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ARTICLE

No clinical relevance of the height of fundal indentation in subseptate or arcuate uterus: a prospective study

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Marco Gergolet studied medicine at the University of Trieste, Italy between 1985 and 1991. In 1992 he moved to Ljubljana, Slovenia where in 1998 he became a specialist in obstetrics and gynaecology and senior clinician at the reproductive medicine unit in S.I.S.ME.R., Bologna. In 2008 he graduated as Master of Science in Biomedical Sciences at the University of Ljubljana. Between 2006 and 2008 he was the deputy co-ordinator and between 2009 and 2011 co-ordinator of the Special Interest Group on Reproductive Surgery at the European Society of Human Reproduction and Embryology. He started a PhD Fellowship at the University of Ljubljana in 2011.

Abstract The American Fertility Society has classified the arcuate uterus as a minor malformation with a benign clinical behaviour. The aim of this prospective study was to verify whether there is any scientific basis for this differentiation. Patients with at least one early miscarriage and a subseptate or arcuate uterus were admitted for hysteroscopic metroplasty. Patients were allocated to a subseptate uterus group, with an indentation of 1.5 cm or more, or an arcuate uterus group, with a smaller indentation. The miscarriage rates after metroplasty were similar between the two groups (14.0% in the subseptate uterus group versus 11.1% in the arcuate uterus group). Before metroplasty, the miscarriage rates were significantly higher in subseptate uterus group, as well as in the arcuate uterus group (both $P < 0.001$). According to these results, there is no evidence to support that the arcuate uterus has a different effect on the reproductive outcome in comparison to the subseptate uterus, neither before nor after surgical correction of the anomaly. Since there is no scientific basis for a separate classification of the arcuate uterus, a review of the classifications of uterine congenital anomalies should be considered as necessary.

KEYWORDS: arcuate uterus, congenital uterine anomalies classification, septate uterus, subseptate uterus, spontaneous miscarriage, hysteroscopic metroplasty

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Introduction

Congenital uterine malformations, particularly septa, are commonly reported as one of the main factors causing pregnancy loss or premature delivery with the poorest infant viability (Acién, 1993; Woelfer et al., 2001). Several studies have confirmed a direct correlation between septate uterus and an increased spontaneous miscarriage rate (Grimbizis et al., 2001; Proctor and Haney, 2003; Valli et al., 2004; Zabak et al., 2001). The presence of a septate or bicornuate uterus in a population of patients who underwent diagnostic hysteroscopy because of abnormal uterine bleeding was associated with a higher incidence of spontaneous miscarriages and of preterm delivery (Maneschi et al., 1995). In a series of 665 women with recurrent miscarriage, patients with septate or bicornuate uterus suffered a significantly increased second-trimester miscarriage rate (Saravelos et al., 2010).

A critical analysis by Saravelos et al. (2008), performed on studies from 1950 to 2007, where different diagnostic tools were used, reported a 6.7% prevalence of congenital uterine anomalies in the general population, 7.3% in the infertile population and 16.7% in the recurrent miscarriage population. The arcuate uterus was the commonest anomaly in the general and recurrent miscarriage populations, whereas septate uterus was the commonest anomaly in the infertile population. In a population of women with septate uterus and endometriosis, an increased miscarriage rate seemed more likely dependent on uterine malformations than on endometriosis (Gergolet et al., 2010).

Several authors consider septate uterus as a possible cause of primary or secondary infertility or, at least, a cause of a prolonged time to conception (Acién, 1993; Grimbizis et al., 2001; Lin et al., 2002). In a prospective trial involving 132 women with septate uterus and otherwise unexplained infertility, patients with septate uterus had higher chances of conception after septum removal with respect to those with idiopathic infertility (Mollo et al., 2009).

