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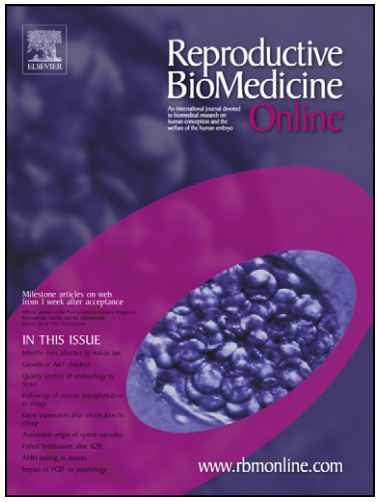

Article

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Marco Gergolet, Luca Gianaroli, Nataša Kenda– Šuster, Ivan Verdenik, M. Cristina Magli, S. Stephan Gordts

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Running head: Role of endometriosis on pregnancy outcome in women with septate uterus

Possible role of endometriosis in the aetiology of spontaneous miscarriage in patients with septate uterus

Marco Gergolet (1), Luca Gianaroli (2), Nataša Kenda–Šuster (3), Ivan Verdenik (3), M. Cristina Magli (2), Stephan Gordts, S. (4.)
1: S.I.F.E.S. Slovene Institute for Fertility and Endoscopic Surgery, Nova Gorica, Slovenia
2: S.I.S.ME.R. Reproductive Medicine Unit, Bologna, Italy
3: Department of Obstetrics and Gynecology, University of Ljubljana, Slovenia
4: L.I.F.E. Leuven Institute for Fertility and Embryology, Leuven, Belgium

Abstract

A recent study found a significant correlation between endometriosis and non-obstructive forms of Müllerian anomalies. Other studies described an increased miscarriage rate in patients with endometriosis. This study assessed the effect of endometriosis on pregnancy outcome in a group of patients with endometriosis and septate uterus. Spontaneously achieved pregnancies were taken into consideration. The outcome of 179 infertile women who underwent surgery for septate uterus was analysed in a retrospective study. Stage I or II endometriosis was found by laparoscopy in 36 patients. The pregnancy outcomes, before and after metroplasty, of the group of 36 patients with septum and endometriosis were compared with the pregnancy outcomes of 143 patients with septate uterus with no endometriosis. Before metroplasty the incidence of pregnancy loss was 67% in patients without endometriosis and 75% in patients with endometriosis and the difference was not significant. After metroplasty, no significant differences have been found between the two groups, suggesting that endometriosis could be an occasional finding not influencing pregnancy outcome.

Keywords: *congenital uterine anomalies, endometriosis, miscarriage, septate uterus*

Introduction

Septate uterus is commonly recognized as one of the main factors causing pregnancy loss or premature delivery and is the most common Müllerian anomaly observed (Acièn, 1997). The incidence of this anomaly in a population of women with three or more spontaneous miscarriages is on average 15% (Grimbizis *et al.*, 2001; Saravelos *et al.* 2009), while higher incidences have been reported in a few studies (Salim *et al.*, 2003, Proctor et Haney, 2003). In studies on the general population, a significant convergence has been found between the history of recurrent miscarriages or preterm delivery and the presence of a septate or bicornuate uterus (Maneschi *et al.*, 1995). Several other studies confirmed a direct correlation between septate uterus and spontaneous miscarriages and/or fetal malpresentations (Grimbizis *et al.*, 2001; Proctor et Haney, 2003; Zabak *et al.*, 2001). Metroplasty dramatically improves the

pregnancy outcome with a concomitant decrease of the miscarriage rate and an increase of live birth rate (Doridot *et al.*, 2003, Pabuccu and Gomel 2004).

A correlation between endometriosis and spontaneous miscarriage has been reported by other studies (Metzger *et al.* 1986, Olive *et al.* 1982). A direct correlation between the miscarriage rate and severity of endometriosis has not been proven (Pittaway *et al.* 1988). Several authors reported a decreased miscarriage rate after surgical therapy of endometriosis (Wheeler *et al.* 1983, Donnez *et al.* 2002), whereas others did not find any difference (Matorras *et al.* 1998, Parazzini *et al.* 1999).

