

Role of morphologic characteristics of the uterine septum in the prediction and prevention of abnormal healing outcomes after hysteroscopic metroplasty

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STUDY QUESTION: Can morphologic measurements (width, length and surface area) of the uterine septum predict healing-dependent abnormal anatomic results [ARs; residual septum (RS) and intrauterine adhesions in other locations (IUA-OLs)] after complete hysteroscopic metroplasty (HM)?

SUMMARY ANSWER: Significant predictors of ARs are the septal width and, to a lesser extent, septal surface area.

WHAT IS KNOWN ALREADY: Anatomic results after hysteroscopic metroplasty have very large variation. A RS > 1 cm and IUA-OLs can aggravate reproductive outcomes, resulting in the need for reoperation. New criteria for diagnosing a uterine septum according to the European Society of Human Reproduction and Embryology (ESHRE) and European Society for Gynaecological Endoscopy (ESGE) have been suggested (ESHRE-ESGE criteria). Autocross-linked hyaluronic acid gel (autocross-linked polysaccharide) has an antiadhesive effect.

STUDY DESIGN, SIZE, DURATION: A prospective, observational cohort study was performed with 96 women consecutively enrolled between 2007 and 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women who had uterine septum and previous miscarriage or infertility presented for evaluation at a university hospital, private hospital or private medical center were included. Preoperative septal width, length and surface area were determined with three-dimensional sonohysterography. Women were treated by hysteroscopy in a standardized manner with three- or four-dimensional transrectal ultrasound guidance (complete resection). Patients received either no adhesion barrier (49 patients) or adhesion barrier with autocross-linked polysaccharide (47 patients). Anatomic results were assessed with three-dimensional sonohysterography and second-look hysteroscopy. Healing-dependent ARs were reported using both American Society of Reproductive Medicine (ASRM) criterion of RS length > 1 cm (ASRM > 1 cm criterion) and ESHRE-ESGE criteria. Univariate and multivariate logistic regression were used to identify predictors of RS, IUA-OLs and ARs.

MAIN RESULTS AND ROLE OF CHANCE: In patients who had no adhesion barrier, ARs were diagnosed in 11 of 49 patients (23%) using the ASRM > 1 cm criterion and in 20 of 49 patients (41%) using the ESHRE-ESGE criteria for RS [odds ratio (OR)_{ESHRE-ESGE:ASRM}, 2.4, $P = 0.05$]. In the patients who had autocross-linked polysaccharide, ARs_{ASRM > 1 cm} were diagnosed in 2 of 47 patients (4%) and ARs_{ESHRE-ESGE} in 4 of 47 patients (9%). RS_{ESHRE-ESGE} was diagnosed significantly more often than RS_{ASRM > 1 cm} 19 of 96 (20%) versus 5 of 96 (5%) in all patients (OR_{ESHRE-ESGE:ASRM > 1 cm} = 4.5, $P < 0.01$). In patients who had no adhesion barrier, logistic regression with ASRM > 1 cm and ESHRE-ESGE criteria showed that the width and surface area were predictors of ARs. Models adjusted by patient group confirmed the significance of width as a predictor of ARs_{ASRM > 1 cm} [OR for width, 3.5 ($P < 0.01$); OR for group, 0.22 ($P < 0.01$)], width as a predictor of ARs_{ESHRE-ESGE} [OR for width, 2.2 ($P < 0.01$); OR for group, 0.26 ($P < 0.01$)] and surface area as a predictor of ARs_{ASRM > 1 cm} [OR for surface area, 1.5 ($P < 0.01$); OR for group, 0.32 ($P < 0.01$)]. In patients who had autocross-linked polysaccharide, these predictors were not significant. Receiver-operating

characteristic curves showed cutoff values for $AR_{ASRM} > 1\text{ cm}$ (septal width, 3.42 cm; septal surface area, 4.68 cm²) and $AR_{ESHRE-ESGE}$ (septal width, 3.42 cm; septal surface area, 3.51 cm²).

LIMITATIONS AND REASONS FOR CAUTION: Patients were enrolled in the adhesion barrier group in a time-dependent, consecutive and non-randomized manner.

WIDER IMPLICATIONS OF THE FINDINGS: A wide septum and large surface area may be indications for adhesion barrier. The use of autocross-linked polysaccharide reduces the risk of ARs. The ESHRE-ESGE criteria may cause greater frequency of recognition of RS than the $ASRM > 1\text{ cm}$ criterion, which could result in more frequent reoperations with use of the ESHRE-ESGE criteria, possibly without any significant effect on reproductive performance.

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Key words: septate uterus / intrauterine adhesions / classification system / autocross-linked hyaluronic acid gel / three-dimensional sonohysterography

Introduction

Hysteroscopic metroplasty is common treatment for women with uterine septa who have had recurrent spontaneous abortions (Homer *et al.*, 2000; Valle and Ekpo, 2013). It is also performed in infertile women (Pabuçcu and Gomel, 2004; Mollo *et al.*, 2009). However, there is controversy about whether to offer hysteroscopic metroplasty to women with uterine septa, or wait until miscarriage occurs or pregnancy fails, because no randomized controlled trial has identified the benefits and risks of this procedure (Bosteels *et al.*, 2010; Chan *et al.*, 2011; Kowalik *et al.*, 2011).

Hysteroscopic metroplasty may have good obstetric outcomes and rare complications as reported in non-controlled reports (Nouri *et al.*, 2010; Valle and Ekpo, 2013), but abnormal anatomic results (ARs) occur with wide variation (Porcu *et al.*, 2000; Mollo *et al.*, 2011; Yang *et al.*, 2013; Ludwin *et al.*, 2014a). Abnormal anatomic results may include a residual septum (RS) at the uterine fundus and isolated intrauterine adhesions in other locations (IUA-OLs) (Ludwin *et al.*, 2014a). A RS may be caused by incomplete resection or adhesions. Due to the surgeons' subjective assessments of the completeness of resection and a lack of standardised post-operative evaluation of the uterine cavity, there is a high risk of bias. In reality, the incidence of healing-dependent RS is unknown.

Various methods have been used to prevent adhesions after hysteroscopic metroplasty, but there is no unequivocal recommendation (Vercellini *et al.*, 1989; Homer *et al.*, 2000; Taskin *et al.*, 2000; Nawroth *et al.*, 2002; Nappi *et al.*, 2007). Some data are available about the effectiveness of autocross-linked polysaccharide, a cross-linked gel derived from hyaluronic acid (De Iaco *et al.*, 2001), during hysteroscopic metroplasty (Guida *et al.*, 2004; Mais *et al.*, 2012). However, there is no information available about the frequency of healing-dependent anatomic outcomes or the effects of uterine parameters such as uterine septum morphology on healing-dependent anatomic results. The varied morphology of the septum may affect the formation of adhesions and may be an indication for the use of targeted adhesion prevention.