Hysteroscopic metroplasty improves the pregnancy outcome with a concomitant significant decrease of the miscarriage rate and an increase of at-term delivery rate (Doridot et al., 2003). After hysteroscopic metroplasty, Homer et al. (2000) observed a decrease in the miscarriage rate from 88% to 14% and an increase in the live-birth rate from 3% to 80%.

On the other hand, in a group of patients with idiopathic recurrent miscarriage, the chance of further favourable pregnancy outcome was 70%, with a 75% of take-home baby rate, only by provision of 'tender loving care' and emotional support: patients did not undergo diagnostic hysteroscopy and the presence or the absence of small uterine anomalies was not taken into consideration (Brigham et al., 1999). According to Kashanian et al. (2006), women who suffered a previous miscarriage presented an increased risk for pregnancy loss, when compared with those who delivered at term in the first pregnancy.

While some authors described a slight but significant increase of pregnancy failures in a population of patients with an arcuate uterus (Grimbizis et al., 2001; Lin et al., 2002), others did not find any effect of arcuate uterus on fertility and pregnancy outcome (Raga et al., 1997). A significant negative impact of either septate, subseptate or arcuate uterus on pregnancy and on live-birth rates in patients who conceived after assisted reproduction treatment, have been reported by Tomaževič et al. (2010). After the surgery the differences disappeared, suggesting the possible importance of minimal uterine malformations in reproductive outcome.

The aim of this prospective study was to verify whether the hysteroscopic metroplasty in a group of patients with a small septum (arcuate uterus group) could yield an improvement of fertility and a reduction of miscarriage rate, as well as metroplasty in a group of patients with a subseptate uterus (subseptate uterus group), and to verify whether there is any scientific basis for a differentiation between septate and arcuate uterus. If not, the arcuate uterus should be defined as a misnomer.

Materials and methods

A flow chart of the study design is presented in **Figure 1**. A total of 227 patients, who experienced one or more miscarriages, were screened for uterine anomalies during the period from January 2003 to December 2008. The diagnostic workout was initially performed by vaginal two-dimensional ultrasound, looking for a separation in the endometrial thickness at the fundal level (cat eyes sign; **Figure 2**) and a normal external shape of the uterus. Ultrasound findings were confirmed by diagnostic office hysteroscopy (Campo et al., 1999) or by three-dimensional ultrasound (3D-US). A total of 103 patients were found to have a fundal indentation, either an arcuate or a subseptate uterus (45.4%) and 102 patients underwent hysteroscopic metroplasty. The study included 96 patients. Patients were definitely allocated either to the arcuate or the subseptate group only at the end of the metroplasty.

Since no appropriate diagnostic method exists to differentiate the size of the septum in an accurate way, the intra-operative observation for the final diagnosis and stratification of the patients was used. The largeness/deepness of the septum was evaluated by comparing the length of the uterus before and after metroplasty and by recording the length on the external sheet of the resectoscope after leaning, at the maximum extension, the tip of the electric knife on the uterine fundus. The same measurement was performed at the end of the surgical procedure. Since no classification clearly defines the differential diagnosis between arcuate and subseptate uterus, an arcuate uterus was arbitrarily defined, as a uterus with an indentation penetrating the cavity for less than 1.5 cm, according to the definition of Tomaževič et al. (2007).

Semen analysis and/or semen culture was carried out in 63.5% of male partners when more than 6 months had elapsed between the last miscarriage and the diagnostic and therapeutic work up. In 13 cases with three or more previous miscarriages, both partners were karyotyped to exclude genetic causes of pregnancy loss. All of them had a normal karyotype. Data on the time trying to achieve a pregnancy before metroplasty were collected from the history of the patients.

An 8-mm Karl Storz monopolar operative hysteroscope with sorbitol/mannitol solution as the distension medium was used. Two authors (MG and NK) performed the metroplasties.

