

Improvement in uterine artery doppler indices via hysteroscopic metroplasty

Sebastiano Pace¹
 Albana Cerekja²
 Kathleen Comalli Dillon³
 Giulia Pace⁴
 Juan Piazze⁵

¹ Ospedale Israelitico, Rome, Italy

² Service of Ultrasound, Radiology, ASL B, Rome, Italy

³ Petaluma, CA, USA

⁴ Perth, WA, Australia

⁵ Poliambulatorio di Ceprano, "SS Trinità", Hospital Sora, Service of Ultrasound in Obstetrics and Gynecology, ASL Frosinone, Italy

Corresponding author:

Juan Piazze
 Poliambulatorio di Ceprano
 Ospedale SS Trinità di Sora
 Service of Ultrasound in Obstetrics and Gynecology,
 ASL Frosinone
 E-mail: jjpiazze2000@hotmail.com

Summary

Objective: the objective of our research was to study uterine artery doppler indices and their evolution over time after metroplasty and subsequent pregnancy in patients whose septate uterus was the only explanation for infertility.

Materials and Methods: a retrospective study. The uterine arteries of 78 patients with septate uteri were evaluated using endovaginal color doppler ultrasound before and after metroplasty. Fifty-one patients became pregnant after metroplasty and were selected as study group, pregnancy occurred within 17 months.

By comparing uterine artery doppler indices before and after metroplasty, we observed that the resistive index (RI) and pulsatility index (PI) post surgery were significantly lower compared to pre-metroplasty levels.

Results: all pregnant women in the study group showed uterine resistive indexes within normal ranges, they all underwent scheduled cesarean intervention. Gestational evolution was normal in all patients (mean score of Apgar and birth weight); no neonatal complications were observed.

Conclusion: metroplastic intervention in women with septate uterus as the sole cause of infertility

may be a plausible alternative for patients wishing to carry a pregnancy.

Key words: metroplasty, hysteroscopy, septate uterus, infertility, pregnancy.

Introduction

The female reproductive system arises from dual Müllerian (paramesonephric) ducts which unite during embryogenesis to create the fallopian tubes, uterus, and upper two-thirds of the vagina. Subsequently, the septum between the two ducts is reabsorbed via apoptosis. Septate or subseptate uterus occurs when there is a failure of apoptotic resorption of the median septum between the paramesonephric ducts. This septum divides the uterine cavity symmetrically in two; the degree of septal extension through the uterine cavity results in classification as a septate or subseptate uterus (1). The introduction of endovaginal ultrasound is an important diagnostic advance in the study of such uterine pathology (2). The endovaginal transducer allows detailed study of the uterine cavity through the combined study of transverse, coronal, and longitudinal planes (3). More recently, three-dimensional ultrasound has opened new diagnostic possibilities for the study of Müllerian malformations (4-8). Color doppler interrogation allows precise assessment of uterine artery flow in real time.

Doppler indices change according to menstrual cycle phases inducing doppler waveforms changes in non gravid women characterized by high resistance to blood flow (9).

In a study of 150 normal women, Kupesic et al. documented that RI (resistive index) is $0.88 + 0.04$ until day 13 of the 28-day menstrual cycle (10, 11). Uterine blood flow resistances are higher in infertile women; non gravid women are characterized by high resistance to blood flow (12, 13). Doppler indices change with the phase of the menstrual cycle: absence of end-diastolic flow (AED) and an early diastolic notch are more pronounced during the follicular phase (14, 15). It was also reported that RI begins to fall one day before ovulation and is stable at this level for the remainder of the cycle (16-18). In this regard, highly resistive flow during the midluteal phase (day 21) is significantly associated with infertility.

Hysteroscopy is the gold standard for uterine sidewall evaluation. It has been shown to be superior to hysterosalpingography (HSG) in diagnosing intrauterine abnormalities, including uterine septa, in cases of infertility.

The aim of this study was: 1) to evaluate by doppler technology possible improvements in uterine blood flow after revision of the uterine walls by hysteroscopic metroplasty, and 2) to assess whether metroplasty might aid in proper blastocyst implantation in the endometrium, resulting in subsequent pregnancy.

