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Clinical Science

Reproductive Outcome after Hysteroscopic Metroplasty in Patients with Infertility and Recurrent Pregnancy Loss

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Abstract

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Introduction: Reproductive outcome can be negatively affected in patients with congenital uterine anomalies (CUA), increasing the number of unsuccessful pregnancies and obstetric complications. Compared with the population with normally formed uterus, patients with CUA have higher abortion rate, higher fetal loss rate and decreased live birth rate. Hysteroscopic metroplasty (HM) is a standard, safe and minimally invasive method for the treatment of correctible types of congenital uterine anomalies.

Aim: The aim of the study was to analyze the reproductive outcome in group of patients with infertility and recurrent pregnancy loss and present CUA, before and after hysteroscopic metroplasty.

Material and Methods: We analyzed 67 patients to whom 78 interventions hysteroscopic metroplasty were performed at the University Clinic of Obstetrics and Gynecology in Skopje during a two year period, between 01.01.2010 and 31.12.2011. Their reproductive outcome was monitored during a two-year period and the same group served as a control group, taking into account their previous reproductive history. Statistical analysis was performed using Chi-square test and $p < 0.05$ was considered to be statistically significant.

Results: Most common CUA were types 5b and 6 represented by 88 %. In a follow up period of two years, 33 of the patients become pregnant. There was a statistically significant decrease of abortion rate from 92% to 21.2%, as well as an increase in the term delivery rate from 0% to 69.7%.

Conclusion: Treatment with hysteroscopic metroplasty is significantly improving the reproductive outcome in patients with CUA and previous fetal loss.

Introduction

The influence of congenital uterine anomalies (CUA) on the reproductive outcome has been a research question for a long period of time, and studies found in the literature showed that the prevalence of the congenital uterine anomalies is around 1-10% in unselected population of women, 2-8% in the group of infertile women, and 5-30% in women with a previous pregnancy loss [1-3].

Congenital anomalies of the female reproductive tract (Mullerian anomalies) represent a heterogeneous group of malformations of the genital tract, which can involve uterus, cervix, vagina and

Fallopian tubes. Majority of reproductive tract anomalies can seriously influence the reproductive and obstetric health of women depending on the specificity of the anomaly. They increase the rate of abortions, preterm deliveries, and obstetric complications. Patients with uterine malformations have decreased reproductive potential and unfavorable reproductive outcome. Overall term pregnancy rate in patients with untreated uterine malformations is around 50%. Term delivery rate in pregnant patients with untreated septate and bicornuate uterus is ~40%, and in patients with arcuate uterus reproductive outcome is slightly better, with term delivery rate of ~65% [4]. Uterine septum is

the most present anomaly in patients with infertility, and possibly the most prone to a surgical correction [5].

Congenital uterine anomalies consist of different groups of malformations of the Mullerian ducts, as a result of arrested embryological development, abnormal development or incomplete fusion of the paramesonephric ducts [6].

Etiology of CUA is not completely explained, majority of patients having normal karyotype, and some environmental, pharmacological and genetics factors might have some influence. Most probably its origin is polygenic or multifactorial [7].

Several classifications were made in order to optimize the diagnosis and treatment of those anomalies. The classification of 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, had the most clinical practice and was adopted by the American Fertility Society (AFS) in 1988 [8], and is used worldwide.

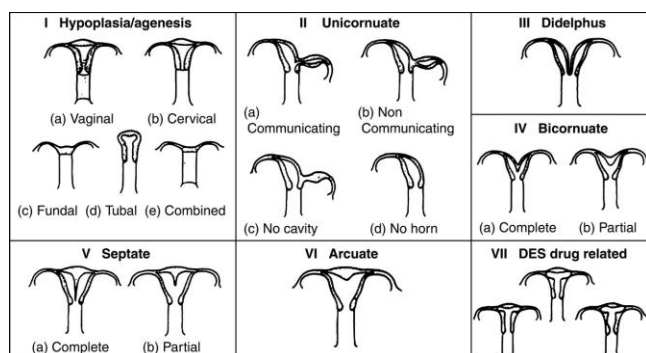


Figure 1: Schematic presentation of AFS classification.