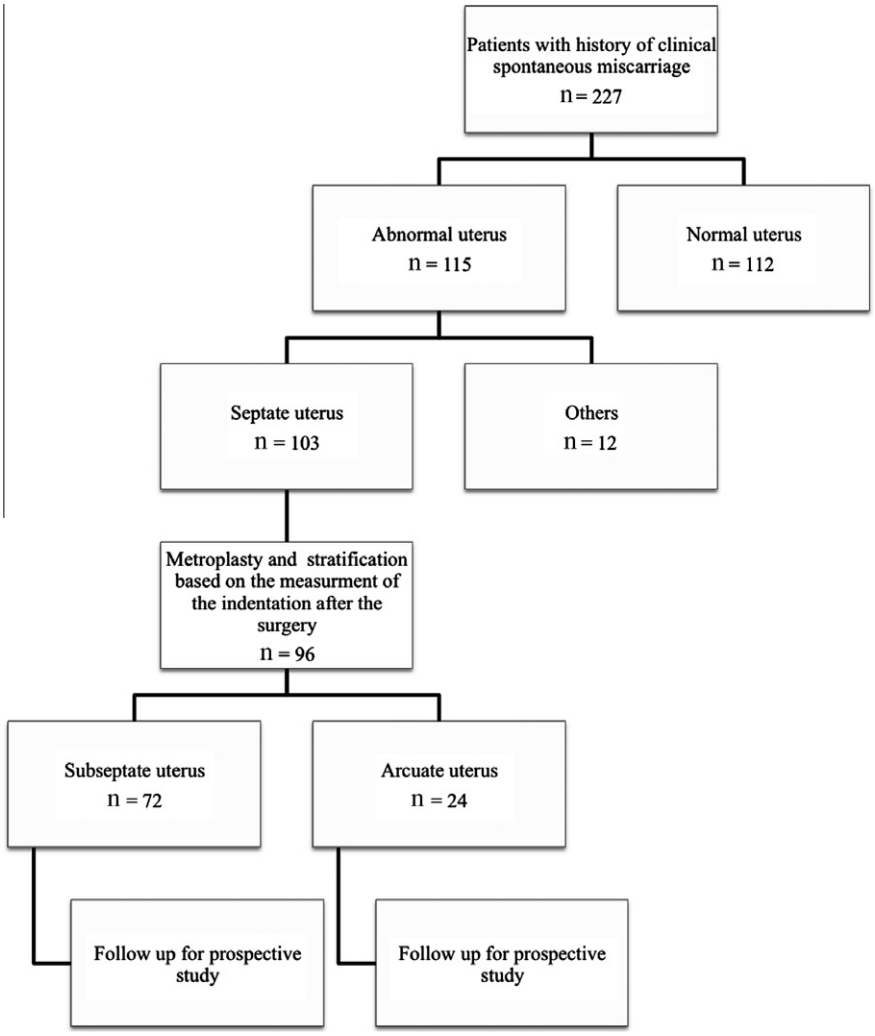

Figure 1 Flow chart of the study.

Figure 2 The 'cat eyes sign', a characteristic separation of the endometrial thickness in proximity to the fundus.

Only spontaneous conceptions and only first pregnancies after metroplasty were considered for statistical analysis.

All patients underwent vaginal 3D-US and/or office hysteroscopy within 3 months after surgery to exclude a residual septum. In four cases of incomplete correction, patients underwent a second surgery.

A database file was set up using Microsoft Excel for Mac (Redmond, WA, USA) to facilitate data entry and analysis. The recorded data were patient's date of birth and age on the day of surgery, body mass index, gravidity, parity and gynaecological history, with particular attention to previous operations and hormonal status (i.e. polycystic ovaries). Patients with anovulatory cycles, polycystic ovary syndrome and those referred to assisted reproduction treatment were excluded from the study (six patients).

The main outcome parameter studied was the miscarriage rate at the first post-operative spontaneous pregnancy. The secondary outcome parameters were the comparison of the time to conception before and after surgery and the final pregnancy outcome.