Endometriosis has been described to be more frequent in women with Müllerian duct anomalies. Reflux bleeding should be cause for a celomatic metaplasia and a successive formation of endometriotic implants (Olive *et al.* 1987). Other studies referred to a correlation between endometriosis and obstructive Müllerian anomalies but exclude a link with non-obstructive anomalies, because it would implicate a different, embryogenic origin of endometriosis (Fedele *et al.* 1992, Ugur *et al.* 1995). Recent studies correlated non-obstructive Müllerian anomalies with an increased incidence of endometriosis. Nawroth *et al.* (2006) observed a higher incidence of endometriosis in women with non obstructive forms of Müllerian anomalies like septate uterus. The aim of the present retrospective study was to verify whether endometriosis is an additional risk factor for pregnancy loss in patients with septate uterus before and after metroplasty.

Materials and methods

A total of 246 infertile patients underwent hysteroscopic metroplasty for uterine septum during the period from January 2000 to December 2008. Since only spontaneous conceptions have been taken into consideration, 179 were included in the present retrospective study. Cases with male factor infertility, patients with bilateral tubal pathology and women with ovulatory disorders were excluded from the study. Unilateral tubal occlusion or ‘status post’ salpingectomy due to ectopic pregnancy were included in the study.

Uterine septum was diagnosed by vaginal ultrasound by looking for a presence of a separation in the endometrial thickness at the fundal level. Ultrasound findings were confirmed by office diagnostic hysteroscopy (Campo *et al.* 1999). Laparoscopy was performed to assess other possible causes of infertility. Endometriotic foci were coagulated by bipolar electrocautery, at the time of laparoscopy. In couples with primary infertility semen analysis was carried out. In couples with secondary infertility semen quality was supposed to be good due to the proven capability to fertilize, except in cases where spontaneous conception occurred 1 or more years before the hysteroscopic procedure. A karyotyping of the couple was performed to exclude genetic cause of pregnancy loss in women who suffered spontaneous miscarriage (i.e. first-trimester pregnancy loss) three or more times.

In order to avoid the bias of increased endometrial thickness, metroplasties were carried out between day 6 and 8 of the menstrual cycle. A Karl Storz monopolar operative hysteroscope (Tubingen, Germany) with mannitol sorbitol solution as a distension medium or, alternatively, an Olympus TCRis bipolar resectoscope with saline solution were used. Two authors (MG and NK) performed all the metroplasties. After achieving good visibility, the ostia were taken as orientation points and the

procedure was stopped when the fundus was aligned with the tubal ostia and the small arterial blood vessels became visible in the myometrial layer. All the patients underwent vaginal ultrasound 1 month after surgery to exclude a residual separation of the endometrial thickness.

A database file was set up using Microsoft Excel for Windows (Redmond, WA, USA) to facilitate data entry and retrieval. Recorded data were birth date and age on the day of the operation, body mass index, gravidity, parity and the duration of infertility before metroplasty. The presence of endometriosis detected during laparoscopy was also noted as well as the male status. In case of pregnancy after metroplasty, the data recorded were the date of last menstrual period, the time between surgery and last menstrual period, the pregnancy outcome, the day and the method of delivery, complications and weeks of pregnancy at delivery and the weight and sex of the newborn. Only the first pregnancy after metroplasty was taken into consideration.

Statistical analysis

Statistical Package for Social Sciences version 14.0 (SPSS, USA) was used for statistical analysis. Kolmogorov–Smirnov test showed abnormal distribution of the variables 'months of infertility before surgery' and 'months of infertility after surgery'. Due to this abnormal distribution a Wilcoxon Mann Whitney non-parametric test was used for analysing those variables. Differences between groups were analysed by the Pearson's chi-squared test. Cumulative clinical pregnancy rate was determined by life table analysis.

Results

Stages I and II endometriosis, according to the American Fertility Society classification (The American Fertility Society 1979 and 1985), were diagnosed by laparoscopy in 36 out of 179 (20.1%) patients with septate uterus undergoing hysteroscopic metroplasty. The pregnancy outcome in this group of patients was compared with the pregnancy outcome in the group of patients with septate uterus but without endometriosis (143 women) either before or after metroplasty (**Table 1**). The average age ± SD in the endometriosis group was 29.62 ± 4.5 years versus 29.41 ± 4.84 years in the group without endometriosis; the mean ± SD body mass index was 21.73 ± 3.28 kg/m^2 versus 21.63 ± 3.11 kg/m^2, respectively. The rate of secondary infertility was 36.1% in the endometriosis group versus 49.7% in the group without endometriosis.

