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REPRODUCTIVE OUTCOME AFTER HYSTEROSCOPIC METROPLASTY IN PATIENTS WITH INFERTILITY AND RECURRENT PREGNANCY LOSS

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A b s t r a c t: *Introduction:* Patients with uterine malformations have decreased reproductive potential and an unfavourable reproductive outcome starting even from the first pregnancy. Patients with untreated uterine malformations have a term delivery rate of 40%–65%. Hysteroscopic metroplasty is a standard, safe and minimally invasive method for treatment of uterine malformations, which provides a normal uterine cavity in patients with hysteroscopically correctible types of uterine malformations.

The aim of the study was to analyse the variables associated with reproductive outcome before and after hysteroscopic metroplasty.

Material and methods: We analysed the variables determining reproductive outcome after 216 interventions with hysteroscopic metroplasty in 202 patients which were done at the University Obstetrics and Gynecology Clinic in Skopje during a three-year period, from 01.01.2006 to 31.12.2008. Patients were divided into three groups: patients with recurrent pregnancy loss, patients with secondary infertility and foetal loss and patients with primary infertility. The follow-up period lasted for two years (24 months). Statistical analysis was performed using the Chi-square test and $p < 0.05$ was considered to be statistically significant.

Results: During the follow-up period of two years after hysteroscopic metroplasty there were a total of 113 pregnancies, of which 46 belonged to the group of primary infertility. Analysis of the reproductive outcome of those patients (compared before and after hysteroscopic metroplasty) showed a significant ($p < 0.05$) decrease in the abortion rate from 89.6% to 12.4%, as well as an increase of term delivery rate from

1.4% to 74.4%. In the group of preterm deliveries there was a rise from 9% to 13.2%, which was not significant. The group of primary infertility had a pregnancy rate of 36%.

Conclusion. Hysteroscopic metroplasty significantly improves the reproductive outcome in patients with surgically correctible uterine malformation.

Key words: hysteroscopy, reproduction, infertility.

Introduction

Congenital anomalies of the female reproductive tract (Mullerian anomalies) are a heterogeneous group of genital malformations, which can involve uterus, cervix, vagina and Fallopian tubes. They represent the majority of reproductive tract anomalies and can seriously influence the reproductive and obstetric health of women depending on the specificity of the anomaly.

According to the newest available data, the incidence of congenital uterine anomalies is around 5% in women with a normal reproductive history, 3–5% in infertile women, 5–10% in women with recurrent abortions in the first trimester, and more than 25% in women with recurrent pregnancy loss [1–3]. Uterine septum is the most common congenital anomaly of the reproductive organs with an incidence of 2–3% in the general population [4].

Embiologicaly, malformations of the Mullerian ducts consist of different groups of congenital anomalies, resulting from arrested development, abnormal development or incomplete fusion of the paramesonephric ducts [5].

The etiology of the congenital anomalies of the female reproductive tract is inadequately explained. Kariotype is normal (46XX) in most of the women with Mullerian anomalies (92%) [6]. There are many hypotheses and theories implicating genetic factors, environmental and pharmacological influences. Family research is inadequate, because some of these women with anomalies have no symptoms and can have a normal reproductive history. The infrequent and sporadic nature of these anomalies can suggest a polygenic or multifactorial mechanism [7].

In clinical practice, classifications made by Buttram and Gibbons [8], and later adopted by the American Fertility Society (AFS) in 1988 [9], classify the anomalies of the female reproductive tract depending on the degree of failure of normal development, in groups of similar clinical manifestations, treatment and prognosis for their reproductive outcome.

The combination of hysteroscopy and laparoscopy is a standard, safe and minimally invasive method for precise detection, classification and treatment of uterine malformations [10–14].

