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Frozen-thawed blastocysts transfer cycle outcomes of patients with dysmorphic uterus following hysteroscopic metroplasty: Case-controlled study in a single IVF Center

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Abstract:	Introduction: Dysmorphic uterus is a rare uterine malformation characterized by an abnormal uterine cavity, and may lead to several reproductive failures such as infertility and adverse pregnancy outcomes. The results of hysteroscopic correction of this uterine malformation on reproductive outcomes are poorly reported. Aim: To evaluate the reproductive outcomes of cases with frozen-thawed single blastocyst transfer (eSBT) who underwent hysteroscopic metroplasty due to dysmorphic uterus and to compare these results with the control group. Methods: This study included 78 patients with primary infertility who have dysmorphic uterine anomaly and 379 age and BMI-matched infertile patients with a normal uterine cavity as a control group. All patients were enrolled in the in-vitro fertilization (IVF) program. Selected top/good quality blastocysts were frozen subsequently transferred in another cycle following the hysteroscopic metroplasty. Reproductive and obstetric outcomes of all cases and characteristics of FET cycles were retrospectively analyzed. Results: Demographic characteristics of both groups were similar. There was no statistically significant difference between the study and control groups regarding implantation (IR), clinical pregnancy (CPR), and live birth rates (LBR) (63.2% vs 64.8%, 57% vs 55%, and 39.8% vs 40.3%, all p>0.05) respectively. Although the rate of clinical pregnancy loss was higher in the study group, this was not statistically significant (27.1% vs 19.5% p>0.05). Preterm delivery was found significantly higher in the study group than in the control group p=0.03; and 23.5% vs 10.9%, p=0.03, respectively). On the other hand, the type of endometrial preparation, day of embryo transfer and grade of transferred embryos were similar in both groups, except for the endometrial thickness, which was significantly lower in the study group than in the control group

	(8.9±1.4 mm vs 10.1±1.7 mm, p<0.001). Conclusions: In patients who underwent hysteroscopic metroplasty, reproductive outcomes of FET cycles were successful as in patients with normal uterine cavity. Single blastocyst transfer with top/good quality embryos after hysteroscopic metroplasty improves live birth rates but preterm birth are higher when compared to the patients with normal uterine cavity.

Frozen-thawed blastocysts transfer cycle outcomes of patients with dysmorphic uterus following hysteroscopic metroplasty: Case-controlled study in a single IVF Center

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Abstract

Introduction: Dysmorphic uterus is a rare uterine malformation characterized by an abnormal uterine cavity, and may lead to several reproductive failures such as infertility and adverse pregnancy outcomes. The results of hysteroscopic correction of this uterine malformation on reproductive outcomes are poorly reported.

Aim: To evaluate the reproductive outcomes of frozen-thawed single blastocyst transfer (SBT) patients who underwent hysteroscopic metroplasty due to dysmorphic uterus, and to compare these results with the control group.

Methods: This study included 78 patients with primary infertility who have dysmorphic uterine anomaly and 379 age- and BMI- matched infertile patients with a normal uterine cavity as a control group. All patients were enrolled in the in-vitro fertilization (IVF) program. Selected top/good quality blastocysts were frozen and then transferred in another cycle following the hysteroscopic metroplasty. Reproductive and obstetric outcomes of all cases and characteristics of FET cycles were analyzed retrospectively.

Results: Demographic characteristics of both groups were similar. There was no statistically significant difference between the study and control groups regarding implantation rates (IR), clinical pregnancy rates (CPR), live birth rates (LBR) (63.2% vs 64.8%, 57% vs 55%, and 39.8% vs 40.3%, respectively; all $p>0.05$). Although the rates of clinical pregnancy loss was higher in study group there was no statistically significant difference (27.1% vs 19.5%, $p>0.05$). Preterm delivery were found significantly higher in the study group than in the control group (23.5% vs 10.9%, $p=0.03$). On the other hand, type of endometrial preparation, day of embryo transfer and grade of transferred embryos were similar in both groups, except for the endometrial thickness, which was significantly lower in the study group than in the control group (8.9±1.4 mm vs 10.1±1.7 mm, $p<0.001$).