Optimal detection and diagnosis of the CUA is using combination of hysteroscopy, laparoscopy, 3D ultrasound, MRI and sonohysterosalpingography [9]. Hysteroscopy and laparoscopy is a standard, safe and minimally invasive method for precise detection, classification and treatment of uterine malformations [10-13].

Uterine cavity abnormality is considered to be one of the factors which influence the reproductive outcome of these patients. A surgical correction by hysteroscopic metroplasty (HM) 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 for a vaginal delivery [13].

It provides anatomically normal uterine cavity, but does not certainly result in a favorable reproductive outcome since uterine vascularization is

probably involved in the uterine function. The theory which is nowadays widely accepted, states that septum is consisted of fibroelastic tissue with inadequate vascularization and changed ratio between blood vessels of the endometrium and myometrium, presenting negative effects on decidualisation and placentation [14].



Figure 2: Hysteroscopic metroplasty in uterus septus.

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 [14, 15]. Partial reconstruction of the uterine cavity by hysteroscopy is possible in some cases of partial bicornuate uterus (type 4b). Hysteroscopic metroplasty obtains normal uterine cavity, but also resolves normal uterine function, by providing normal reproductive outcome in these patients [16-18].

Pregnancy loss

Pregnancy loss (unsuccessful pregnancy) can be manifested in any period of pregnancy, starting even before implantation. Largest number (around 2/3) of fetal loss after implantation cannot be clinically detected, only by means of HCG testing, so called biochemical pregnancy [19-21]. Clinical rate of abortion diagnosis is 10-12%, which is well documented in a large number of retrospective and prospective studies. Fetal death occurs before the presence of clinical signs, and only 2-3 % of viable pregnancies are lost after 8 gestational week of pregnancy, usually in the following two months [22-24].

Abortion causes can be of idiopathic, genetic, anatomical, autoimmune, endocrine and infective origine [25]. As a most present causes are considered chromosomal anomalies, infective agents, presence of uterine anomalies or other uterine pathology, antiphospholipid syndrome, uncontrolled diabetes etc.

According to the definitions for infertility and recurrent pregnancy loss by the American Society for Reproductive Medicine, the following table was made (Table 1):

Even after one pregnancy loss, the risk for failure of the following pregnancy has been increased by 16-25%, and after second and third fetal pregnancy loss (unsuccessful pregnancy), the risk for following fetal loss has been increasing up to 40% [26,27].

Table 1: Terms Used to Describe Pregnancy Loss.

Term	Definition
Chemical pregnancy loss	Loss of a biochemically evident pregnancy
Early pregnancy loss	Abortion of the first trimester, loss of a histologically recognized pregnancy, or a loss based on ultrasonographic findings
SAB*	Pregnancy loss before 20 weeks' gestation, as based on last menstrual period
Habitual or recurrent abortion	2 or more consecutive SABs*
Stillbirth	Pregnancy loss after 20 weeks' gestation (Neonatal loss is the death of a liveborn fetus.)

* The American Society for Reproductive Medicine (ASRM) Practice Committee Report redefined recurrent pregnancy loss in January, 2013

That is why all patients with previous history of spontaneous abortion should include all necessary examinations searching for preventable causes for prevention of a future pregnancy loss. Investigation should be consisted of taking good medical history, thoroughly medical exam, patient counseling and adequate laboratory tests. Ultrasound scan should be mandatory in searching for the existence of uterine pathology, with special interest in detecting CUA.

Table 2: Calculated risk for repetitive pregnancy loss for counselling patients with previous spontaneous abortions [26].

	Previous abortion	Risk (%)
Patients with previous live birth	0	5-10
	1	20-25
	2	25
	3	30
	4	30
Patients without previous live birth	3	30-40

The aim of this study was to analyze the reproductive outcome after hysteroscopic metroplasty in patients with infertility and recurrent pregnancy loss.

Material and Method

We analyzed 71 patients with infertility and RPL to whom 84 interventions hysteroscopic metroplasty (HM) were performed at the University Clinic of Obstetrics and Gynecology in Skopje during a two year period, between 01.01.2010 and 31.12.2011. 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 other intrauterine pathology (submucous myoma, polyp, etc.).

Inclusion criteria were met by 67 patients, who underwent 78 interventions. Patients were divided in two groups: patients with recurrent pregnancy loss (RPL), and patients with infertility and previous pregnancy loss. 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. 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 and 9 mm, in general anesthesia and sterile conditions. Monopolar and bipolar 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) or NaCl 0.9% solution, sterile and apyrogenic served as a distension media.