The purpose of this study was to determine the frequency of healing-dependent abnormal anatomic results after complete hysteroscopic septal resection and to assess the effect of uterine septal morphology (width, length and surface area) on these results. In addition, we evaluated the effect of using different criteria for the diagnosis of uterine RS

including (i) the American Society for Reproductive Medicine (ASRM) (Buttram *et al.*, 1988) criterion with an internal fundal indentation length $> 1\text{ cm}$ (Fedele *et al.*, 1996; Ludwin *et al.*, 2014a) and (ii) the European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy (ESHRE-ESGE) classification of female genital tract congenital anomalies with an internal indentation at the fundal midline $> 50\%$ myometrial thickness (Grimbizis *et al.*, 2013). The effect of adhesion barrier on healing-dependent ARs was also determined.

Materials and Methods

Patients

This prospective observational study was performed as part of a larger research project to assess the use of ultrasonographic and endoscopic methods in the diagnosis and treatment of congenital uterine anomalies (Ludwin *et al.*, 2014a). Patients were recruited from three centers: the Department of Gynecology and Oncology, Jagiellonian University; Ludwin & Ludwin—Private Medical Center and Centermed—Private Hospital. Included patients (i) had a uterine septum, (ii) were of reproductive age, (iii) had a history of ≥ 1 miscarriage or infertility; (iv) intended to have children in the future and (v) provided informed consent for the study. Patients were excluded for (i) pregnancy; (ii) menopause; (iii) precancerous state or malignancy of the reproductive organs; (iv) benign lesions in the myometrium of the uterine fundus (myomas or adenomyosis) (Hirai *et al.*, 1995; Anderson, 1999) or lesions distorting the uterine cavity (submucosal myomas or intrauterine adhesions) on ultrasonography; (v) withdrawal of patient consent; (vi) rare complex uterine congenital anomalies without an ASRM classification such as uterine septum with double cervix (Ludwin *et al.*, 2013b); (vii) presence of external intercervical cleft; (viii) incomplete (internal fundal indentation $> 10\text{ mm}$) or non-standardized septum resection (internal fundal indentation $< 10\text{ mm}$ and uterine myometrial thickness $> 10\text{ mm}$ at the fundus), confirmed intraoperatively and (ix) excessive fundal incision (uterine myometrial thickness $< 6\text{ mm}$ at the fundus confirmed intraoperatively) (Ludwin *et al.*, 2014a).

The patients were divided into two groups: (i) the no adhesion barrier group, who were women recruited before December 2009 and who were treated hysteroscopically with no adhesion barrier (Nawroth *et al.*, 2002) and (ii) the autocross-linked polysaccharide group, who were women recruited after December 2009 and who received an intrauterine application of autocross-linked polysaccharide (Hyalobarrier Gel, Fidia Advanced

Biopolymers, Abano Terme, Italy) (Guida et al., 2004). The study was approved by the Jagiellonian University Review Board and informed consent was obtained from all participants.

Evaluation

All patients of reproductive age who presented for diagnosis and/or treatment for miscarriage, infertility or uterine septum (suspected or diagnosed by hysteroscopy, hysterosalpingography, two- or three-dimensional transvaginal sonography, sonohysterography or magnetic resonance imaging) had three-dimensional transvaginal sonography in a standardized manner from certified examiners. The diagnosis of uterine septum was confirmed by three-dimensional sonohysterography (3D-SIS) (performed by I.L., K.P. or A.L.) in the early proliferation phase in all patients who had a septate, bicornuate or arcuate uterus noted on three-dimensional transvaginal sonography. Uterine septa were classified according to the descriptive classification of ASRM, including the distinction between complete (class VA) and partial (class VB) uterine septum (Buttram et al., 1988), and additional morphometric criteria for differentiating between septate and bicornuate (Homer et al., 2000; Salim et al., 2003a; Ludwin et al., 2011; 2013a, 2014a) or septate, arcuate and normal uteri (Bermejo et al., 2010; Ludwin et al., 2011, 2013a, 2014a; Gergolet et al., 2012). A uterine septum was diagnosed when the uterine cavity was divided into two parts at >1.5 cm from the interstitial line (Bermejo et al., 2010; Ludwin et al., 2013a, 2014a), with a normal or nearly normal external outline and intercornual cleft depth <1 cm (Salim et al., 2003a,b; Ludwin et al., 2013a, 2014a).

All three-dimensional volume acquisitions were performed in a standardized manner after obtaining a sagittal view of the central part of the uterus (maximum sweep angle, 180° ; approximate angle between uterine axis and ultrasound beam, 90° ; ultrasound probe held steadily) (Ludwin et al., 2014a). Preoperative, intraoperative and post-operative ultrasonography was performed with an ultrasound system (Voluson E8 Expert or 730 Expert, GE Healthcare Ultrasound, Milwaukee, WI, USA) with volumetric intravaginal probes (GE RIC 5–9 MHz 3D/4D; GE Healthcare Ultrasound). For 3D-SIS, saline was used as the contrast medium in the uterine cavity. For three- or four-dimensional transrectal ultrasonography (3D/4D-TRUS) during hysteroscopic metroplasty, a mixture of mannitol and sorbitol (Purisol, Fresenius, Bad Homburg, Germany) was used as a contrast and distention medium. All measurements were taken after obtaining a coronal view with visible intramural parts of both fallopian tubes.

Septal width, length and surface area were determined with preoperative 3D-SIS (Fig. 1). The septal width was measured between the inner contours of the apices of the horns of the uterine cavity. The length of the septum was determined by measuring the distance between the interstitial line and the parallel line running through the lowest point of the septum in the lower part of the uterus. The septal surface area was determined by outlining the entire surface of the myometrium forming the septum, including the lateral edges of the septum and septal base formed by the interstitial line.

Hysteroscopic metroplasty with three- or four-dimensional transrectal ultrasonography

Women were treated with hysteroscopic metroplasty in a standardized manner guided by information from 3D/4D-TRUS. In all patients, the bowel was prepared using a 150-ml sodium dihydrophosphate-sodium hydrophosphate enema (Laboratorium Galenowe, Olsztyn, Poland) 2 h before transrectal ultrasonography (Ludwin et al., 2013c). Antibacterial prophylaxis was with cefuroxime (1.5 g intravenous) (Biofuroksym, Polpharma, Poland). No patient received any hormonal treatment during the 3 months before or after hysteroscopy.

The procedures were performed during the early proliferation phase by the same surgeon (A.L.), who had 10–15 years' experience in hysteroscopic metroplasty, using the same operative technique, hysteroscope (diameter, 4 mm; 30°), monopolar resectoscope, needle electrode (Collins, Karl Storz, Tuttlingen, Germany) and device parameters. The septum was cut from its lower to upper part until the optimal uterine cavity shape was obtained, tailored to the anatomy of the fundus. In patients who had a complete (class VA) uterine septum associated with a vaginal septum, the procedure began with resection of the vaginal septum and lower part of the cervical septum with an electro-surgical knife before hysteroscopic resection of the remaining part of the cervical and uterine septa. Resection of the uterine septum in the upper part of the uterus was performed with guidance from 3D/4D-TRUS until a uniform fundal myometrial thickness (6–10 mm) was obtained (Supplementary data, Fig. S1) (Ludwin et al., 2014a). The maximum cutoff corresponded to that previously used during ultrasound-guided hysteroscopic metroplasty (Querleu et al., 1990). The minimum cutoff was based on our experience during 10 years with two- and three-dimensional transrectal ultrasonography (no uterine rupture during pregnancy) (Ludwin et al., 2014a).