Conclusions: In patients who underwent hysteroscopic metroplasty of the uterine cavity, reproductive outcomes of FET cycles were successful as in patients with normal uterine cavity. Single blastocyst transfer with top or good quality embryos after hysteroscopic metroplasty in patients with a dysmorphic uterus, improves live birth rates but preterm birth are higher when compared to the patients with normal uterine cavity.

Keywords: dysmorphic uterus, frozen embryo transfer, hysteroscopy, infertility, metroplasty

Introduction

Dysmorphic uterus is a rare uterine malformation and was thought to be due to dietilstilbestrol (DES) exposure during the intrauterine period.[1] Although the use of DES is completely discontinued in women of reproductive age (20-45 years), the prevalence of dysmorphic uterus is higher than before.[2] In 1977, Kaufman first described dysmorphic uterus, and later, in 1988 The American Fertility Society (AFS) defined it as a DES-related defect or type VII defect in its classification.[3,4] According to the definition made by the ESHRE-ESGE consensus in 2013 dysmorphic uterus defines T-shaped uterus and uterus infantilis, which are characterized by a narrow uterine cavity. T-shaped uterus has thickened lateral walls with 2/3 uterine corpus and 1/3 cervix, but uterus infantilis has no lateral wall thickening and has 1/3 uterine body and 2/3 cervix.[5] There are no universal diagnostic criteria for this type of uterus, but general opinion is that narrow uterine cavity as a result of thickened lateral walls is defined dysmorphic uterus. In studies, dysmorphic uterus was diagnosed with HSG, hysteroscopy, or 3D ultrasound, since HSG and hysteroscopy do not provide enough information about uterine wall thickness and contours the most common method used in recent years is 3D ultrasound**.**[6-9]

Available data show that poor reproductive outcomes, obstetric complications and infertility are more common in women with dysmorphic uterus than those with normal uterine cavity.[10,11] Therefore, surgical correction of the dysmorphic uterus has been approved as the standard modality of treatment by many authors.[8,12-15] However, this is a new topic and there are scarce data showing the impact of an expanded uterine cavity with intervention on reproductive and obstetric outcomes in the dysmorphic uterus. So, the reproductive outcomes of surgical intervention are not well known. According to our knowledge, many studies evaluated spontaneous pregnancy rates after metroplasty[12,16,17], only one study evaluated pregnancy rates from combined fresh and FET cycles[18], and there is no study evaluating FET pregnancies alone in patients with dysmorphic uterus after hysteroscopic metroplasty.
Therefore, we aimed to evaluate the effect of hysteroscopic metroplasty on postoperative FET cycle results in patients with dysmorphic uterus and to compare these data with those of patients with normal uterine cavity.

Methods

This retrospective study was conducted at Istanbul Memorial Hospital ART and Genetic Centers between January 2011 and June 2021. The study protocol was approved by the institutional ethics committee of Istanbul Memorial Hospital ART and Genetics Center (IMH-04.12.2020/004). All patients signed informed consent for all procedures they underwent and allowed data collection and analysis for research purposes. Seventy eight women who underwent hysteroscopic metroplasty due to the infertility releated with dysmorphic uterus and 379 age- and BMI- matched patients with normal uterine cavity were included. Patients with repeated pregnancy loss, intrauterine adhesions, thin endometrium, and adenomyosis were excluded.