Procedure starts with the patient placed in a lithotomic position, after previous disinfection of the operative field and vagina. Then cervix is pull forward with a tenaculum and dilatation is done using Hegar dilators; 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. End point is the moment when the following has been achieved: hysteroscope can move freely from one to the other ostium 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. In cases where major anomaly or uncertainty about achieving the end point of the resection was present, the patient is assigned for a control ultrasound and eventual re-resection.

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

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

Results

The 67 patients were divided into two groups: the group with recurrent pregnancy loss consisted of 24 patients (35.8%) and the group with infertility and previous fetal loss consisted of 43 patients (64.2%). Out of 78 performed HM, twenty-eight interventions

(35.9%) were done in the group of patients with RPL, and 50 (64.1%) in the infertility group.

Comparing the number of diagnosed anomalies – the largest number of 45 (67.1%) hysteroscopic metroplasties were done in the group of patients with arcuate uterus (type 6), followed by the group of patients with partial septate uterus (type 5b) - 14 cases (20.9%) and the group of patients with partial bicornuate uterus (type 4b) -6 cases (9%). The least present anomaly was complete septate uterus (type 5a) in 2 patients (3%).

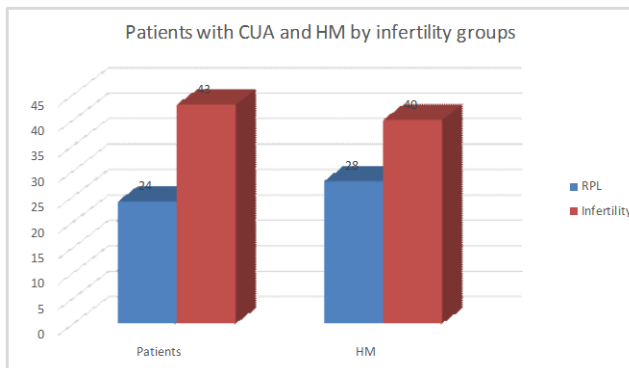


Figure 3: Graphic presentation of patients and hysteroscopic metroplasty by infertility groups.

As represented in the most of the published literature, congenital uterine anomalies most present were types 5b and 6 - partial septate uterus and arcuate uterus, represented by 88 %.

Table 3: Frequency of certain types of CUA by groups.

Type of CUA	RPL (%)	Infertility (%)	Total (%)
4b	0	6 (14%)	6 (9%)
5a	0	2 (4.6%)	2 (3%)
5b	8 (33.3%)	6 (14%)	14 (20.9%)
6	16 (66.7%)	29 (67.4%)	45 (67.1%)
Total	24 (100%)	43 (100%)	67 (100%)

According to the need for re-intervention (repeating the hysteroscopic metroplasty and resecting the residual septa) and types of CUA, the need to re-intervene was statistically significant in the groups with types 4b and 5a (3/8 – 37.5%), compared to the need for re-intervention of types 5b and 6 (9/59 – 15.2%). This was expected since such types of uterine malformations have a bigger septum or indentation of the uterine fundus, requiring more careful resection and taking care not to perforate the uterus.

Table 4: Types of CUA and need for re-intervention.

Type of CUA	Number of patients	Re-interventions	Re-reinterventions	Total repeated HM by groups
4b	6	1 (16.7%)	0	
5a	2	1 (50.0%)	1 (50%)	3 (37.5%)
5b	14	3 (21.4%)	0	
6	45	6 (13.3%)	0	9 (15.2%)

In the two-year period following hysteroscopic metroplasty, there were 33 patients who conceived. Analysis of the reproductive outcome in those patients (before and after hysteroscopic metroplasty) showed a statistically significant decrease ($p < 0.05$) of the abortion rate from 92% to 21.2%, as well as an increase in the term delivery rate from 0% to 69.7%. We noted increased preterm delivery rate (from 2% to 9,1%), and no ectopic pregnancy after the hysteroscopic metroplasty (from 5% to 0%).

Table 5: Reproductive outcome before and after metroplasty.