Materials and methods

This is a retrospective study conducted in the Department of Gynecology, Perinatology, and Child Health of the Sapienza University of Rome, from October 2001 to May 2011. Seventy-eight women with septate uteri were initially included in the study. The diagnosis of septate uterus was made by endovaginal ultrasound performed in women with an obstetrical history of two or more spontaneous abortions during the first trimester, or alternately in the course of a gynecological ultrasound control group.

Cases with recurrent pregnancy loss were studied by means of thrombophilia, haemostasis parameters and couple karyotype. In all cases, the suspect of septate uterus, as first stated by 2D ultrasound, was later re-confirmed by three-dimensional diagnostic ultrasound scan and a diagnostic hysteroscopy.

Color doppler assessment of uterine arteries was performed using an endovaginal probe (7.5 MHz) with color duplex doppler ultrasound color (Aloka SSD 2000, Japan) as described in other articles (19).

The evaluation was conducted in the same phase of the menstrual cycle (21th day of menstrual cycle, midluteal phase) in all patients to avoid variations due to hormonal influences on uterine artery doppler profiles. All patients had regular menstrual intervals ranging from 25 to 30 days; the periovulatory phase was determined by monitoring dominant follicle size and echogenicity.

Only two operators performed velocimetry (JP, AC) to avoid variations between operators; the average of at least two measurements was calculated in order to prevent further intra-operator variations. The parameters considered were the RI, PI, and the presence or absence of an early diastolic notch in bilateral uterine artery waveforms.

Patients once diagnosed as having a septate uterus underwent hysteroscopic metroplasty (septoplasty). Four to eight weeks after surgery, doppler indices of uterine arteries were evaluated in the 21^o day of the cycle (midluteal phase), as described above (Tab. 1). After hysteroscopy, a group of patients decided to opt for pregnancy (n = 63). All pregnancies occurred within 17 months after metroplasty. The remaining subjects withdrew their intention for pregnancy, began contraceptive therapy and in four cases opted for voluntary pregnancy termination.

In order to avoid statistical bias, pregnant subjects with cervical cerclage were excluded (20) (three pregnant patients underwent cervical cerclage, leaving finally 51 patients recruited for statistical

Table 1. Descriptive data of pre-post metroplasty patients (n= 78).

	Median	25°	75°	Min.	Max.
Age	34	31	38	21	42
Parity	2	0	2	0	6
Day of cycle°	21	20	22	20	22
Day after metroplasty*	42	37	45	32	49

25° - 75° centiles corresponding to median values.

°Basal uterine arteries evaluation days after first day of menses.

*Doppler velocimetry evaluation: 21° day of menstrual period.

calculations).

Color doppler uterine artery indices and placental location were documented in patients in the second trimester (20-22 weeks of gestation); fetal evolution was monitored in all pregnancies. Gestational age at delivery, birth weight, Apgar score at 1 and 5 minutes, no neonatal complications were registered. Data were recorded on a spreadsheet and all hysteroscopic procedures recorded on video (AVI).

For the differences among groups, a t-test was performed. When the test for normality did not satisfy the criteria of Gaussian distribution, a non-parametric test (Mann-Whitney rank sum test) was performed. Statistical analysis was performed using Sigma Stat 3.01 (Jandel Scientific, Ekrath, Germany).

We considered statistical significance to be $p < 0.05$.

All participants gave full informed consent for the study. Prior authorization for this study was granted by the Bioethics Committee of our institution.

Results

When comparing color doppler indices of uterine arteries before and after metroplasty, we observed that the RI and PI after intervention were significantly lower compared to previous values, both unilateral measures in the arithmetic means (Tab. 2). No differences were observed regarding the presence or absence of a bilateral early-diastolic notch.

Doppler parameters in pregnant women (n = 51) were compared with the corresponding values of gestational-age reference curves by means of dedicated software; resistive indices in post metroplasty women varied always within normal limits (as compared with normal pregnancies resistive indices curves) (Tab. 2). No statistically significant differences were seen between left and right sides. Predilection for placental implantation was not noted to be predominantly on one side or the other. Delivery in all cases was performed by elective cesarean intervention. Pregnancy outcomes (standard birth weight and Apgar score) were normal in all cases and there were no neonatal complications.

Table 2. Doppler velocimetry in pre-post metroplasty (n: 78) and in pregnant women (n: 51).