The diagnosis of dysmorphic uterus was made according to the to the ESHRE/ESGE classification.[5] After 2016, a new classification system proposed by the CONgenital UTerine Anomalies Working Group classifies dysmorphic uterus. We evaluated the uterine wall thickness, interostial distance, isthmic diameter, and morphology of the uterine cavity by three-dimensional transvaginal ultrasound (3D-TVS) after 2016.[7,8] Since there was no 3D-TVS in previous years the diagnosis was made with HSG and confirmed by hysteroscopy, and in 42 patients the diagnoses were made with 3D-TVS.[6,13] After hysteroscopic metroplasty patients were evaluated with HSG and 3D-TVS before frozen embryo transfer (figure-1-2).

Hysteroscopy was planned at follicular phase (days 6-11) and performed under general anesthesia. After vaginal cleaning with povidine-iodine solution, the cervix was dilated with Hegar dilator up to 7.5- mm. After cervical dilatation an obturator was placed in uterine cavity and a continuous-flow hysteroscope with a diameter of 5 mm with 30°oblique telescope was used for the procedure (Karl Storz, Tuttlingen, Germany/ Bettocchi® Inner Sheath, Size 5.4 mm, with a channel for semirigid 5 Fr. operating instruments). Uterine cavity was distended with 0.9% saline solution. The pressure of the irrigation solution was set to 100 mmHg. On hysteroscopy, if the uterine cavity was narrow and tubal ostia were not seen after the hysteroscope passed the internal cervical os because of constriction rings around the lateral walls of intrauterine cavity it was identified as dysmorphic uterus. Thickened uterine walls were corrected with Bipolar Versapoint System (Gynecare Versapoint, Bipolar Electrosurgery System, Ethicon, US) until the tubal orifice was visible through the isthmus. Hysteroscopic metroplasty in the study group was performed by a single experienced surgeon (SK).

Firstly, each patient underwent controlled ovarian hyperstimulation and IVF. Embryos obtained from the procedure were frozen to transfer in another cycle. A preimplantation genetic testing for aneuploidy (PGT-A) was performed using next-generation sequencing technology on all women ≥37 years in both the study and control groups. Then, hysteroscopic metroplasty was performed to the study group, and within three months after the operation, a single embryo of top (≥ 5AA) or good (≥ 3AA) quality was selected and transferred (on the 5th or 6th day) with appropriate endometrial preparation for each patient.

The primary reproductive outcomes included the implantation rate (IR), clinical pregnancy rate (CPR), live birth rates (LBR) including term and preterm births, spontaneous pregnancy losses rates including biochemical and clinical pregnancy losses, in both groups. CPR was defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs; LBR was defined as delivery of a live fetus after 24 completed gestational weeks; term- and preterm deliveries were defined as delivery of a live baby born after- and before 37 weeks of gestation, respectively; and clinical pregnancy loss was defined as the spontaneous loss of a clinical pregnancy before 20 completed gestational weeks. Secondarily, the characteristics of all FET cycles performed to both groups were evaluated retrospectively. Additionally, any adverse outcomes such as ectopic pregnancy, retained placenta, and need for the second operation following the procedure were also evaluated in the study group.

Demographic and clinical characteristics of patients, including age, body mass index (BMI), serum AMH level, duration of infertility, PGT-A test results, and characteristics of FET cycles, were obtained from their recorded files.

FET cycle preparation

On the second day of menstruation, uterus and ovaries were evaluated by ultrasonography and the presence of ovarian cyst was excluded. The endometrial preparation of each patient was performed with either modified natural cycles for ovulatory patients or artificial cycles for anovulatory patients or for patients living outside of the city. In modified natural cycle, patients with regular menstrual cycles and preferring less medication were monitored with TVS and blood hormone levels until the trigger day. After confirming initiation of the LH surge, recombinant hCG at a dose of 250 µg (Ovitrelle 250 µg/0.5 mL, Merck Switzerland) was administered, and transvaginal progesterone gel (Crinone 8% Vaginal Gel, Merck Switzerland) treatment was started two days later for use twice daily until 12th weeks of gestation if the patients became pregnant. In the artificial cycle, oral estradiol hemihydrate (Estrofem, Novo Nordisk, Denmark) was started on the second day of menstrual cycle at a daily dose of 6 mg for at least 14 days. Serial ultrasound examinations were performed starting from the 10-11th days of the treatment. Transvaginal progesterone gel was also started twice daily on 15th day of estradiol usage, after endometrial thickness was more than 7 mm. Embryo transfer was scheduled depending on the blastocyst stage of embryos (5th or 6th day). If the patient was pregnant with the artificial cycle, estradiol continued until 10 weeks of pregnancy and progesterone until 12 weeks of pregnancy.

