INFLUENCE OF HYSTEROSCOPIC METROPLASTY ON REPRODUCTIVE OUTCOME IN PATIENTS WITH INFERTILITY AND RECURRENT PREGNANCY LOSS

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Abstract

Introduction: Patients with congenital uterine anomalies (CUA) have decreased reproductive potential and an unfavourable reproductive outcome compared to the population with normal uterine cavity. Patients with untreated CUA have a higher abortion rate, higher foetal loss rate and decreased live birth rate. Hysteroscopic metroplasty is a standard, safe and minimally invasive method for the treatment of correctible types of congenital uterine anomalies.

The aim of the study was to analyse the reproductive outcome in certain groups of patients with CUA and infertility, before and after hysteroscopic metroplasty.

Material and methods: We analyzed 115 patients on whom 129 hysteroscopic metroplasty interventions were performed at the University Clinic of Obstetrics and Gynaecology in Skopje over a one-year period, between 01.01.2011 and 31.12.2011. Patients and their reproductive outcome were monitored over a two-year period and the same group served as a control group, taking into account their previous reproductive history before and after metroplasty. Statistical analysis was performed using the Chi-square test and $p < 0.05$ was considered to be statistically significant.

Results: The most common CUA were types 5b and 6, represented by 83.3%. In a follow-up period of two years, there were 55 patients with previous foetal loss treated by hysteroscopic metroplasty, and 31 of them had pregnancies. There was a statistically significant decrease of abortion rate from 88.5% to 19.3%, and a significant increase in term delivery rate from 2.3% to 71%.

Conclusion: Hysteroscopic metroplasty significantly improves the reproductive outcome in patients with previous foetal loss.

Key words: hysteroscopy, reproduction, infertility, pregnancy.

Introduction

The influence of congenital uterine anomalies (CUA) on the reproductive outcome has been a research question for a long period of time. 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. The majority of reproductive tract anomalies can seriously influence the reproductive and obstetric health of women depending on the specificity of the anomaly.

Newly published literature showed that the prevalence of congenital uterine anomalies is around 1–10% in an unselected population of women, 2–8% in the group of infertile women, and 5–30% in women with a previous miscarriage (early and late abortions, early preterm delivery) [1–3]. Prevalence of the anomalies differs depending on the method used for detection and diagnosis, with variable test performance, and the use of different classification systems to define the congenital uterine anomaly. Septum of the uterus is the most frequent

congenital anomaly of the genital tract with an incidence of 2–3% in the general population [4].

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 [5].

The etiology of the congenital anomalies of the female reproductive tract is still not adequately explained. In most women with Mullerian anomalies, karyotype is normal (92%). There are many hypotheses and theories implicating genetic factors, environmental and phar-

macological influences, but probably polygenic or multifactorial mechanisms are present [6].

Several classifications have been made in order to optimize the diagnosis and treatment of these anomalies, but the one adopted by the American Fertility Society (AFS) in 1988 [7] has been most beneficial in clinical practice. It classifies 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.

Figure 1 – Schematic presentation of AFS classification

Detection and diagnosis of the CUA can be considered optimal using a combination of hysteroscopy, laparoscopy, 3D ultrasound or MRI and sonohysterosalpingography [8]. In most medical centres hysteroscopy and laparoscopy is a standard, safe and minimally invasive method for precise detection, classification and treatment of uterine malformations [9–13].

Abnormality of the uterine cavity is considered to be one of the factors which influence the reproductive outcome of these patients. A good surgical correction by metroplasty provides an anatomically normal uterine cavity, but does not unfailingly 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 septum consists of fibro-elastic tissue with inadequate vascularization and a changed ratio between blood vessels of the endometrium and myometrium, presenting negative effects on decidualisation and placentation [14].