Statistical Package for Social Sciences version 18.0 (SPSS, USA) was used for statistical analysis. Differences between groups were analysed by the Pearson's chi-squared test for categorical variables. Kolmogorov—Smirnov test showed a non-normal distribution of the variables 'time to conceive

Table 1 Obstetric outcome before and after metroplasty in both groups.

Outcome	*Septate uterus (n = 72)*		*Arcuate uterus (n = 24)*	
	Before	*After*	*Before*	*After*
Pregnancy seeking (months; median, range)	18 (2–120)	4.9 (0–40)	18 (3–108)	4.4 (1–25)
Pregnancies	140	57	39	18
Deliveries	22 (15.7)	48 (84.2)	1 (2.6)	16 (88.9)
Miscarriages	115 (82.1)	8 (14.0)	37 (94.9)	2 (11.1)
Ectopic	3 (2.1)	1 (1.8)	1 (2.6)	0

Values are *n* (%) unless otherwise stated.

before surgery' and 'time to conceive after surgery'. Due this abnormal distribution, the Wilcoxon Mann–Whitney non-parametric test was used for analysis of those variables. *P*-values <0.05 were considered significant.

Results

Ninety-six patients, who experienced one or more miscarriages and underwent hysteroscopic metroplasty, were allocated to either the septate or the arcuate uterus group. The first group included 72 women with an incomplete septum of 1.5 cm or more (subseptate uterus group), whereas the second group included 24 patients with a septum smaller than 1.5 cm (arcuate uterus group). The mean age on the day of surgical procedure was 31.33 ± 2.67 years in the subseptate uterus group versus 31.41 ± 2.34 years in the arcuate uterus group (not significant), and body mass index was 21.64 ± 3.11 kg/m^2 versus 21.58 ± 3.28 kg/m^2 (not significant). The obstetric history, in terms of delivery and miscarriage rates, did not differ between the two groups.

Before metroplasty, 72 patients from the subseptate group achieved 140 spontaneous pregnancies, of which 115 (82.1%) miscarried, three (2.1%) were ectopic and 22 (15.7%) delivered viable babies. Similar poor reproductive outcomes occurred in the 24 patients with arcuate uterus, who achieved 39 spontaneous pregnancies of which 37 (94.9%) miscarried, one was ectopic and only one pregnancy delivered at term (**Table 1**). After metroplasty, 57 patients in the subseptate uterus group (79.2%) and 18 patients in the arcuate uterus group (75.0%) conceived spontaneously. The time needed for achieving a pregnancy after surgery was significantly shorter in both groups after metroplasty ($P < 0.001$) (**Figure 3**). Comparing the two groups, the median time to spontaneous conception was 4.9 months in the subseptate group versus 4.4 months in the arcuate uterus group (not significant). The improvement of pregnancy outcome was similar in both groups. The term delivery rate was 84.2% in the subseptate group, with a spontaneous miscarriage of 14.0% and an ectopic pregnancy rate of 1.8%, versus 88.9% in the arcuate group, with a miscarriage rate of 11.1%. The differences in pregnancy outcomes between the two groups were not significant (**Table 2**).

No complications occurred either during the surgical procedures or during the pregnancy, labour and delivery. In particular, no cases of placenta increta or accreta or uterine rupture were observed.

