with a history of primary infertility

Table 2

Postoperative reproductive outcomes

Outcome	Primary infertility (group 1), n/N (%)	Repeated early spontaneous miscarriage (group 2), n/N (%)	Total, n/N (%)
Number of patients (%)	166 (77.6)	48 (22.4)	214
Clinical pregnancy rate	119/166 (71.6)	37/48 (77)	156/214 (72.9)
Miscarriage rate	23/119 (19.3)	8/37(21.6)	31/156 (19.9)
Term delivery rate	87/96 (90.6)	21/29 (72.4)	108/125 (86.4)
Delivery $>34^0$ wk	91/96 (94.7)	27/29 (93.1)	118/125 (94.4)
Live birth rate (per woman)	96/166 (57.8)	29/48 (60.4)	125/214 (58.4)
Live birth rate (per pregnancy)	96/119 (80.6)	29/37 (78.3)	125/156 (80.1)
Mode of delivery: cesarean section	52/96 (54.2)	16/29 (55.2)	68/125 (54.4)
Vaginal delivery	44/96 (45.8)	13/29 (44.8)	57/125 (45.6)
Mode of conception: spontaneous	53/119 (44.5)	21/37 (56.7)	74/156 (47.4)
Assisted reproductive technology	66/119 (55.4)	16/37 (43.2)	82/156 (52.6)

or early repeated miscarriages of otherwise unexplained etiology. The overall clinical pregnancy rate after metroplasty was 72.9%, considerably higher than that reported in our previous study (55%), as well as in other reports. The greater reproductive success observed in this study compared with our previous experience [19] warrants some exploration. First, this study had a significantly longer follow-up period was significantly longer in the present study compared with our previous study (median, 60 months vs 15 months). Moreover, the present study had a considerably larger sample size (214 vs 30 patients) and a greater number of patients conceiving with ART (52.6%). In 2011, Fernandez et al [9] reported a clinical pregnancy rate of 49.5% with a follow-up of 39 months. Similarly, Garbin et al [22] reported a clinical pregnancy rate of 45.8% among 24 patients at a mean follow-up of 20.3 months after surgery. In this context, Giacomucci et al [23] found an approximately 10-fold higher term delivery rate after surgery in women with various uterine malformations, with the correction of T-shaped uterus yielding the highest term delivery rate. In a recent study, Ducellier-Azzola et al [24] confirmed reproductive improvement in patients with a T-shaped uterus after hysteroscopic metroplasty, with a significantly increased rate of live births (60% vs 2.5%) and a reduced rate of early spontaneous miscarriage (22% vs 78.3%). These data may support the amelioration of reproductive performance observed in our series. In addition, because we applied more rigorous criteria for patient selection compared with other studies, our results may more genuinely reflect the actual improvements in reproductive function after metroplasty for dysmorphic uterus in women with reproductive impairment of unexplained etiology.

Another important finding of the present study is the high rate of spontaneous pregnancy after surgery (47.4%), with a median time to pregnancy of 5.5 months. Interestingly, a non-negligible percentage of the women who conceived spontaneously (32.4%) had previously failed 1 or more IVF/ICSI cycles. Once again, these data demonstrate that along with embryo quality, proper anatomy of the uterine cavity is crucial for achieving a pregnancy [25].

Another relevant finding of our study is the absence of cervical incompetence after metroplasty, as confirmed by the 5.6% rate of preterm deliveries, which is similar to that in the general population [26]. This was probably related to the minimally invasive approach used in our study that avoided cervical dilatation, a known risk factor for cervical incompetence and for preterm birth.

A further interesting finding was that 8 women had a retention of deciduous tissue after delivery (9.2% among those who had a live birth), of whom 7 were treated conservatively and 1 underwent hysterectomy for placental accreta. Although this may suggest a possible correlation between metroplasty and the risk of placental remnants, our small sample size precludes us from drawing a firm conclusion. Moreover, it should be stressed that the only woman who required a hysterectomy due to placental accreta had a personal history of repeated uterine curettages after spontaneous abortions. For these reasons, the correlation between hysteroscopic metroplasty for dysmorphic uterus and the risk of retention of decidual tissue requires further clarification.

Interestingly, we found intrauterine adhesions in 16.8% of the women (36 of 214) at the hysteroscopic follow-up evaluation. Although we acknowledge that this rate of adhesions is remarkable, we note that the adhesions were filmy and easily cut using scissors or the tip of the hysteroscope. Not surprisingly, all the adhesions were found at the same location where the intrauterine incisions were made. This finding confirms that hysteroscopic surgery in which there is contact of contralateral incised areas is one of the most important risk factors for the development of intrauterine adhesions [27,28]. In line with the conclusions of a recent review, we decided to apply an intrauterine antiadhesion barrier gel after the procedure, which may have reduced the severity of the adhesions in our patients [28]. The mechanism of action of an antiadhesion gel barrier is

to keep the uterine walls separated after surgery for at least 48 hours [29]. This mechanism may potentially reduce the severity of de novo adhesions formation after hysteroscopic surgery; however, we acknowledge that further research is needed to draw firm conclusions [28,30].

Limitations

The main limitations of our findings are inherent to the study design. The absence of an untreated control group precluded us from making direct inferences as to the effect of the intervention on the reproductive outcomes. In this regard, we may argue that the infliction of an endometrial damage at the time of hysteroscopic metroplasty may itself improve endometrial receptivity, in line with the results of recent meta-analyses focusing on women undergoing intrauterine insemination or IVF [31,32]. Thus, it remains to be clearly demonstrated whether the reproductive outcomes observed in our study are correlated with the correction of uterine dysmorphism or with other factors (e.g., endometrial injury). In addition, all of our patients were Caucasian, which may preclude the extrapolation of our data to patients of others races/ethnicities. Finally, the procedures were performed exclusively by high-volume experienced hysteroscopists, which could also decrease the external validity of our study.

In conclusion, our data show that outpatient hysteroscopic metroplasty with miniaturized instruments is an effective minimally invasive approach to treating dysmorphic uteri in women with history of reproductive failure and is associated with an exceptionally high rate of live births. This less invasive approach has proven to be very safe with low risk of surgical and obstetric complications. Future prospective studies are needed to confirm our results and to better understand the impact of uterine remodeling on endometrial function.

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