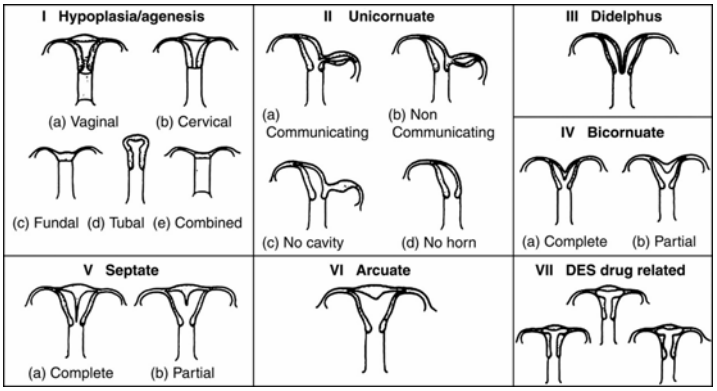

Figure 1 – Shematic presentation of AFS classification

Uterine malformations (UM) are associated with an abnormal uterine cavity, which is considered to be one of the reasons influencing the reproductive outcome of these patients. Obtaining a normal uterine cavity is the basis of the treatment. A good surgical correction of the uterine cavity does not necessarily result in a favourable reproductive outcome since uterine vascularization is probably involved in the uterine function. The theory which is nowadays widely accepted states that the septum consists of fibroelastic tissue with inadequate vascularization and a changed ratio between blood vessels of the endometrium and myometrium, presenting negative effects on decidualisation and placentation [15].

The introduction of operative hysteroscopy has regained the interest in transcervical techniques for the treatment of congenital uterine malformations, because it simplifies and alleviates the procedure. Hysteroscopic metroplasty has all the benefits of a good operative treatment: decreased intra- and postoperative morbidity, short-time intervention, less analgesic requirements, shorter hospital stay, shorter interval to conception and possibility of a vaginal delivery.

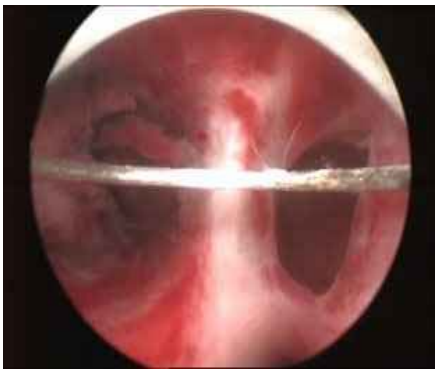

Figure 2 – Hysteroscopic metroplasty in uterus septus

These features make hysteroscopic metroplasty superior and a method of choice compared to abdominal metroplasty.

Most research findings have revealed that the majority of uterine malformations (> 55%) are presented with septate and arcuate uterus (type 5 and 6 according to AFS classification), which can be effectively treated by means of operative hysteroscopy [2, 15, 16].

Hysteroscopic metroplasty obtains a normal uterine cavity, but also resolves the normal uterine function, by providing a normal reproductive outcome in these patients [17–19]. Partial reconstruction of the uterine cavity by hysteroscopy is possible in some cases of partial bicornuate uterus (type 4b) [20].

Influence on reproductive outcome

The presence of uterine malformations can influence the reproductive outcome by increasing the rate of abortions, preterm deliveries, and obstetric complications [21]. Patients with uterine malformations have decreased reproductive potential and an unfavourable reproductive outcome, starting even from the first pregnancy. The overall term pregnancy rate in patients with untreated uterine malformations is around 50%. Patients with uterus didelphus and unicornuate uterus have a term delivery rate of ~ 45%, and pregnancies with untreated septate and bicornuate uterus of ~ 40%. In patients with arcuate uterus the reproductive outcome is slightly better, with term delivery rate of ~ 65% [14].

In 1993 Acien [22] compared the reproductive outcome in 173 patients with untreated uterine malformation who had 383 pregnancies, and a second group of 28 patients with normal uterus and 47 pregnancies. The abortion rate in patients with uterine malformations was 36%, and the preterm delivery rate was 18%, which was significantly higher ($p < 0.01$) than the rate of abortions of 8% and preterm delivery rate of 6% in patients with a normal uterus. The term delivery rate in patients with uterine malformations was 44% and the live birth rate was 53%, which was lower and statistically significant ($p < 0.001$) compared with the group with normal uterus where term delivery rate was 85% and live birth rate of 89%.

The aim of this study was to analyse the reproductive outcome before and after hysteroscopic metroplasty, which obtained a normal uterine cavity in hysteroscopically correctible types of uterine malformations.