	Max.	Min.	Median	25°	75°	P
RI Ut r. pre*	1.00	0.65	0.81	0.74	0.84	
PI Ut r. pre*	3.50	1.22	1.92	1.50	2.19	
RI Ut l. pre	1.00	0.64	0.79	0.75	0.83	
PI Ut l. pre	3.50	1.36	2.16	1.73	2.27	
RI Ut mean pre	1.00	0.65	0.90	0.75	0.83	
PI Ut mean pre	3.50	1.45	1.99	1.70	2.19	
RI Ut r. post°	0.90	0.68	0.75	0.71	0.78	< 0.02
PI Ut r. post°	2.12	1.45	1.50	1.45	2.11	< 0.02
RI Ut l. post	0.89	0.60	0.73	0.71	0.76	< 0.002
PI Ut l. post	2.99	1.01	1.32	1.01	1.74	< 0.03
RI Ut mean post	0.89	0.65	0.74	0.71	0.77	< 0.04
PI Ut mean post	3.15	2.12	2.84	2.71	2.92	< 0.01
RI Ut r. preg^	0.90	0.68	0.75	0.71	0.78	
PI Ut r. preg^	2.12	1.45	1.50	1.45	2.11	
RI Ut l. preg^	0.89	0.60	0.73	0.71	0.76	
PI Ut l. preg^	2.99	1.01	1.32	1.01	1.74	
RI Ut mean preg^	0.89	0.65	0.61	0.68	0.77	
PI Ut mean preg^	1.83	1.23	1.62	1.28	1.77	

r: right, l: left. *pre - °post metroplasty. p values correspond to post - metroplasty data.

^Doppler velocimetry evaluation coinciding with morphological-middle pregnancy evaluation (20-22 wks' gestation) and always within normal value ranges. Values in bold represent mean values for uterine resistances regarding RI and PI indexes.

Discussion

Uterine abnormalities have been associated with infertility and adverse obstetric events often resulting in either increased morbidity or perinatal fetal mortality (20).

It has been suggested that spontaneous miscarriage may be the result of inadequate blood supply to the fibroelastic uterine wall negatively altering the hemodynamics of a properly implanted blastocyst. Candiani et al. (21) observed alterations in the pattern of vascularization in samples of the lining of the uterine septum, reinforcing the idea that septal implants can result in suboptimal embryologic development. The literature describes the existence of deficient estrogen and progesterone receptors in malformed uteri and, in particular, in septate uteri due to poor vascularization within the connective septum. Changes in blood flow in the uterus during the menstrual cycle in nonhuman species have been shown to be temporally related to the daily relationship of estrogen / progesterone in systemic blood (22, 23).

Pulsed doppler of the septal area showed in this report vascularization in 71.2% of septate uteri. Based on these data, we hypothesize that there may be an association of septate uterus with highly resistive uterine artery blood flow.

Leible et al. (24) noted that all pregnant women with Müllerian anomalies demonstrated both distinct laterality of the placenta and pregnancy complications.

Their hypothesis posited suboptimal vascular anastomotic communication impinging upon effective recruitment of uterine arteries into placental circulation. In the present study, we observed that bilateral uter-

ine artery resistive indices after metroplasty were significantly lower compared to previous levels. A possible explanation for this observation may be that hysteroscopic septum resection leads to better vascularization of the mucosa with consequent increased sensitivity to steroids in the residual area.

No differences were observed regarding the presence/absence of early diastolic notch. The notch is the expression of diastolic reflux of blood and represents an intrinsic characteristic of the elastic vessel walls. This explains why presence/absence of the notch of the uterine arteries remained unchanged after hysteroscopic metroplasty in our patients.

Metroplasty in septate uteri causes the uterine cavity to become wider and more regular, increasing its volume capacity. In post-metroplasty pregnancies, removal of the septum allows more secure implantation of the gestational sac in the uterine cavity and more regular placentation (25).

We suggest that because of its simplicity, minimal invasiveness, low morbidity, and low cost, a hysteroscopic approach in the treatment of uterine anomalies be given full consideration. Removal of the fibromuscular septum eliminates excess muscle tissue that has been hypothesized to cause abortions. It also promotes better uterine perfusion, creating optimal conditions for a pregnancy to evolve smoothly from implantation until delivery.

Conflicts of interest

The authors state no conflicts of interest related to the publication of this work.

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