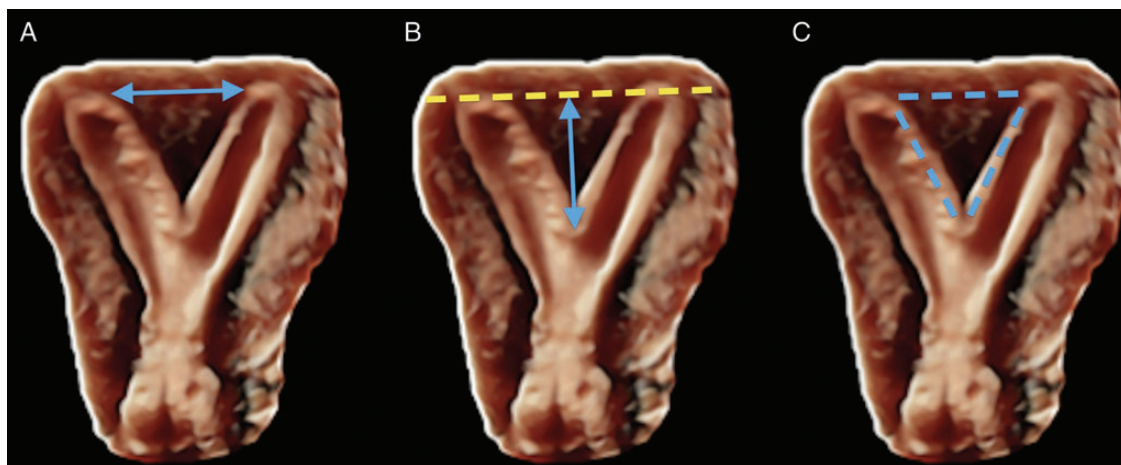


Figure 1 Preoperative three-dimensional sonohysterography to measure morphological parameters of the uterine septum. (A) Width. (B) Length. (C) Surface area.

Completion of septal resection during and at the end of the procedure was confirmed by measuring the myometrium in the central fundus using 3D/4D-TRUS (I.L.). The shape of the uterine cavity was assessed in the coronal view with 3D/4D-TRUS. The intrauterine application of autocross-linked polysaccharide gel (10 mL) was performed immediately after this procedure using a 3-mm-diameter silicone tube cut with scissors to a length of 10–12 cm. Patients were hospitalized for 1 day after the procedure.

Post-operative evaluation

Post-operative evaluation included 3D-SIS and second-look hysteroscopy. All women were monitored for possible occurrence of early post-operative complications such as bleeding, infection, fever and allergic reactions. The 3D-SIS (I.L.) and office second-look hysteroscopy (A.L.) were performed at 6–8 weeks after hysteroscopic metroplasty to assess the anatomic results, consistent with general practice (Homer *et al.*, 2000). Both 3D-SIS and hysteroscopy were used for post-operative diagnosis to evaluate the comparative accuracy of 3D-SIS and hysteroscopy, reported elsewhere (Ludwin *et al.*, 2014a). Anatomic parameters assessed by post-operative 3D-SIS were (i) myometrial thickness in the central fundus and (ii) internal fundal indentation/fundal notch length/RS. The latter parameters were evaluated by measuring the distance between the interostial line and a parallel line running through the lowest point of the uterine cavity fundus. Hysteroscopic findings of IUA-OLs were reported in the present study because hysteroscopy had a higher (non-significant) diagnostic accuracy than 3D-SIS in detecting intrauterine adhesions (Ludwin *et al.*, 2014a).

Measurements of internal fundal indentation and *myometrial thickness of the uterine fundus* enabled additional categorization of anatomic results (Table I, Fig. 2). This categorization of uterine cavity shape was justified because of common present use (ASRM classification; Buttram *et al.*, 1988; Bermejo *et al.*, 2010; Ludwin *et al.*, 2011, 2013a, 2014a), reproductive outcome

results (RS ≥ 1 cm; Fedele *et al.*, 1996), expert consensus (ESHRE-ESGE system; Grimbizis *et al.*, 2013) and the known effects of intrauterine adhesions on fertility.

Additional surgical intervention was performed during second-look hysteroscopy (A.L.), including removal of any observed adhesions and resection of residual septa with the length ≥ 10 mm (Fedele *et al.*, 1996). The goals of this intervention were to achieve a uterine cavity shape as close to normal as possible and a myometrial thickness of 6–10 mm. Myometrial thickness was controlled indirectly by second-look hysteroscopy calibrated with a 5-French hysteroscopic probe (intraoperative myometrial thickness during additional resection = difference between fundal thickness assessed by 3D-SIS and intraoperative measurement of the resected RS).

The mean fundal myometrial thickness was measured during the initial hysteroscopy, immediately after resection, and after a 6–8-week healing period (Homer *et al.*, 2000). The thickness was compared within and between groups and within the entire study population.

The frequency of RS, IUA-OLs, ARs and additional surgical interventions performed during second-look hysteroscopy were determined and compared between groups. The results were compared with the initial morphology of the uterine septum, including the ASRM classification of complete or partial septum, septal width in the upper part of the uterus, septal length and surface area. The frequency of RS was compared with and without the inclusion of IUA-OLs (Table I).

Validation of reproducibility among diagnostic methods

The validity of all ultrasonographic imaging methods (three-dimensional transvaginal sonography, 3D-SIS and 3D/4D-TRUS) was assessed by determining interrater/intrarater agreement (off-line blinded diagnosis) in 30 patients selected randomly from the study population. This showed almost perfect correlation for the differentiation of septate uterus and measurement of septal width, length and surface area (3D-SIS), measurement of myometrial thickness (3D-SIS and 3D/4D-TRUS) (unpublished data) and post-operative evaluation of uterine cavity shape and length of fundal notch/RS (3D-SIS) (Ludwin *et al.*, 2014a).

Sample size

The sample size *a priori* was determined according to the main objective of the study (to determine the prevalence of healing-dependent abnormal anatomic results after hysteroscopic metroplasty) based on the assumption that the prevalence of ARs $\neq 50\%$ (frequency of intrauterine adhesions or ARs in previous reports, a retrospective analysis in women treated by surgeons with average experience, and a small preliminary study) and the anticipated prevalence of healing-dependent ARs is 27% (based on a larger retrospective analysis of operator- and healing-dependent ARs by ASRM > 1 cm criteria in women treated by an expert surgeon; post-operative two- or three-dimensional sonohysterography). Assuming the alternative hypothesis to test for equality ($0.27_{\text{true}} \neq 0.50_{\text{reference}}$), with $\alpha = 0.05$ and $1 - \beta = 0.90$, the required group size was 46 (Chow *et al.*, 2012). For this sample size, the anticipated prevalence of ARs, with a confidence level of 95%, the margin of error calculated *post hoc* using Kish formula was 13% (Kish, 1965). With these assumptions, the prevalence of ARs may vary from 14 to 40%, significantly different from 50%. Thus, we found that the margin of error and sample size would be sufficient. A more precise estimation of prevalence of healing-dependent ARs with a common 5% margin of error and 95% confidence level, and based on the study results (prevalence of ARs according to ASRM > 1 cm criteria), would require a very large sample of 269 patients with septate uterus (Kish, 1965), which exceeded our recruitment opportunities. Additional patients were enrolled in a group of comparable size in which autocross-linked polysaccharide was used to achieve the other objectives of the study.