Material and Method

We analysed 239 hysteroscopic metroplasty interventions performed at the University Obstetrics and Gynecology Clinic in Skopje during a three-year

period, between 01.01.2006 and 31.12.2008. Inclusion criteria for the study was diagnosis of uterine malformation of correctible types (4b, 5a, 5b and 6), according to the AFS classification, and exclusion criteria were existence of intrauterine pathology (intramural and submucous myoma, polyp, etc.) and age above 37 years at the time of the intervention (to exclude bias due to the patient age).

Inclusion criteria were met by 202 patients, who underwent 216 interventions. Patients were divided into three groups: patients with recurrent pregnancy loss (RPL), patients with secondary infertility and previous pregnancy loss, and patients with primary infertility. Patients and their reproductive outcome were monitored during a two-year period and the same group served as a control group for themselves, taking into account their previous reproductive history before and after metroplasty. Hysteroscopic metroplasty was done after previously signed informed consent by the patient.

Intervention was done with endoscopic equipment (Olympus and Storz types), using a rigid hysteroscope of 5.5 mm and a resectoscope of 8 mm, in general anesthesia and sterile conditions. Monopolar current was used for the resection, with 50–70W strength and a special electrode (eza needle) of 4 mm length. A mixed solution Ispirol® (solution of 2.7% sorbitol and 0.54% manitol) sterile and apyrogenic in a 3 litre package served as a distension media.

The procedure starts with the patient placed in a lithotomic position, after previous disinfection of the operative field and vagina. Then vagina is pulled forward with a tenaculum and dilatation is done using Hegar dilatators; the hysteroscope is placed transcervically into the uterine cavity. After visualization of both tubal ostia, resection of the septum starts in the midline between the anterior and posterior uterine wall and continues cranially towards the end point. The nd point is the moment when the following has been achieved: the hysteroscope can move freely from one ostium to the other without obstruction, when both ostia are easily visualized from the upper part of the cavity or when more intensive bleeding starts from the place of the resection as a sign of proximity to the junction between the septum and the myometrium. When a bigger septum is present or uncertainty is present about achieving the end point of the resection, intervention is interrupted and the patient is assigned for a control ultrasound and eventual re-resection.

In order to make a correct diagnosis of the uterine malformation or due to infertility, in several patients laparoscopy was done. During the procedure for hysteroscopic metroplasty laparoscopic control is not necessarily needed.

The following variables associated with the reproductive outcome were monitored in our group of patients: pregnancy rate (whole number and each group separately), abortion rate, preterm delivery rate and term delivery rate.

Data were analysed using the SPSS programme for Windows, version 11.0. Statistical analysis was done using the Chi-square test and a p-value of 0.05 was considered to be statistictically significant.

Results

The 202 patients were divided into three groups: the group with recurdrent pregnancy loss consisted of 31 patients (15.3%); the group with seconddary infertility consisted of 52 patients (25.7%) and the group with primary infertility consisted of 119 patients (59%).

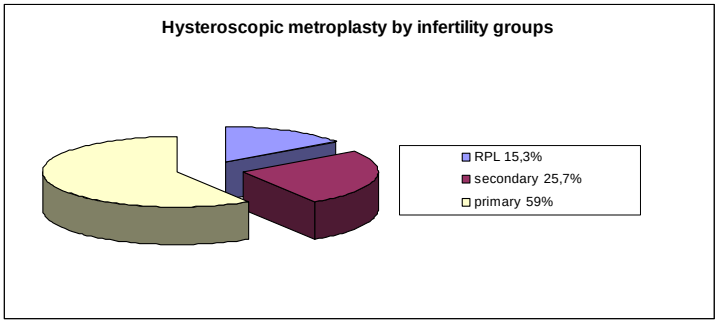

Figure 3 – Graphic presentation of hysteroscopic metroplasty by infertility groups

Thirty-six interventions (16.7%) were done in the group of patients with RPL, 53 (24.5%) in the secondary infertility group and 127 (58.8%) intervenetions in the primary infertility group.

Table 1

Number of patients, metroplasty and re-metroplasty done

	Number of interventions	Number of patients	Number of reinterventions
RPL	36	31	5
Secondary infertility	53	52	1
Primary infertility	127	119	8

Comparing the number of diagnosed anomalies – the largest number of 158 (78%) hysteroscopic metroplasties were done in the group of patients with arcuate uterus (type 6), followed by the group of patients with partial bicornuate uterus (type 4b) – 20 cases (10%) and the group of patients with partial septate uterus (type 5b) – 19 cases (9.4%). The smallest number of patients – 5 (2.5%) were those with complete septate uterus (type 5a).