Transcervical treatment with hysteroscopy, since its innovation, has been the most efficient and easy method of surgical correction, allowing the operator to diagnose and treat the CUA. Hysteroscopic metroplasty has all the benefits of a good operative treatment: decreased intra- and post-operative morbidity, short-time intervention, fewer analgesic requirements, a shorter hospital stay, a shorter interval to conception and the possibility of a vaginal delivery.

Figure 2 – Hysteroscopic metroplasty in uterus septus

Most research findings have revealed that the majority of uterine malformations (> 55%) are presented with septate and arcuate uterus (type s5 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 a normal uterine cavity, but also resolves normal uterine function, by providing a normal reproductive outcome in these patients [16–18].

Spontaneous abortion (foetal loss)

Foetal loss (unsuccessful pregnancy) can be manifested in any period of pregnancy, starting even before implantation. The largest number (around 2/3) of foetal losses after implantation cannot be clinically detected, only by

means of HCG testing, known as biochemical pregnancy [19–21].

The clinical rate of abortion diagnosis is 10–12%, which is well documented in a large number of retrospective and prospective studies. Foetal 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 origin [25]. The most frequent causes are considered chromosomal anomalies, infective agents, the 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

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

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

Table 2

Calculated risk of repetitive pregnancy loss for counselling patients with previous spontaneous abortions [26]

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

This is the reason patients with a previous history of spontaneous abortion should undergo all the examinations searching for preventable causes for a prevention of a future pregnancy loss. It should comprise taking a good medical history, a thorough medical examination, patient counselling and laboratory tests. An ultrasound scan is mandatory to search for the existence of uterine pathology (anomalies, polyp, myoma), and microbiological swabs for infective agents. Analysis of TSH and glycaemia should also be done. In cases of recurrent foetal loss tests should be done for antiphospholipid antibodies, karyotype, and HLA status.

Influence on reproductive outcome

The presence of uterine malformations can have a further negative impact on the reproductive outcome, by additionally increasing the rate of abortions, preterm deliveries, and obstetric complications. Patients with uterine malformations have decreased reproductive potential and an unfavourable reproductive outcome, starting even from the first pregnancy. 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 a term delivery rate of ~65% [12].

The aim of this study was to analyse the influence of hysteroscopic metroplasty of congenital uterine anomalies in patients with infertility and recurrent pregnancy loss on their consecutive reproductive outcome.

Material and method

We analysed 115 patients on whom 129 hysteroscopic metroplasty interventions (HM) were performed at the University Clinic of Obstetrics and Gynaecology in Skopje over a one-year period, between 01.01.2011 and 31.12.2011. Inclusion criterion for the study was diagnosis of uterine malformation of correctable types (4b, 5a, 5b and 6), according to the AFS classification, and exclusion criteria were the existence of other intrauterine pathologies (submucous myoma, polyp, etc.).

The inclusion criterion was met by 113 patients, who underwent 127 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 performed following previously signed informed consent by the patient.

The intervention was made with endoscopic equipment (Olympus and Storz types), using a rigid hysteroscope of 5.5 mm and a resectoscope of 8 and 9 mm, under general anaesthesia and in 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 of Ispiro® (solution of 2.7% sorbitol and 0.54% manitol) or NaCl 0.9% solution, sterile and apyrogenic, 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 the cervix is pulled forward with a tenaculum and dilatation is done using Hegar dilators; the hysteroscope is placed transcervi-

cally 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 end point is the moment when the following has been achieved: the 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. When a bigger septum is present or uncertainty is present about achieving the end point of the resection, the 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 cause of 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, abortion rate, preterm delivery rate and term delivery rate.

Data were analysed using the SPSS program 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 statistically significant.

Results

The 113 patients were divided into three groups: the group with recurrent pregnancy loss consisted of 22 patients (19.5%); the group with secondary infertility consisted of 33 patients (29.1%) and the group with primary infertility consisted of 58 patients (51.4%). Twenty-seven interventions (21%) were done in the group of patients with RPL, 35 (28%) in the secondary infertility group and 65 (51 %) interventions in the primary infertility group.