Table I Classification of anatomic results after hysteroscopic metroplasty.

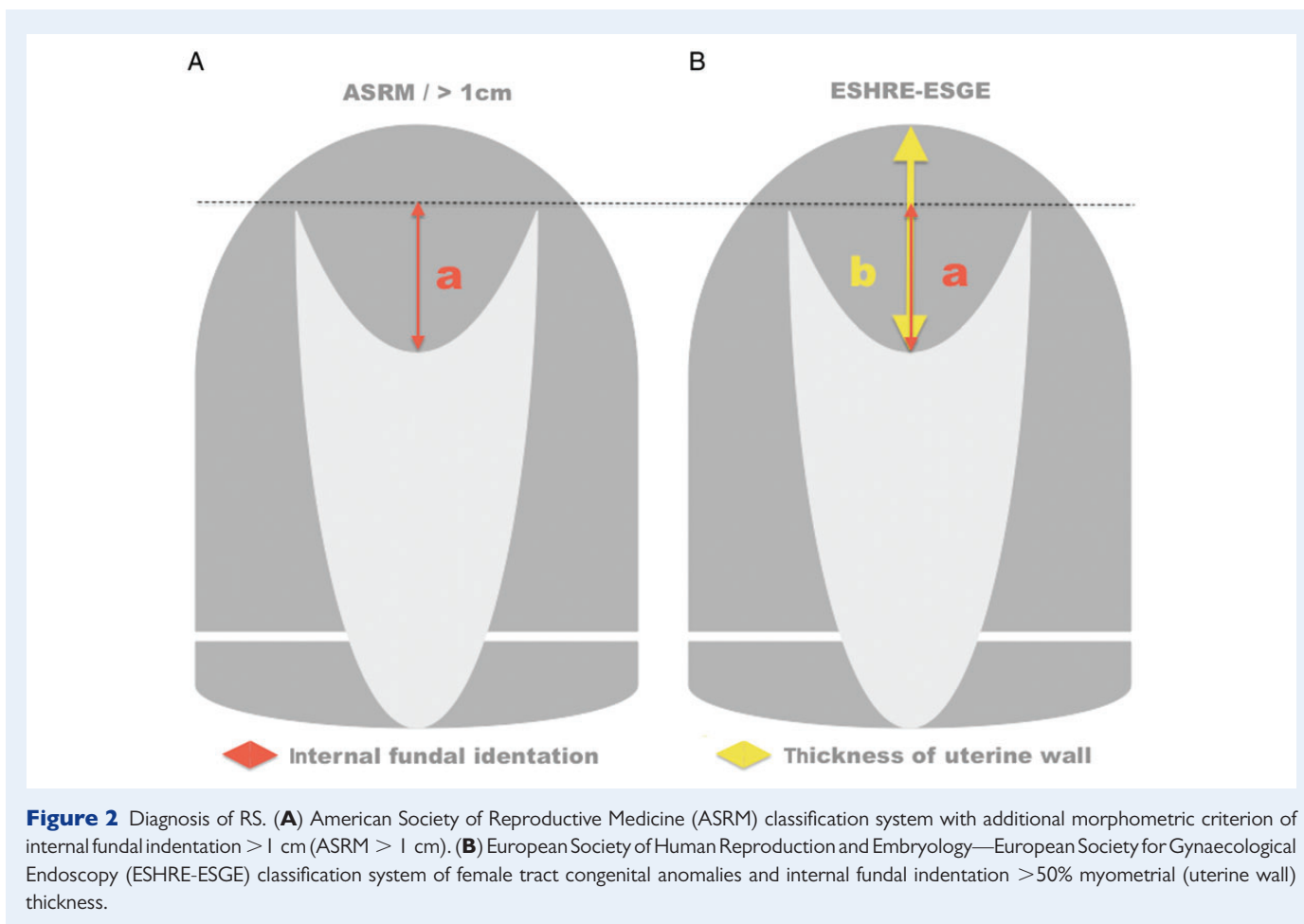
Classification	Uterine cavity shape	Intrauterine adhesions in other locations
ASRM ^{a,b}		
Normal	Normal (internal fundal indentation/RS < 1 cm)	Absent
Abnormal ^c	Abnormal (internal fundal indentation/RS ≥ 1 cm)	Present
ESHRE-ESGE ^b		
Normal	Normal [internal fundal indentation $< 50\%$ myometrial (uterine wall) thickness]	Absent
Abnormal ^c	Residual septate uterus [internal fundal indentation $> 50\%$ myometrial (uterine wall) thickness]	Present

ASRM, American Society for Reproductive Medicine; ESHRE-ESGE, European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy.

^aASRM classification system and criterion of RS by length > 1 cm after hysteroscopic metroplasty (Fedele *et al.*, 1996; Ludwin *et al.*, 2014a).

^bModified to include the presence/absence of intrauterine adhesions in other locations (Ludwin *et al.*, 2014a).

^cPresence the RS or adhesions in other locations or both.



Statistical analysis

All analyses were performed with statistical software (STATISTICA, version 10.0, StatSoft, Inc., Tulsa, OK, USA; R, version 2.15.2, R Foundation, Vienna, Austria). Continuous measurements are presented as mean \pm standard deviation for normally distributed data (age, weight, septal area, intraoperatively evaluated myometrial thickness of uterine fundus after metroplasty and myometrial thickness of uterine fundus after healing period), and as median values with lower and upper quartiles for non-normally distributed data (body mass index, septal length, RS length after healing period, procedure time and medium absorption). Minimum and maximum values also are shown. Categorical variables are presented as numbers of subjects and percentages. The Shapiro–Wilk test was used to evaluate the normality of distribution of continuous variables. The *t*-test was used to compare differences between normally distributed continuous variables. Differences between non-normally distributed variables were tested using the non-parametric Mann–Whitney test. Comparisons between measurements of fundal myometrial thickness at two different times (intraoperative after resection and follow-up) were made with paired *t*-test. To compare differences between categorical variables, the Pearson χ^2 test (chi-square test) or Fisher exact test was used. Pearson product moment and Spearman rank correlation were used to assess the functional dependence between the order of inclusion of the patient in the study, procedure duration and medium absorption. The effects of RS, IUA-OLs and ARs were evaluated using univariate and multivariate logistic regression, with morphologic parameters serving as independent variables [categorical data: subclassification of septate uterus by ASRM [subclass, VA or VB]; continuous variables: width (cm), length (cm),

surface area [cm²]]. Models were created for ASRM > 1 cm and ESHRE-ESGE criteria for all 96 patients and separately for the two groups. Stepwise and forward methods were used for multivariate logistic regression. Group-adjusted models were created for all data models. The results are shown as odds ratios (normal-to-abnormal state) with 95% confidence intervals and *P* values determined by Wald test. Group-adjusted models were created. Receiver-operating characteristic curves were created to determine cutoff values for continuous parameters such as RS, IUA-OLs and ARs. Statistical significance was defined by two-sided *P* \leq 0.05.