The comparison of different groups of patients showed a statistical significance in the increased frequency of type 4b and 5a (partial bicornuate and complete septate uterus) in the group of patients with RPL (19.4%) in com-

parison with the groups of secondary and primary infertility where they were represented by 11.5% and 11% ($p < 0.05$), respectively. In contrast, types which are most often presented in the literature (5b and 6 – partial septate uterus and arcuate uterus), were found in our analysed groups in 80% of the RPL group, and up to 88.5% and 89% in the secondary and primary infertility groups, respectively.

Table 2

Frequency of certain types of UM by groups

Type of UM	RPL (%)	Secondary infertility (%)	Primary infertility (%)	Total (%)
4b	4 (12.9%)	4 (7.7%)	12 (10%)	20 (10%)
5a	2 (6.5%)	2 (3.8%)	1 (0.8%)	5 (2.5%)
5b	7 (22.6%)	6 (11.5%)	6 (5.2%)	19 (9.4%)
6	18 (58%)	40 (77%)	100 (84%)	158 (78%)
Total	31 (100%)	52 (100%)	119 (100%)	202 (100%)

According to the need for re-intervention (repeating the hysteroscopic metroplasty and resecting the residual septa) and types of UM, the need to re-intervene was greater in the groups with types 4b and 5a (32%), followed by types 5b and 6 (3.4%). This was to be expected since such types of uterine malformations have a bigger septum or indentation of the uterine fundus, requiring more careful resection and care not to perforate the uterus.

Table 3

Types of UM and need for re-intervention

Type of UM	Number of patients	Re-interventions	Re-reinterventions	Total repeated HM by groups
4b	20	5 (25%)	0	8 (32%)
5a	5	2 (40%)	1 (20%)	
5b	19	5 (26.3%)	0	6 (3.4%)
6	158	1 (0.6%)	0	

In the two-year period following hysteroscopic metroplasty, there were 113 pregnancies in these patients, of which 46 pregnancies belonged to the group with primary infertility. Analysis of the reproductive outcome in those patients (before and after hysteroscopic metroplasty) showed a statistical decreease ($p < 0.05$) of the abortion rate from 89.6% to 12.4%, as well as an

increase in the term delivery rate from 1.4% to 74.4%. In the group of preterm delivery there was no statistical difference (9% vs. 13.2%). In the group of patients with primary infertility the pregnancy rate increased to 36%, which was a significant rise.

Table 4

Reproductive outcome before and after metroplasty

Variables	**Before metroplasty** % (n = 202) (144 pregnancies)	**After metroplasty** % (n = 202) (113 pregnancies)	**P value** *(S/NS)
Abortion rate	89.6% (129/144)	12.4% (14/113)	P < 0.01 (S)
Pre-term delivery rate	9% (13/144)	13.2% (15/113)	P < 0.1(NS)
Term delivery rate	1.4% (2/144)	74.4% (84/113)	P < 0.01(S)
Patients with primary infertility	59% (119/202)	36.1% (73/202)	P < 0.05 (S)

*S – significant, NS – non-significant

Discussion

Patients with congenital uterine malformations are the most significant group for the treatment and improvement of reproductive outcome. They include UM that are hysteroscopically correctible, and the types are: 4b (partial bicornuate), 5a (complete septate), 5b (partial septate) and 6 (arcuate uterus). Systematic analysis of the obtained data showed a significant improvement in their reproductive outcome before and after hysteroscopic metroplasty.

The analysis by Buttram and Golan [23, 24] showed that in patients with untreated septate uterus, usually associated with the worst reproductive outcome, the abortion rate was as high as 43%, while prematurity rate was 22.4%. Term delivery rate was 33%, with a live birth rate of 50.1%.

The reproductive outcome in patients with arcuate uterus (considered to be an easier degree of partial septate uterus) was also decreased, although slightly better than the rest of the uterine malformations. In the systematic review of Grimbizis from 2001 [14] where he analysed the results from previous studies by Raga, Buttram and Heinonen [2, 23, 25] in 102 patients with untreated arcuate uterus and the number of 241 pregnancies, the abortion rate was 25.8% and the prematurity rate was 7.5%. The rates for term delivery and live birth were 62.7% and 66%, respectively.