Figure 3 – Graphic presentation of hysteroscopic metroplasty by infertility groups

Comparing the number of diagnosed anomalies – the largest number of 69 (61.1%) 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) – 24 cases (21.2%) and the group of patients with partial bicornuate uterus (type 4b) – 13 cases (11.5%). The least frequ-

ent anomaly was complete septate uterus (type 5a) in 7 patients (6.2%).

As represented in most of the published literature, in all of the infertility groups we analysed the most frequent congenital uterine anomalies were types 5b and 6 – partial septate uterus and arcuate uterus, represented by 83.3%.

Table 3

Frequency of certain types of CUA by groups

Type of CUA	RPL (%)	Secondary infertility (%)	Primary infertility (%)	Total (%)
4b	0	6(18.2%)	7(12.1%)	13(11.5%)
5a	0	2(6.1%)	5(8.6%)	7(6.2%)
5b	7(31.8%)	6(18.2%)	11(19.0%)	24(21.2%)
6	15(68.2%)	19(57.5%)	35(60.3%)	69(61.1%)
Total	22(100%)	33(100%)	58(100%)	113(100%)

Table 4

Types of CUA and need for re-intervention

Type of CUA	Number of patients	Reinter-ventions	Rereinter-ventions	Total repeated HM by groups
4b	13	2(15.4%)	0	4(20%)
5a	7	1(14.3%)	1(14.3%)	
5b	24	3(12.5%)	0	10(10.8%)

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 greater in the groups with types 4b and 5a (4/20–20%) compared to the need for re-intervention of types 5b and 6 (10/93–10.8%). 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 while taking care not to perforate the uterus.

In the two-year period following hysteroscopic metroplasty, there were 31 pregnancies in the group of patients with recurrent pregnancy loss and secondary infertility, which comprised 55 patients. 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 88.5% to 19.3%, as well as an increase in the term delivery rate from 2.3% to 71%. A significant decrease was noted in the preterm delivery group, and no ectopic pregnancy after the hysteroscopic metroplasty.

Table 5

Reproductive outcome before and after metroplasty

Secondary infertility and RPL group (55 patients)	No. of pregnancies (%)	No. of abortions (%)	Fetal loss after 22 gw (%)	Ectopic pregnancy (%)	Preterm delivery (%)	Term delivery (%)
Before HM	87(100%)	77(88.5%)	3(3.5%)	4(4.6%)	1(1.1%)	2(2.3%)
After HM	31(56.4%)	6(19.3%)	0(0%)	0(0%)	3(9.7%)	22(71%)
*S/NS	/	S	S	S	S	S

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

Discussion

Patients with congenital uterine malformations are the most significant group for treatment and improvement of reproductive outcome. They include CUA 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.

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. 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 normal uterus.

The term delivery rate in patients with uterine malformations was 44% and the live birth rate of 53%, which was statistically significant ($p < 0.001$) and lower than the group with normal uterus where term delivery rate was 85% and live birth rate 89%.

In the systematic review by Grimbizis in 2001 [12], where he analyzed the results from previous studies by Raga, Buttram and Heinonen [4, 29, 30], in 102 patients with untreated arcuate uterus and the 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.

A large number of studies have analysed the reproductive outcome in patients where congenital uterine anomalies were treated by hysteroscopic metroplasty, and they 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 previous poor reproductive outcome.

After performing hysteroscopic metroplasty, a significant decrease in rates of abortions and preterm delivery has been 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). On the contrary, 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) [12].

In one of the recently-published studies by Sendag in 2010 [31] who analyzed 30 patients with different degrees of septate uterus, patients had a total of 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 after hysteroscopic metroplasty, a total of 20 pregnancies occurred. Of these, 11 (55%) were carried to term, two (10%) ended in preterm delivery, and seven (35%) ended in spontaneous abortion.