Results

Patients were enrolled between January 2007 and December 2011 and data collection was completed in February 2012. There were 161 patients who were potentially eligible for the study, and 108 patients included in the study. Finally, data of 96 women [no adhesion barrier group, *N* = 49 (university hospital—27 patients; private hospital or private medical center—22 patients); autocross-linked polysaccharide group, *N* = 47 [university hospital—20 patients; private hospital or private medical center—27 patients]] were analyzed (Supplementary data, Fig. S2).

The mean age and median body mass index were similar between patients who had autocross-linked polysaccharide or no adhesion barrier (Table II). There were 56 patients (58%) who had miscarriages, 31 patients (32%) who were infertile, and 9 patients (9%) who were

Table II Clinical parameters of patients who had hysteroscopic metroplasty^a.

Parameter	Total	No antiadhesion	Autocross-linked polysaccharide	P
Age (years)	29 ± 5 (20–41)	29 ± 5 (20–41)	29 ± 5 (20–41)	0.47
Body mass index (kg/m ²)	22 [20–24] (17–38)	23 [20–24] (18–38)	21 [20–24] (17–34)	0.82
Procedure duration (min)	17 [15–20] (9–41)	17 [15–18] (9–40)	17 [16–21] (10–41)	0.1
Medium absorption (ml)	310 [230–400] (50–750)	290 [230–380] (50–700)	310 [240–400] (50–750)	0.62

^aN = 96 patients. Data reported as mean ± SD or median [interquartile range] (range, minimum–maximum).

Table III Characteristics of uterine septum before, fundal myometrial thickness during metroplasty, fundal myometrial thickness and fundal notch/RS after a 6–8-week healing period^a.

Assessment	Variable	Total	No antiadhesion	Autocross-linked polysaccharide	P
No. patients		96	49	47	
Preoperative	ASRM subclass				
	VA	19 (20%)	9 (18%)	10 (21%)	0.72
	VB	77 (80%)	40 (82%)	37 (79%)	
	Width (cm)	3.3 ± 0.8 (1.8–4.8)	3.3 ± 0.8 (1.8–4.7)	3.4 ± 0.8 (1.8–4.8)	0.48
	Height (cm)	2.2 [1.9–3.2] (1.5–7.1)	2.2 [1.9–3.2] (1.5–7.1)	2.2 [1.9–2.5] (1.7–6.8)	0.88
	Surface area (cm ²)	4 ± 1 (1.4–7.6)	4 ± 1 (1.4–7.6)	4 ± 1 (1.6–7.4)	0.57
Intraoperative after resection	Myometrial thickness (mm)	8 ± 1 (6–10)	8 ± 1 (6–10)	8 ± 1 (6–10)	0.99
Follow-up	Myometrial thickness after healing (mm)	12 ± 4 (7–24)	13 ± 4 (7–24)	11 ± 3 (7–18)	<0.01
	Length of fundal notch/RS (mm)	4.5 [3.0–7.1] (1–15)	4.9 [4.2–7.9] (1–15)	3.2 [2.1–4.5] (1–8)	<0.01

^aData reported as number (%), mean ± SD (range, minimum–maximum), or median [interquartile range] (range, minimum to maximum). Assessments: preoperative parameters assessed with three-dimensional sonohysterography; intraoperative myometrial thickness after septum resection assessed with three-dimensional transrectal ultrasonography; follow-up (6–8 weeks) myometrial thickness and RS length assessed with three-dimensional sonohysterography.

infertile after miscarriage. The procedure duration, medium absorption, and preoperative and intraoperative (after resection) morphologic characteristics of uterine septa were similar between patients who had no adhesion barrier or autocross-linked polysaccharide (Tables II and III). There was no significant correlation between the order of patient inclusion in the study and procedure duration or medium absorption in either surgical center. There were no intraoperative or early post-operative complications observed.

The fundal myometrial thickness measured after the healing period was significantly greater than that measured immediately after hysteroscopic metroplasty in both the groups (no adhesion barrier, $P < 0.01$; autocross-linked polysaccharide, $P < 0.01$) and the entire sample ($P < 0.01$) (Table III). However, at follow-up, the mean myometrial thickness and RS length were significantly lower in patients who had autocross-linked polysaccharide than patients who had no adhesion barrier (Table III). According to the ASRM classification with morphometric criteria, uterine cavity shape after the healing period was normal in 91 (95%) patients and arcuate (RS by ASRM > 1 cm criterion) in 5 patients (5%, all had no adhesion barrier). There were no healing-dependent uterus septate (internal fundal indentation > 15 mm) observed according to the ASRM classification with morphometric criteria (Ludwin et al., 2013a).

Independent of the criteria used for RS detection (ASRM > 1 cm or ESHRE-ESGE), residual septa and ARs were detected significantly

more frequently in patients who had no adhesion barrier than patients who had autocross-linked polysaccharide (Table IV). The frequency of IUA-OLs did not differ significantly between the two patient groups (Table IV).

RS was diagnosed significantly more frequently with the ESHRE-ESGE classification than with the ASRM > 1 cm criteria in all patients (odds ratio, 4.5; 95% confidence interval, 1.6–12.6; $P < 0.01$) (Table IV). Intrauterine adhesions occurred as isolated changes, and the inclusion of frequency of occurrence of intrauterine adhesions in the analysis weakened the significance of the effect of the diagnostic criteria for RS (ASRM > 1 cm versus ESHRE-ESGE) on the frequency of ARs (odds ratio, 2.1; 95% confidence interval, 1.01–4.49; $P = 0.05$).

Univariable logistic regression with the dependent variable RS determined by either criteria (ASRM > 1 cm or ESHRE-ESGE criteria) demonstrated that septal width (cm) and surface area (cm²) were predictors of RS in patients who had no adhesion barrier and in the entire study population. For patients who had no adhesion barrier, RS was significantly predicted by width (both criteria) and surface area (ASRM > 1 cm criteria only) (Table V). Group-adjusted models (odds ratio for no adhesion barrier to autocross-linked polysaccharide group) for RS (ESHRE-ESGE criteria) confirmed the significance of septal width and weakened the significance of septal surface area (Table V). Models for the autocross-linked polysaccharide group and adjusted by group for RS

Table IV Abnormal anatomic results after complete hysteroscopic metroplasty^a.

Anatomic result	Total	No antiadhesion	Autocross-linked polysaccharide	P
No. patients	96	49	47	
Intrauterine adhesions in other locations	9 (9%)	7 (14%)	2 (4%)	0.16
ASRM and morphometric criteria (RS > 1 cm)				
Residual septum	5 (5%)	5 (10%)	–	0.03
Abnormal anatomic result	13 (14%)	11 (23%)	2 (4%)	0.02
ESHRE-ESGE criteria				
Residual septum	19 (20%)	16 (33%)	3 (6%)	<0.01
Abnormal anatomic result	24 (25%)	20 (41%)	4 (9%)	<0.01

ASRM, American Society of Reproductive Medicine; ESHRE-ESGE, European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy.

^aData reported as number (%). Abnormal anatomic result defined as RS or/and intrauterine adhesions in other locations.

(ASRM > 1 cm criterion) could not be performed because no patient in the autocross-linked polysaccharide group had an RS > 1 cm.