Analyses done in patients treated with hysteroscopic metroplasty usually divide the patients into three groups: patients with recurrent pregnancy loss, patients with secondary infertility and previous pregnancy loss, and patients with primary infertility. The first and the second groups are treated with hysteroscopic metroplasty as a treatment for their poor reproductive outcome, while patients with primary infertility are prophilactically treated the for prevention of expected spontaneous abortions and complications in pregnancy.

After performing hysteroscopic metroplasty, a significant decrease in rates of abortions and preterm delivery was reported in treated patients. In the analysis by Grimbizis in 2001, in patients who were pregnant after HM, the abortion rate was decreased to 16.4%, while the preterm delivery rate was only 6.4%, much lower than the previously mentioned rates in untreated septate uterus (44.3% and 22.4%, respectively). In contrast, a significant rise of term deliveries and live births was reported (76.3% and 83.2%), in comparison with the rates before the HM that were lower (33% and 50.1%, respectively) [14].

In the study done by Saygili in 2002 [26] the reproductive outcome was analysed in 361 patients with septate uterus and hysteroscopic metroplasty who were followed during 18 months after the surgical intervention. The overall pregnancy rate was 49.8%, and during the 18 months follow-up period 58% of them were term deliveries, and 18.8% preterm deliveries. In the group with previous spontaneous abortions a huge decrease in the abortion rate was noted, from 91.4% to 10.4%. In the primary infertility group the pregnancy rate was up to 27.6%. Research done by Fedele *et al*. in 2006, who were monitoring the reproductive outcome before and after HM, observed a decrease in the abortion rate from 80–90% to 20%, while the term delivery rate rose from 5% to 80% [21].

In recently published literature in 2011, Roy [27] analysed 170 cases with HM over a period of 8.5 years where a significant decrease of unsuccessful pregnancies rate was noted, from 91.5% before metroplasty to 12.5% after metroplasty, and an increase in term delivery rate from 2.5% to 79.5%. In the primary infertility group, the pregnancy rate increased to 56.5%.

The analysis of our material also showed a significant improvement in the reproductive outcome, which was in agreement with the published medical literature. The comparison of the results before and after HM revealed a significant decrease in the abortion rate from 89.6% to 12.4%, which was comparable with the analyseis of Roy, Fedele and Saygili [21, 27, 28]. In the analysed two-year period there was an even more significant improvement in the reproductive outcome resulting in a term delivery rate that increased from 1.4% to 74.4%, which was also significantly increased in all previously mentioned studies (from 50–80%) [14, 21, 26, 27]. This is a confirmation of the fact that obtaining a normal uterine cavity in cases with congenital uterine malformations

which have been hysteroscopically corrected, significantly influences not only the pregnancy rate, but also the capacity of the uterus for successful continuation of the pregnancy to term delivery. Moreover, it decreases the complications associated with the delivery and prematurity of the foetus.

In recent years, special interest has been placed on analysing patients with primary infertility and no other notable causes for the infertility (the so-called idiopathic infertility). In the absence of any other concomitant pathology – non existence of tubal factor, normal hormonal analysis, normal spermiogram and absence of uterine pathology (intramural and submucous), several studies were published that reported a significant increase in the fecundity rate and a better reproductive outcome in this group of patients.

Pabucu in 2004 made a prospective study following 61 patients with septate uterus and idiopathic infertility after hysteroscopic metroplasty during a 14-month period, and found a pregnancy rate of 41.5%, of which 73% had a successful pregnancy and live births, and 17% pregnancies were terminated with spontaneous abortion [28]. Mollo [29] in his publication in 2009, presented a prospective study comparing the reproductive outcome of patients with idiopathic infertility and septate uterus, where HM was performed, and a group of patients with idiopathic infertility and non-existing UM. After a follow-up of one year, he reported a significant increase in the pregnancy rate (38.6% vs. 20.4%) and in the live birth rate (34.1% vs. 18.9%). The presence of septate and arcuate uterus on abortion rates, preterm deliveries and term deliveries were suggested by Tomazevic some time ago, and partially presented in his reports and lectures [30, 31]. The reproductive outcome before and after HM was analysed in 1573 patients treated at the University Obstetrics and Gynecology Clinic in Ljubljana over a 10-year period. Thebortion rate, which was 78% before HM, dropped to 17% after HM. The preterm delivery rate was 35% before the operation and decreased afterwards to 7.5%. In patients with septate and arcuate uterus, the pregnancy rate for IVF/ET treatment increased from 13% and 14% to 23% and 26%, respectively. The study by Rai in 2009 [32] where he analyzed 72 patients with idiopathic infertility and HM showed a pregnancy rate of 45.8% in the follow-up period of one year. Twelve percent of this group had a spontaneous abortion and 15% had a preterm delivery.