Statistical Analysis

The Statistical Package for the Social Sciences software version 20.0 (SPSS Inc., Chicago, IL) was used for the statistical evaluations. The continuous variables were presented as mean ± standard deviation (SD). While comparisons of normally distributed continuous variables between the groups were performed using an independent sample t-test, Mann-Whitney U test was used for data that did not show normal distribution. Categorical variables were compared with the Pearson chi-squared test. The results were expressed as percentages. A p value <0.05 was considered statistically significant.

Results

A total of 457 patients were included in the study. The mean age of the patients were 34.2 ± 4.3 years and 33.9 ± 3.7 years in the study and control groups, respectively. In terms of demographic characteristics, the data showed that there was no significant difference between the groups (Table 1).

Elective single frozen-thawed blastocysts (eSBT) were transferred to 78 patients in 128 FET cycles in the study group, and to 379 patients in 481 FET cycles in the control group. We used the PGT-A test for all patients over the age of 37 to eliminate the influence of age factor on reproductive outcomes and to better understand the impact of uterine remodeling on endometrial function. When the two groups were compared in terms of primary reproductive outcomes, the rates of implantation, clinical pregnancy, live birth and biochemical pregnancy loss was similar in both groups (63.2% vs 64.8%, 57% vs 55%, and 39.8% vs 40.3%, 7% vs 9.7%, respectively; all p>0.05) (Table 2). Although clinical pregnancy loss rates were higher in the study group compared to the control group (27.1% vs 19.5%) there was no statistically significant difference. But preterm delivery was higher in study group compared to control group(23.5% and 10.1% vs 11.3% p=0.03; respectively). Additionally, term delivery rate was lower in the study group than in the control group (76.5% vs 89.1%, p=0.03) (Table 2).

When the two groups were assessed according to secondary outcomes, the number of FET cycles for each patient in both groups was minimum of 1 and maximum of 7. The days of transferred blastocysts (day 5 or 6), transferred blastocysts grade, and endometrial preparation methods (natural or artificial), and the mean number of frozen and frozen-thawed blastocysts were similar in both groups (all $p>0.05$). However, the mean endometrial thickness on the day of hCG trigger or the progesterone initiation was significantly lower in the study group than in the control group (8.9±1.4 mm vs 10.1±1.7 mm, $p<0.001$). The total FET cycle results of both groups are presented in Table 2.

There were 1 ectopic pregnancy (1.5%) and 2 retained placentas (3%) as complications in the study group. None of the patients needed a second operation.

Discussion

Although many researchers have tried to determine diagnostic criteria for the diagnosis of dysmorphic uterus, simple and universally accepted diagnostic criteria are not yet available so true prevalence of dysmorphic uterus is still unknown.[11,19-22] In recent years, different methods have been used to define dysmorphic uterus. Alonso-Pacheco et al. have subclassified dysmorphic uteri according to interostial distance (IOD) and fundus morphology (FM) into T-shaped uteri, Y-shaped uteri and I-shaped uteri.[19] Ludwin et al. described three sonographic criteria lateral indentation depth, lateral indentation angle and T-angle.[20] Sood and Akhtar reported that most studies carry a risk of bias, as the definition of anomalies (dysmorphic, septate, and bicorporeal uteri) was based solely on the subjective impression of the clinician performing the test.[23] However, both new imaging modalities such as 3D-TVS and hysteroscopy, and diagnostic standardization for dysmorphic uteri by ESHRE/ESGE consensus have led to improved detection in these cases.[5] In the current study, the diagnosis of dysmorphic uterus was made by HSG or 3D ultrasound, diagnosis was confirmed during hysteroscopy, and metroplasty was performed on all patients. Different studies have shown that a dysmorphic uterus will cause reproductive failure if not surgically corrected.[12] Relationship between dysmorphic uterus and infertility is still unclear, because there are no studies including control group. Although some authors recommend surgical treatment for the T-shaped uterus, evidence is very low quality.[9]