Univariate logistic regression in patients who had no adhesion barrier with the dependent variable abnormal anatomic results (RS and/or IUA-OLs) showed that septal width and surface area were significant predictors of ARs (both ESHRE-ESGE and ASRM > 1 cm criteria) (Table V). Group-adjusted models for abnormal anatomic results (odds ratio for no adhesion barrier to autocross-linked polysaccharide group) confirmed the significance of septal width and weakened the significance of surface area for the ESHRE-ESGE criteria, and confirmed the significance of septal width and surface area for the ASRM > 1 cm criteria (Table V).

In patients who had no adhesion barrier, receiver-operating characteristic curve analysis revealed the cutoff values for RS with the greatest sensitivity for width (ASRM > 1 cm criteria) and greatest specificity for width and surface area (ASRM > 1 cm criteria) (Table VI, Fig. 3), as well as the cutoff values for abnormal anatomic results with the greatest sensitivity for width (ASRM > 1 cm criteria) and greatest specificity for surface area (ASRM > 1 cm criteria) (Table VI, Fig. 3).

Univariate logistic regression in all patients identified septal width as a predictor of intrauterine adhesion in other locations (odds ratio, 1.9; 95% confidence interval, 1.1 to 3.4; $P < 0.01$). The model adjusted by group confirmed the significance of this parameter (odds ratio for width, 2.2; 95% confidence interval, 1.2–4.2; $P \leq 0.02$; odds ratio for group, 0.4; 95% confidence interval, 0.15–0.93; $P \leq 0.05$). These results were obtained for the whole group ($N = 96$). Receiver-operating characteristic curves showed that the cutoff value was a septal width of 3.42 cm (sensitivity, 86%; specificity, 62%). In eight of nine adhesions, the septal width was > 3.42 cm. Separate models for the two patient groups had a low predictive value because of the small numbers of IUA-OLs, especially in patients who received autocross-linked polysaccharide.

No other morphologic factor, either alone or in group-adjusted analyses, had a significant effect on RS, ARs or IUA-OLs. No multivariate model including the morphologic factors studied had a predictive value for the occurrence of healing-dependent RS, IUA-OLs or general healing-dependent abnormal anatomic results after hysteroscopic metroplasty.

Additional surgical interventions were performed during repeat hysteroscopy in 13 patients (14%) who had abnormal anatomic results by ASRM > 1 cm criteria. These interventions were performed significantly less frequently in the autocross-linked polysaccharide group

[2 of 47 patients (4%)] than in patients who had no polysaccharide [11 of 49 patients (23%); $P \leq 0.05$].

Discussion

This prospective study is the first to show the frequency of occurrence of healing-dependent ARs after complete hysteroscopic metroplasty using the ESHRE-ESGE classification as well as ASRM and morphometric criteria. In patients who had no adhesion barrier, ARs occurred in 23% of patients according to the ASRM > 1 cm criterion or in 41% of patients according to the ESHRE-ESGE criteria for diagnosis of RS (Table IV). The most important study findings were that septal width and, to a lesser extent, septal surface area were significant predictors of abnormal anatomic results (Table V, Fig. 4). The risk of ARs increased significantly above the cutoff values determined for these parameters, and these cutoff values can be used to target adhesion prophylaxis and plan future studies about the effectiveness of new antiadhesion methods. In the entire sample, the study showed that autocross-linked polysaccharide significantly decreased the frequency of ARs (Table IV).

The measurements of myometrial thickness of the uterine fundus immediately after metroplasty and at follow-up also may be useful (Table III). These measurements confirm that adhesion processes may be a natural component of healing after hysteroscopic metroplasty. Furthermore, adhesion processes may be a natural attempt to restore primary anatomy that may cause a fundal notch, an RS or intrauterine adhesions in other locations. The observed changes in myometrial thickness of the uterine fundus confirm the findings of a recent report of *de novo* adhesion formation in most women after hysteroscopic metroplasty (Yang et al., 2013). However, the extent of these adhesions may not necessarily be important and they are not diagnosed in most patients.

In contrast with patients who had no adhesion barrier, septal width and surface area were not significant predictive risk factors for ARs after metroplasty in patients who received autocross-linked polysaccharide. The use of autocross-linked polysaccharide may not completely eliminate ARs, but may reduce the extent of adhesions, reduce the RS size and improve anatomic outcomes after hysteroscopic metroplasty.

In the present study, the ESHRE-ESGE classification criteria for the assessment of hysteroscopic metroplasty resulted in a higher frequency of diagnosis of RS (20%) than the ASRM > 1 cm criterion (5%) (Table IV).

Table V Univariate analysis of predictors of RS and abnormal anatomic results in patients who had no adhesion barrier during hysteroscopic metroplasty^a and group-adjusted models^b.

Parameter	Criteria	Predictors	No antiadhesion		
			Odds ratio	95% Confidence interval	P
RS	ESHRE-ESGE	Width	3.2	1.7–6.5	<0.01
		Surface area	1.3	1.0–1.8	0.07
	ASRM > 1 cm	Width	9.7	2.4–21.0	0.02
		Surface area	1.8	1.2–3.3	0.02
Group-adjusted models for RS ^{c,d}	ESHRE-ESGE	Width	2.0	1.3–3.1	<0.01
		Group	0.30	0.14–0.60	<0.01
		Surface area	1.2	0.9–1.5	0.18
		Group	0.33	0.16–0.63	<0.01
Abnormal anatomic results ^e	ESHRE-ESGE	Width	3.4	1.8–6.9	<0.01
		Surface area	1.4	1.0–1.9	0.04
	ASRM > 1 cm	Width	3.1	1.6–6.7	<0.01
		Surface area	1.7	1.2–2.6	<0.01
Group-adjusted models for abnormal anatomic results	ESHRE-ESGE	Width	2.2	1.5–3.5	<0.01
		Group	0.26	0.12–0.55	<0.01
		Surface area	1.2	1.0–1.5	0.10
		Group	0.31	0.16–0.57	<0.01
	ASRM > 1 cm	Width	3.5	1.9–7.5	<0.01
		Group	0.22	0.07–0.55	<0.01
		Surface area	1.5	1.2–2.1	<0.01
		Group	0.32	0.13–0.69	<0.01

ASRM, American Society of Reproductive Medicine; ESHRE-ESGE, European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy.

^aN = 49 patients; ^bN = 96 patients.

^cRatio between no adhesion barrier to autocross-linked polysaccharide group.

^dModels adjusted by group for RS with the ASRM > 1 cm criterion could not be performed because no patient in the autocross-linked polysaccharide group had an RS > 1 cm.

^eRS or/and intrauterine adhesions in other locations.

The ESHRE-ESGE criteria for diagnosis of uterine septum are based on expert consensus, but not validated by any prospective or retrospective studies, and have not been evaluated in practice (Ludwin *et al.*, 2014b). Therefore, the ESHRE-ESGE criteria should be used with caution when considering reoperation for a uterine septum that is diagnosed after hysteroscopic metroplasty and when the absolute length of the RS is < 1 cm. These criteria may cause the diagnosis of all internal fundal indentations > 50% wall thickness as a uterine septum. In a patient who has an average (12.3 mm) myometrial thickness of the uterine fundus after hysteroscopic metroplasty, a fundal notch slightly > 6 mm would be classified as an RS according to the ESHRE-ESGE criteria. However, there are no data available that show that an RS (Fedele *et al.*, 1996) or internal indentation < 1 cm affects reproductive outcomes or that these small findings require surgical correction (Tomazevic *et al.*, 2007; Gubbini *et al.*, 2009; Gergolet *et al.*, 2012). The two classification systems originally refer to the natural preoperative status of the uterus, not the uterus after any surgical correction. It is paradoxical that the ESHRE-ESGE criteria applied before treatment (internal indentation 6 mm; uterine wall thickness 10 mm) may be an indication for surgery as uterus septate but the identical morphology after hysteroscopic metroplasty has been defined as a satisfactory outcome (Fedele *et al.*, 1996).