The results of our study are in agreement with the already published research papers, showing a significant improvement of the reproductive outcome in patients with primary infertility before and after HM. During the two-year-follow-up period there was a pregnancy rate of 36% (46 pregnancies of 119 patients), which is comparable with the results of the previously mentioned authors, ranging from 23–45.8% [28–32]. This fact implies the possible influence of the septum on fecundity in these patients, with reasons not yet clearly defined. The theory that inside the septum there is an unbalanced ratio of a normal

uterine structure (more fibroelastic tissue with inadequate vascularisation and an unbalanced ratio between blood vessels of the endometrium and myometrium), is probably one of the explanations for a possible negative effect on decidualisation and placentation [22], which could be a reason for the existence of idiopathic infertility.

Conclusion

We have analysed the reproductive outcome before and after HM in patients diagnosed with recurrent pregnancy loss, secondary and primary infertility. A significant difference in the reproductive outcome has been noted in the decreased abortion rate and increased term delivery rates. Patients with idiopathic infertility have an increased fecundity rate after the treatment of the uterine malformation with hysteroscopic metroplasty. Hysteroscopic metroplasty significantly improves the reproductive outcome in patients where surgically correctible congenital uterine malformation exists.

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Р е з и м е

РЕПРОДУКТИВЕН ИСХОД ПО ХИСТЕРОСКОПСКА МЕТРОПЛАСТИКА КАЈ ПАЦИЕНТКИ СО ИНФЕРТИЛИТЕТ И РЕКУРЕНТНА ФЕТАЛНА ЗАГУБА

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А п с т р а к т: *Вовед:* Пациентките со утерини малформации имаат намален репродуктивен потенцијал и понеповолен репродуктивен исход, почнувајќи дури и од првата бременост. Пациентките со нетретирани утерини малформации имаат стапка на доносена бременост од 40–65%. Хистероскопската метропластика е стандардниот, безбеден и најминимално инвазивен метод за третман на утерините малформации, која овозможува добивање на нормална утерина празнина кај хистероскопски коректибилните типови на утерини малформации.

Цел на студијата е да се анализираат варијаблите поврзани со репродуктивниот исход пред и по хистероскопската метропластика.

Материјал и методи. Анализирани се варијаблите поврзани со хистероскопската метропластика и репродуктивниот исход кај 202 пациентки и направените 216 интервенции на Универзитетската клиника за гинекологија и акушерство во Скопје, во тригодишен период од 01. I 2006 до 31. XII 2008 година. Пациентките се поделени во три групи: пациентки со рекурентна фетална загуба, пациентки со секундарен инфертилитет со претходна фетална загуба и пациентки со примарен инфертилитет и се следени во тек на двегодишен период според метропластиката. Статистичката анализа е направена со употреба на X2 тест и вредноста $p < 0,05$ се определи за статистички сигнификантна.

Резултати: Во периодот на двегодишното следење кај пациентките имаше 113 бремености, од кои 46 бремености во групата со примарен инфертилитет. Репродуктивниот исход кај пациентките (компариран пред и по хистероскопската метропластика) има статистички значително ($p < 0,05$) намалување на стапката на абортуси од 89,6% на 12,4%, како и зголемување на стапката на термински породувања од 1,4% на 74,4%. Во групата на предвремени породувања нема статистички значителна разлика (9% vs. 13,2%). Кај групата со примарен инфертилитет има стапка на бременост од 36%.

Заклучок: Хистероскопската метропластика значително го подобрува репродуктивниот исход кај пациентките каде што постои хируршки коректибилна конгенитална утерина малформација.

Клучни зборови: хистероскопија, репродукција, инфертилитет.

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