Infertility and RPL group (67 patients)	No. of pregnancies (%)	No. of abortions (%)	Fetal loss after 22gw (%)	Ectopic pregnancy (%)	Preterm delivery (%)	Term delivery (%)
Before	100 (100%)	92 (92%)	1 (1%)	5 (5%)	2 (2%)	0 (0%)
After	33 (49.2%)	7 (21.2%)	0 (0%)	0 (0%)	3 (9.1%)	23 (69.7%)
*S/NS	/	S	S	S	S	S

*S-significant ($p < 0.05$), NS-non-significant

Discussion

Hysteroscopic metroplasty is intervention designed for the treatment of patients with CUA that are hysteroscopically correctible, which are types 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.

One of the first published trials made on this topic by Acien in 1993 [28] 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. Abortion rate in patients with uterine malformations was 36%, and 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 normal uterus. Term delivery rate in patients with uterine malformations was 44% and live birth rate of 53%, which was lower and statistically significant ($p < 0.001$) from the group with normal uterus where term delivery rate was 85% and live birth rate of 89%.

Analyzing the results from previous studies of Raga, Buttram and Heinonen [5, 29, 30] in a systematic review in 2001, Grimbizis found that in 102 patients with untreated arcuate uterus and number of 241 pregnancies, the abortion rate was 25.8% and prematurity rate was 7.5%. The rates for term delivery and live birth were 62.7% and 66%, respectively. In the group with untreated septate uterus he found an abortion rate of 44.3% and a preterm delivery rate of 22.4%. After performing hysteroscopic metroplasty, a significant decrease in rates of abortions and preterm delivery was reported in treated patients. Abortion rate

decreased to 16.4%, while preterm delivery rate decreased to 6.4%, while a significant rise of term deliveries and live birth was reported (76.3% and 83.2%), in comparison with the rates before the HM that were lower (33% and 50.1%, respectively) [13].

In the previous study, done by Saygili in 2002 [31], the reproductive outcome was analyzed 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 of abortion rate was noted, from 91.4% to 10.4%. In the primary infertility group 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 % [32].

Study of Sendag in 2010 [33] who analyzed 30 patients with different degrees of septate uterus, patients had a total 74 pregnancies before metroplasty. Of these, ten (14%) were carried to term, six (8%) ended in preterm delivery, and 58 (78%) ended in spontaneous abortion. At least one year following hysteroscopic metroplasty, a total of 20 pregnancies occurred. Of these, 11 (55%) were carried to term, two (10%) ended in preterm delivery, seven (35%) ended in spontaneous abortion.

In a recent study of Nouri in 2010 [34], reproductive outcome was evaluated after hysteroscopic metroplasty in 64 women with septate uterus and primary or infertility. Complete follow-up was available for 49/64 (76%) patients, with overall pregnancy rate after HM was 69% (34/49) and overall life birth rate was 49% (24/49).

Roy et al. [35] in the published study in 2011 have analyzed 170 cases with HM during the 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%.

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 of abortion rate from 92 % to 21.1%, which was comparable with the analysis of Roy, Fedele and Saygili [31, 32, 35]. In the analyzed two-year period there was even a more significant improvement in the reproductive outcome resulting with term delivery rate that has increased from 0% to 69.7%, which was also significantly increased in all previously mentioned studies (from 50-80%) [13, 31, 35]. This is a confirmation of the fact that obtaining normal uterine cavity in cases with congenital uterine malformations who have been

hysteroscopically corrected, significantly influences the capacity of the uterus for successful continuation of the pregnancy to term delivery.

In conclusion, congenital uterine anomalies, as a uterine factor for pregnancy loss, have been pointed in several published scientific papers concerning this topic. Even minor types of anomalies with small defect of the uterine cavity, have been shown as an important cause for pregnancy and recurrent pregnancy loss. After treatment with hysteroscopic metroplasty in patients where surgically correctible congenital uterine anomaly exists, a significant improvement of the reproductive outcome in these patients has been reported.

We have analyzed the reproductive outcome before and after hysteroscopic metroplasty in our study group of patients diagnosed with infertility and recurrent pregnancy loss. A significant difference in the reproductive outcome has been noted, by decreased abortion rate and increased term delivery rates. The knowledge of the importance of detection and correction of congenital uterine anomalies will give new opportunities for a better reproductive outcome for this group of patients.

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