The ESHRE-ESGE classification did not contain recommendations about how to measure the thickness of the uterine wall, which may vary at different regions of the uterus (Grimbizis *et al.*, 2012, 2013; Ludwin *et al.*, 2014b). Temporary guidelines have been suggested, with measurement of the mean thickness of the anterior and posterior wall (Grimbizis *et al.*, 2014). However, this may not solve the basic problem with the ESHRE-ESGE criteria, because linking the internal indentation and thickness of the uterine wall may generate more frequent diagnosis of uterine septum or RS in women who have a thin wall, and less frequent diagnosis in women who have a thick wall, than a real degree of distortion of uterine cavity architecture (Salim *et al.*, 2003b). However, women of childbearing age typically have wall thickness < 20 mm (Traiman *et al.*, 1996; Youm *et al.*, 2011), and the risk of overdiagnosis of RS or septate uterus may be higher with the ESHRE-ESGE criteria than with the classification of ASRM and simple criterion to differentiate between normal and abnormal uterine cavity shape after metroplasty (Ludwin *et al.*, 2014a) or between normal (internal indentation < 1 cm), arcuate and septate uteri (Bermejo *et al.*, 2010; Ludwin *et al.*, 2013a,b,c, 2014b).

Further studies with reproductive outcomes may verify whether the ESHRE-ESGE criteria are relevant for the diagnosis and treatment of septate uterus. The ideal classification should suggest appropriate

Table VI Cutoff values from receiver-operating characteristic curves in patients who had no antiadhesion prevention adhesion barrier during hysteroscopic metroplasty^a.

Result	Criteria	Parameter	Cutoff	Sensitivity (%)	Specificity (%)
Residual septum	ESHRE/ESGE	Width (cm)	3.4	81	73
		Surface area (cm ²)	3.2	81	55
	ASRM > 1 cm	Width (cm)	3.84	100	86
		Surface area (cm ²)	4.73	80	84
Abnormal anatomic result	ESHRE/ESGE	Width (cm)	3.42	80	79
		Surface area (cm ²)	3.51	70	62
	ASRM > 1 cm	Width (cm)	3.42	91	68
		Surface area (cm ²)	4.68	64	87

ASRM, American Society of Reproductive Medicine; ESHRE-ESGE, European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy. ^aN = 49 patients.

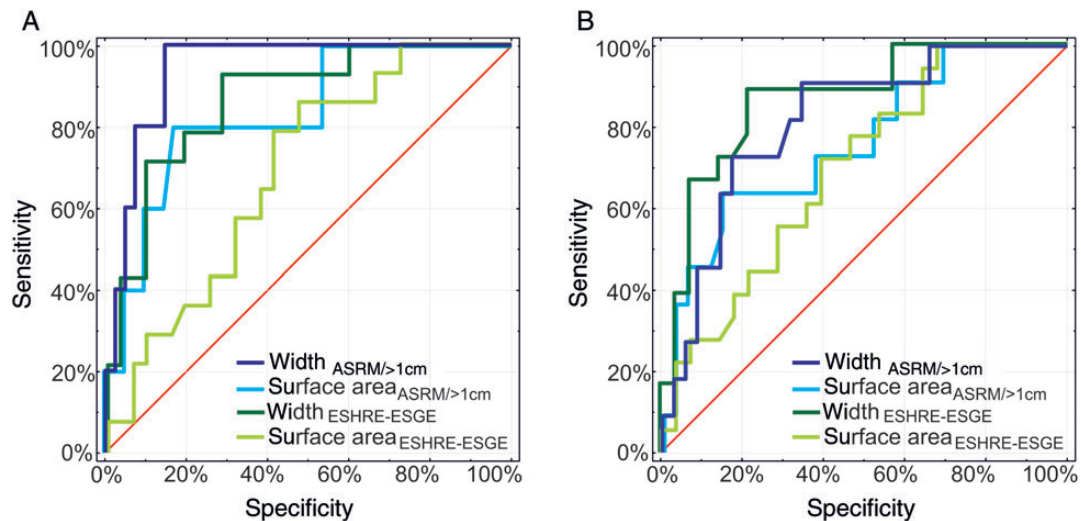


Figure 3 Receiver-operating characteristic curves of septal width and surface area to predict healing outcomes after complete hysteroscopic hystero-plasty. (A) RS. (B) Abnormal anatomic results (RS and intrauterine adhesions in other location). ASRM > 1 cm, American Society of Reproductive Medicine (ASRM) classification with additional morphometric criterion of internal fundal indentation > 1 cm; ESHRE-ESGE, European Society of Human Reproduction and Embryology—European Society for Gynaecological Endoscopy classification.

therapy and avoid inadequate or unnecessary surgery (Acién and Acién, 2011).

A strength of the present study was the use of standardized and reproducible three-dimensional imaging including preoperative and postoperative 3D-SIS, intraoperative 3D/4D-TRUS and complementary imaging for the prospective assessment of adhesion formation upon the completion of hysteroscopic metroplasty. This assessment is important because hysteroscopy has low reproducibility in assessing the shape of the uterine cavity (Smit et al., 2013). The use of intraoperative 3D/4D-TRUS enabled unification of the range of septum resection by achieving similar fundal myometrial thicknesses in the tested patients. However, this may not eliminate the risk of incomplete or non-standardized resection caused by early termination of the procedure

because of hypoosmolar negative (> 1 L) medium balance or excessive bleeding. Nevertheless, intraoperative 3D/4D-TRUS provided an objective measure of resection completion and minimized subjective or arbitrary evaluation by the surgeon. A limitation of this method is that the diagnostic accuracy of 3D/4D-TRUS is unknown; this method is based on advanced volume imaging technology and negative contrast of the uterine cavity by the medium, and visualization may be impaired by the high mobility of the uterus, blood clots, gas bubbles or ultrasonic interference with a resectoscope (Ludwin et al., 2013c).