In a study by Nouri in 2010 [32], the reproductive outcome was evaluated after hysteroscopic septoplasty in 64 women with septate uterus and primary or secondary infertility. A complete follow-up was available for 49/64 (76%) patients, and the overall pregnancy rate after hysteroscopic septoplasty was 69% (34/49). The overall live birth rate (LBR) was 49% (24/49).

In a previous study by Saygili in 2002 [33] the reproductive outcome was analysed in 361 patients with septate uterus and hysteroscopic metroplasty who were followed for 18 months after the surgical intervention. The overall pregnancy rate was 49.8%, and during the 18 month 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% [34].

In the recently published literature, in 2011 Roy [35] 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 published medical literature. The comparison of the results before and after HM revealed a significant decrease of abortion rate from 88.5% to 19.3%, which was comparable with the analysis of Roy, Fedele and Saygili [33–35]. In the analyzed two-year period there was even a more significant improvement in the reproductive outcome resulting with a term delivery rate that had increased from 2.3% to 71%, which was also significantly increased in all the previously-mentioned studies (from 50–80%) [12, 33–35]. This is a confirmation of the fact that obtaining a normal uterine cavity in cases with congenital uterine malformations who 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.

Conclusion

In recent years, many published scientific papers concerning this topic have shown that congenital uterine anomalies represent an important factor for infertility and recurrent pregnancy loss. Even anomalies considered to be minor, such as an arcuate or partially septate uterus, have been detected as a cause of pregnancy loss, and after their surgical correction a significant improvement of the reproductive outcome in these patients has been reported.

We analysed 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, in decreased abortion rate and increased term delivery rates. Hysteroscopic metroplasty significantly improves the reproductive outcome in patients where surgically correctable congenital uterine anomaly exists. 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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Резиме

ВЛИЈАНИЕТО НА ИСТЕРОСКОПСКАТА МЕТРОПЛАСТИКА ВРЗ РЕПРОДУКТИВНИОТ ИСХОД КАЈ ПАЦИЕНТКИ СО ИНФЕРТИЛИТЕТ И РЕКУРЕНТНА ФЕТАЛНА ЗАГУБА

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Вовед: Пациентките со вродени утерини малформации (ВУМ) имаат намален репродуктивен потенцијал и понеповолен репродуктивен исход споредено со популацијата со нормална утерина празнина. Пациентките со нетретирани ВУМ имаат поголема стапка на абортуси, поголема стапка на фетална загуба и намалена стапка на живороденост. Хистероскопската метропластика е стандарден, безбеден и најминимално инвазивен метод за третман на коректибилни типови ВУМ.

Цел на студијата е да се анализира репродуктивниот исход кај одделни групи пациентки со ВУМ и инфертилитет, пред и по хистероскопска метропластика.

Материјал и методи: Анализирани се 115 пациентки кај кои се изведени 129 интервенции хистероскопска метропластика на Универзитетската клиника за гинекологија и акушерство во Скопје, во едногодишен период од 1 јануари 2011 до 31 декември 2011 година. Пациентките и нивниот репродуктивен исход се следени во тек на двегодишен период и тие служеа како контролна група, имајќи ја предвид нивната претходна репродуктивна историја. Статистичката анализа е направена со употреба на Х2 тест и вредноста $p < 0,05$ се определи за статистички сигнификантна.

Резултати: Најчести детектирани ВУМ беа типовите 5б и 6, присутни со 83,3%. Во тек на двегодишното следење кај 55 пациентки со претходна фетална загуба, по направената хистероскопска метропластика $\ddagger$ имаше 31 бременост. Има статистички значајно намалување на стапката на абортуси од 88,5% на 19,3%, како и зголемување на стапката на термински породувања од 2,3% на 71%.

Заклучок: Хистероскопската метропластика значително го подобрува репродуктивниот исход кај пациентките со претходна фетална загуба.

Клучни зборови: хистероскопија, репродукција, инфертилитет, бременост.