Figure 1 presents the improvement in the time to pregnancy before and after metroplasty in both groups. The graph clearly shows the shortening of time to conception after metroplasty, which is similar between the two groups.

The incidence of spontaneous miscarriage before metroplasty was 75% in the group with septate uterus and endometriosis and 67% in the group with septate uterus and no endometriosis (not significant; **Table 2**).

After metroplasty, 95/143 (66.4%) women with septate uterus and no endometriosis and 20/36 (55.6%) women with septate uterus and endometriosis group conceived (**Table 3**). One-year cumulative pregnancy rates were 66.7% in the control group and 54.5% in the endometriosis group, while 2-year cumulative pregnancy rates reached

75.8% in the control group and 62.1% in the endometriosis group, although these differences were not statistically significant. Eighty-eight patients (92.6%) of the group without endometriosis and 16 patients (80.0%) delivered at term (**Table 4**). Mean ± SD week of delivery was at 39.84 ± 2.52 weeks of pregnancy in the group without endometriosis and 39.62 ± 2.94 weeks in the group with endometriosis. The miscarriage rate was 8.3% (8/96) in the group without endometriosis whereas in the endometriosis group it was 20% (4/20). The differences between groups were not statistically significant (**Table 4**).

Discussion

No differences were found between women with endometriosis and those without endometriosis either in the miscarriage rate before metroplasty or in the pregnancy outcome after surgery. Women entering the two groups were similar in several clinical characteristics such as average age, body mass index, history of infertility, parity and miscarriage rate. The only different variable was the presence or the absence of endometriosis. According to these results, the miscarriage rate before surgery seems to be independent of the presence of endometriosis. The results of pregnancy outcome after metroplasty showed no significant differences between the two groups and endometriosis seems to be only an occasional finding. The data on time to conception before metroplasty and cumulative pregnancy rate after metroplasty were similar between the two groups.

The influence of endometriosis on miscarriage rate is controversial. An increased concentration of macrophages, cytokines and other immunological mediators in the abdominal cavity seems to have an embryotoxic effect (Halme and Surrey 1990). Endometriotic cells in culture produce interleukin 6, which is considered to have negative effects on early implantation (Punnonen *et al.* 1996). Wheeler observed an improved pregnancy outcome after conservative surgical treatment of endometriosis, but the same author expressed doubts about surgery as an effective tool to reduce miscarriage rate. Looking for other co-factors, leading to this improvement, he postulated a more accurate care of the patients after the first miscarriage (Wheeler *et al.* 1983). Other studies did not confirm a direct correlation between pregnancy loss and the degree of severity of endometriosis (Pittaway *et al.*, 1988, Vercammen *et al.* 2000). The surgical treatment of stage I endometriosis did not reduce the miscarriage rate in the series of Matorras *et al.* (1998).

Endometriosis was found in 20.1% of the present study's population and is comparable to the prevalence reported from above mentioned studies. Although endometriosis was found in 11.2% of women with congenital uterine anomalies, Acien (1992) refuses any correlation between them. In a series of 46 patients who underwent surgery for septate uterus, Grimbizis *et al.* (1998) described an incidence of endometriosis of 26.1%. In a retrospective study, 120 women with a septate uterus were compared with 486 infertile women with a normal uterus, assessed by hysteroscopy and laparoscopy. The incidence of dysmenorrhoea was similar in the two groups whereas the incidence of endometriosis was higher in the group of patients with septate uterus (25.8%) compared with the group with a normal uterus (15.2%). The hypothesis, referring also to other authors (Leydenecker *et al.* 2004), is that abnormal uterine peristaltic waves could lead to peritoneal colonization of endometrial stem cells (Nawroth *et al.* 2006).

Batt *et al.* (2003) postulates two different clinical forms of endometriosis, according to the age of manifestation: an adolescent form with an early clinical manifestation and an adult one, which should have a different pathogenesis. The adolescent form of endometriosis occurs as a consequence of a metaplasia of Müllerian embryonic extrauterine residual inlets. The theory could provide a possible explanation of the increased incidence of endometriosis in women with Müllerian anomalies, even in non-obstructive forms. It could be postulated that defects in intrauterine development, could be due to a common genetic origin leading both to incomplete resorption of intervening septum and some types of endometriosis.

According to the literature, septate uterus may lead to an increased risk of miscarriage. In the present study, endometriosis does not seem to be a factor affecting pregnancy outcome either before or after metroplasty.