The suggested optimal range of 6–10 mm for intraoperative fundal myometrial thickness was based on our personal experience (Ludwin et al., 2014a). There are no data that suggest that thinner fundal myometrium may be associated with an increased risk of uterine rupture during

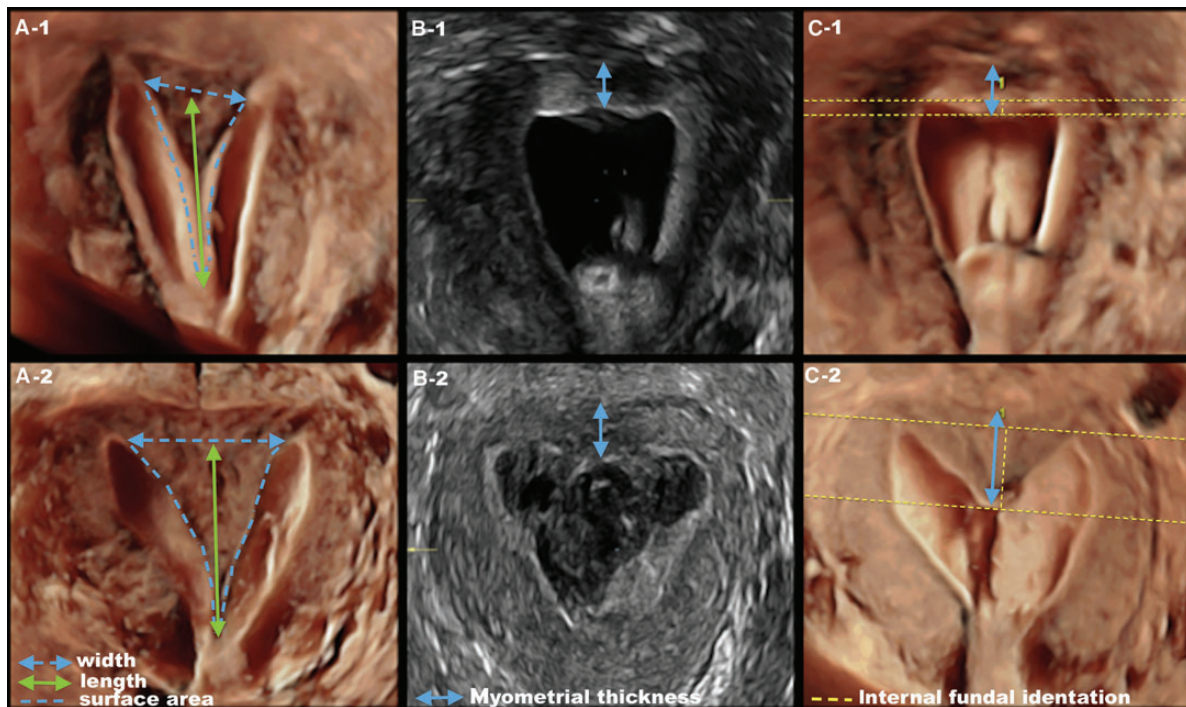


Figure 4 Representative uterine septa from two patients who were treated with hysteroscopic metroplasty and no antiadhesion prophylaxis. Top row (33-year-old woman): (A-1) Preoperative three-dimensional sonohysterography showing the uterine width <3.5 cm and surface area <4.5 cm². (B-1) Myometrial thickness achieved at the completion of surgery (three- or four-dimensional transrectal ultrasonography). (C-1) After healing, RS was absent. Bottom row (30-year-old woman): (A-2) Preoperative three-dimensional sonohysterography showing uterine width >3.5 cm and surface area >4.5 cm²; the length was similar to other patient in (A-1). (B-2) Myometrial thickness achieved at the completion of surgery (three- or four-dimensional transrectal ultrasonography). A similar myometrial thickness was achieved as in other patient in (B-1). (C-2) After healing, RS was present.

pregnancy. Other surgeons have suggested that hysteroscopic metroplasty may be completed when the internal fundal indentation is <10 mm and the fundal myometrial thickness >10 mm.

Limitations of the present study included the lack of randomization of patients who had autocross-linked polysaccharide, which may limit the importance of observations about the effectiveness of autocross-linked polysaccharide in decreasing healing-dependent abnormal anatomic results. In addition, the patient groups were defined by earlier or later inclusion, and unidentified time-dependent factors may have introduced bias, even though consistent standardization of procedures was feasible. All septal resections were performed by the same surgeon who had reached a plateau on the learning curve of hysteroscopic metroplasty. Although sufficient statistical power (1.0) was achieved for comparisons between groups, a double-blinded randomized controlled trial is justified to better assess the efficacy of autocross-linked polysaccharide. Nevertheless, the present results with autocross-linked polysaccharide are useful initial outcomes that helped determine the sample size needed for the double-blinded randomized controlled trial that was started after completing this study.

The occurrence of abnormal anatomic results in patients who did not have adhesion barrier was similar to the worst outcomes (reoperations in 23% women) presented in previous reports (Litta *et al.*, 2004). In a literature review, Nouri *et al.* (2010) reported that reoperations were

conducted in 6% of 1324 women who underwent hysteroscopic metroplasty. Most previous studies have been retrospective and have lacked qualification criteria for repeat hysteroscopy, specific methods and validation of post-operative assessment. It is important to identify which patients may obtain the greatest benefit of antiadhesion treatments such as autocross-linked polysaccharide (Acunzo *et al.*, 2003; Guida *et al.*, 2004; Ducarme *et al.*, 2006; Deans and Abbott, 2010; Di Spiezio Sardo *et al.*, 2011). Autocross-linked polysaccharide may have good efficacy in the prevention of intrauterine adhesions after hysteroscopic metroplasty, polypectomy and myomectomy (Guida *et al.*, 2004). Adhesion barriers may be considered in patients who have an increased risk of adhesion formation.

The most important clinical implication of the present study is the identification of septal width as the primary factor that may predict healing-dependent abnormal anatomic results after hysteroscopic metroplasty. This finding may help target adhesion barrier and optimize the cost of care by avoiding antiadhesion methods in patients who are at low risk of developing abnormal anatomic results and by minimizing reoperation in patients who are at high risk for ARs. In addition, the present results showed that caution may be required in using the ESHRE-ESGE classification for the post-operative diagnosis of problems related to uterine septa. Additional studies are needed to evaluate the effects of septal morphology, the suitability of the ESGE-ESGE criteria in evaluating

uterine septa, the use of autocross-linked polysaccharide and the effects of various anatomic results on reproductive outcomes such as frequency of pregnancy, miscarriage and live birth.

In the present study, additional surgical interventions were performed during second-look hysteroscopy. The potential effects of these interventions on the final reproductive outcomes may have neutralized the effects of autocross-linked polysaccharide. This issue may be addressed in a further study that includes patients who have no corrective intervention during second-look hysteroscopy.

Using advanced three-dimensional imaging to determine preoperative parameters, the septal width was the most important morphologic parameter. The septal width is the only tested parameter that may also be determined easily with two-dimensional ultrasonography.

Conclusion

The uterine septal width and, to a lesser extent, surface area may predict the development of healing-dependent abnormal anatomic results after complete hysteroscopic metroplasty. These factors may help determine which patients may benefit from targeted antiadhesion prophylaxis. The use of autocross-linked polysaccharide reduces the risk of abnormal anatomic results.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

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Authors' roles

A.L.: substantial contributions to conception, design, acquisition of data, analysis and interpretation of data; drafting and revision of the article and final approval of the version to be published. I.L. and K.P.: substantial contributions to acquisition of data, article revision and final approval of the version to be published. K.P.: substantial contributions to acquisition of data, article revision and final approval of the version to be published. T.B. substantial contributions to analysis and interpretation of data, article revision and final approval of the version to be published. R.J.: substantial contributions to interpretation of data, article revision and final approval of the version to be published.

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Conflict of interest

The authors declare that they have no conflict of interest.

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