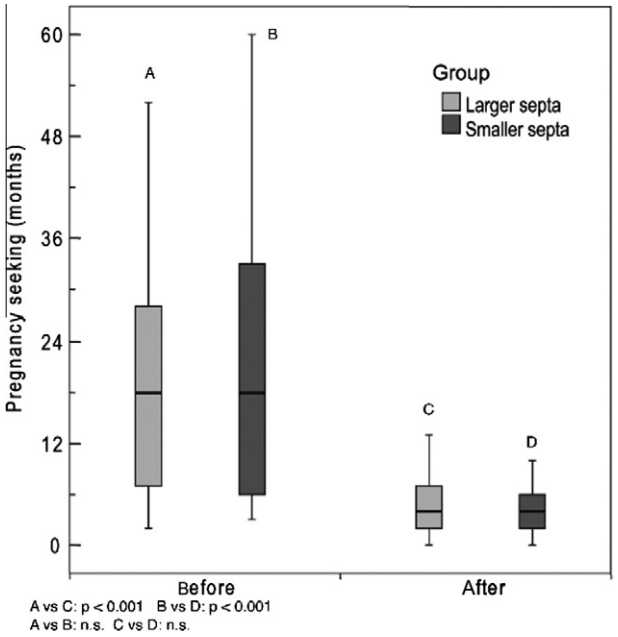

Figure 3 Pregnancy seeking before and after surgery. The median time to conceive before surgery was 18 months in both the subseptate and arcuate uterus groups. After surgery, the median time to conceive was 4.9 months in the subseptate uterus group and 4.4 months in the arcuate uterus group (not significant). Box = upper and lower quartiles; whiskers = minimum and maximum. Septate or subseptate (partial septate) uterus = American Fertility Society class V; arcuate uterus = class IV.

In this population, there were three cases of preterm deliveries. In one patient from the subseptate uterus group, pre-eclampsia occurred at week 30 of pregnancy and healthy twins were born after Caesarean section. Two women delivered between weeks 35 and 36, while the remaining patients delivered after week 37. The incidence of prematurity was 4.6%. This incidence fits with that observed in the general population of pregnant women in the study country, according to the National Perinatal Informative System of Slovenia from the last 10 years: 6.5% (range 6.2–6.8%). Furthermore, in the two University tertiary centres, the prematurity rate is 9–10%, whereas in the remaining hospitals in the country, including the present setting, it is 4–5%. Cerclage does not seem to be clearly

Table 2 *P*-values comparing time of pregnancy seeking and pregnancy failure before and after metroplasty and between the septate and arcuate uterus groups.

	Before versus after metroplasty		*Septate uterus versus arcuate uterus*	
	Septate uterus	*Arcuate uterus*	*Before metroplasty*	*After metroplasty*
Pregnancy-seeking duration[a]	$P < 0.001$	$P < 0.001$	NS	NS
Pregnancy failure rate[b]	$P < 0.001$	$P < 0.001$	NS	NS

NS = not significantly different.
[a]Mann–Whitney test.
[b]Chi-squared test.

indicated after metroplasty, which is why it is not included in patient management after metroplasty in the study centre. All patients had a normal cervical anatomy and this study differentiated only between a large and a small septum.

Mean pregnancy duration was 39.52 ± 2.40 weeks in the subseptate uterus group and 39.53 ± 2.43 weeks in the arcuate uterus group (not significant), including the premature deliveries described above.

Discussion

The most commonly used and accepted classification is the American Fertility Society (AFS) classification. The AFS has defined the arcuate uterus separately from the partial and total septate uterus, under the belief that the arcuate uterus is a benign form with no or minimal influence on the reproductive outcome (American Fertility Society, 1988). Several authors have not only questioned the allocation of the arcuate uterus to an individual class, but also the possible negative influence of the reproductive capacity of the arcuate uterus has been debated (Grimbizis et al., 2001; Saravelos et al., 2010; Tomaževič et al., 2010; Woelfer et al., 2001).