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Figure 1. The time taken for the conception to occur in the two groups: septate uterus without endometriosis and septate uterus with endometriosis. The time taken for conception to occur before and after surgery is comparable between the two groups. Box-and-whisker graphs represent the median (bold line), upper and lower quartiles (boxes) and minimum and maximum data values (whiskers).

Table 1. Comparison of biometric characteristics and obstetric history of with septate uterus before metroplasty.

History	n	*%*	*Age (years, SD)*	*BMI (kg/m^2, SD)*	*No. of primary infertility (%)*	*No. of secondary infertility (%)*
No endometriosis	143	79.9	31.33 (2.76)	21.64 (3.11)	72 (50.3)	71 (49.7)
Endometriosis	36	20.1	31.41 (2.34)	21.58 (3.28)	23 (63.9)	13 (36.1)

There were no statistically significant differences between the two groups.
BMI = body mass index.

Table 2. Pregnancy outcome in women with septate uterus before metroplasty.

History	*No. of pregnancies*	*No. of miscarriages (%)*	*No. of ectopic pregnancies (%)*
No endometriosis	120	80 (66.7)	10 (8.3)
Endometriosis	20	15 (75.0)	0 (0.0)
Total	140	95 (67.9)	10 (7.1)

There were no statistically significant differences between the two groups.

Table 3. Cumulative pregnancy rate after metroplasty in women with septate uterus as determined by life table analysis.

History	*Interval start time (months)*	*Number entering interval*	*Number withdrawing during interval*	*Number trying to conceive*	*No. of all pregnancies*	*Pregnancy rate (%)*	*Cumulative pregnancy rate at end of interval*
No endometriosis	0	143	28	129	86	67	66.7
	12	29	14	22	6	27	75.8
	24	9	4	7	3	43	86.1
Endometriosis	0	36	6	33	18	55	54.5
	12	12	0	12	2	17	62.1
	24	10	6	7	0	0	62.1

There were no statistically significant differences between the endometriosis and control groups.

Table 4. Outcome after metroplasty in women with septate uterus.

Outcome	*No endometriosis (*n = *143)*	*Endometriosis (*n = *36)*
Conceived	95 (66.4)	20 (55.6)
Miscarriage (of all patients)	8 (5.6)	4 (11.1)
Miscarriage (of all pregnancies)	8 (8.3)	4 (20.0)

Values are *n* (%).
The difference in the miscarriage rates between the two groups did not reach statistical significance, either comparing to the whole studied population or only to those who conceived.

SUMMARY FOR LAY READERS

Septate uterus is a relatively common minor anomaly. The septum may be complete, which is rare, or incomplete. In incomplete cases, the uterus is divided in two cavities or, more often, hemi cavities by a midline indentation of the fundus. Endometriosis is described as a cause of increased miscarriage rate. It is characterized by the presence of the mucosa covering the internal part of the uterus outside the uterus, most of times in the abdominal cavity in the form of peritoneal implants, like hundreds of pinpoints, or in the form of ovarian (chocolate) cysts. The connection between obstructive forms of Müllerian anomalies and endometriosis is commonly accepted, according to the theory of retrograde reflux of menstrual blood throughout the tubes. Few studies found an increased incidence of endometriosis even in women with non-obstructive forms of Müllerian anomalies such as septate uterus. The aim of our study was to assess the hypothesis that, even in patients with endometriosis, uterine septum is the cause that leads to miscarriage. Before surgical correction of septate uterus, the incidence of miscarriage was 67% in patients without endometriosis and 75% in patients with endometriosis. After surgery, a clear reduction of miscarriage rate was obtained, but no difference between the two groups was found. In our study, increased abortion rate depends more likely on uterine malformations than on endometriosis. Endometriosis seems to be an occasional finding not influencing pregnancy outcome.

Marco Gergolet studied medicine at University of Trieste, Italy. In 1992 he moved to Ljubljana, Slovenia. In 1998 specialized in obstetrics and gynaecology and became senior clinician at the reproductive medicine unit in SISMER, Bologna. In 2003 he was elected Assistant Professor at Ljubljana University School of Medicine. In 2008 he obtained an MSc with a thesis on the influence of uterine anomalies on miscarriage rate in women with endometriosis. Between 2006 and 2008 he was deputy coordinator and since 2009 has been coordinator of the Special Interest Group on Reproductive Surgery at European Society of Human Reproduction and Embryology.