In medicine, categorization enables a better understanding of disease processes, more precise diagnosis and effective treatment. The accurate diagnosis of an arcuate uterus is not possible with the commonly used diagnostic methods. Hysterosalpingography has proven to be insufficient as it does not provide any information regarding the outer shape, whereas laparoscopy and hysteroscopy do have their limitations for minor malformations (Pundir and El Toukhy, 2010; Saravelos et al., 2008). Although two-dimensional ultrasound, with the possibility of sonohysterography, was a major non-invasive step forward in the diagnosis of congenital malformations (Ludwin et al., 2011), the real improvement was made with the introduction of 3D-US, enabling the physician to estimate both the endometrial cavity and the outer shape of the uterus in a more accurate and patient-friendly way (Bermejo et al., 2010; Saravelos et al., 2008). 3D-US obtains the coronal vision in a systematic way, thus making evident the relationship between cavity and fundus and making possible exact measurements, such as the depth of the septum and the volume of the cavity (Caliskan et al., 2010). Today 3D-US is not generally available but it is expected that in the near future this technology will be broadly available. Also magnetic resonance imaging (MRI) provides high accuracy for the diagnosis of complex anomalies and myometrial deformations (Pellerito et al., 1992; Troiano and McCarthy, 2004), but is not very accurate in differentiating subseptate from arcuate uterus. In a retrospective study, Mueller et al. (2007) reported discordance between MRI and clinical diagnosis in nine out of 30 cases, which could be the cause, according to the authors, of an 'unnecessary surgery'. The disagreements in the diagnosis between experts in abdominal MRI and clinicians were definitely reallocated by expert clinicians, involved in infertility surgery. In all cases the anomaly diagnosed by MRI, an objective and reproducible tool, was 'downsized' by the subjective decision of experienced clinicians. The lack of uniformity in the differentiation of either septate or arcuate uterus and the bypassing of a tool such as MRI, by several clinicians, is maybe another reason to abandon the old AFS classification or at least the differentiation between septate and arcuate uterus. An Italian group, combining data from 3D-US and office hysteroscopies, produced a geometric model system for arcuate and septate uterus in order to address a more precise definition of the uterine anomaly and to overcome the definition of arcuate uterus (Gubbini et al., 2009). Uterine septum length and fundus thickness were the two parameters considered. According to the indentation, the authors reclassified the septate uterus not in function of the clinical behaviour, such as the AFS classification, but on the ratio between the indentation and the remaining cavity (0.5 cm, less than one-third, more than one-third and complete) The aim of this classification was to choose the most appropriate tool for the metroplasty and not to give a prognosis on pregnancy outcome based on the depth of the indentation.

The grade of the distortion of the uterine cavity, which can be clinically relevant, has been matter of discussion. In a prospective study, Salim et al. (2003) tried to explain which kind of uterine congenital anomaly has adverse effects on pregnancy outcome. The ratio between fundal distortion of the cavity and its length, measured by 3D-US, was found to be more important in a recurrent miscarriage group, rather than the type of malformation (arcuate or septate).

In a series that included 826 singleton deliveries of 730 women with a previous hysteroscopic metroplasty, Tomaževič et al. (2007) detected an improvement in the pregnancy outcome after metroplasty both in the subseptate uterus and arcuate uterus groups. He concluded that the clinical behaviour of the arcuate uterus is not different from that of septate uterus. On the other hand, Woelfer et al. (2001) reported a higher proportion of first-trimester

pregnancy loss only in women with a subseptate uterus, whereas arcuate uterus was linked with a higher incidence of second-trimester loss and preterm labour.

Kupesic and Kurjak (1998) found no correlation between septal dimension and rate of obstetric complications. Using colour and pulsed Doppler sonography the authors report a higher prevalence of obstetric complications in particular in patients with vascularized septa. A vascular aberrancy in the arcuate uterus, identified by MRI, has also been reported (Troiano and McCarthy, 2004). Furthermore, every mentioned study is limited by the lack of a correct and universal definition and classification of septate and arcuate uterus.

The present results corroborate the belief supported by data from the literature that there is no scientific basis for a separate classification of the arcuate uterus. Since the clinical behaviour, either before or after surgery is not significantly different between patients with arcuate or septate uterus, there is no sense in discriminating the types of malformation into two different classes. For this reason this study supports the proposal of other authors for a review of the current classification and a provision of a universal and correct definition of septate uterus (Grimbizis and Campo, 2010).

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