In a recently published systematic review, Coelho Neto et al., evaluated the definition, prevalence, and clinical relevance with respect to reproductive outcome, of T-shaped uterus.[9] The authors reported that different inclusion criteria, non-standardized diagnostic methods and various surgical techniques were used for women in the studies. The benefit and safety of surgical treatment of the T-shaped uterus raise doubts due to the lack of clear diagnostic criteria and the lack of strong evidence from well-conducted randomized controlled trials for this condition. Therefore, they suggested that in routine practice, expectant management an appropriate choice for women with a dysmorphic / T-shaped uterus.[9] On the other hand, Carugno et al. disagreed with this review because it was not a meta-analysis and lacked the quality of evidence needed to safely recommend a change in clinical practice. Thus, Carugno et al. suggested continuing to offer hysteroscopic metroplasty to patients with T-shaped uterus and primary infertility in order to improve reproductive outcomes.[24]

Di Spiezio et al. showed that the increased uterine volume with hysteroscopic metroplasty gave high CPR (55%) and LBR (75%) in 17 women with a history of repeated miscarriages. They evaluated postoperative uterine volume by office hysteroscopy and 3D-TVS.[11]

As a primary reproductive outcome, we observed significantly higher rates of preterm delivery with dysmorphic uterine anomaly, in which the uterine cavity was hysteroscopically corrected, compared to patients with a normal uterine cavity. However, IR, CPR, LBR, multiple pregnancy rate, and biochemical pregnancy loss rate in the study group were comparable with those in the control group. To our knowledge, this is the first report demonstrating reproductive outcomes only in eSBT cycles of patients with hysteroscopic metroplasty and comparing these results with those of controls.

Ducellier-Azzola et al. showed a reproductive improvement in patients with a T-shaped uterus after hysteroscopic metroplasty, with an increased rate of live birth (3.6% vs 74.5%) and a decreased rate of early spontaneous miscarriage (19.7% vs 85.6%).[15] Fernandez et al. reported a CPR of 49.5% with a follow-up of 39 months.[13] Also, Sükür et al.[14] reported a LBR of 45.1% similar to the 50% result of Boza et al.[17] In our study, the rates of implantation (63.2% vs 64.8%), clinical pregnancy (57% vs 55%) live birth (39.8% vs 40.3%) and clinical pregnancy losses(27.1% vs 19.5%)were comparable in both groups. But preterm delivery was significantly higher in the study group compared to the control group (23.5% vs 10.9%, respectively).

It is well known that dysmorphic uterus causes a functional narrowing of the uterine cavity and therefore leads to defective endometrial receptivity and negative reproductive consequences, including infertility.[14] In addition to endometrial factor, there are several other major factors affecting LBR results, such as the age of patients and the quality of embryos. Most of the studies designed for reproductive outcomes after hysteroscopic metroplasty in women with dysmorphic uterus have not ruled out these confounding factors. We used the PGT-A test for all patients over the age of 37 to eliminate the influence of age factor on reproductive outcomes and to better understand the impact of uterine remodeling on endometrial function. Also, we selected and transferred TQ or GQ blastocysts for all patients to eliminate the influence of embryo factor on the results. The higher success rates than above studies in our study parameters (i.e., LBR, CPR, IR), may have result from several factors; such as, younger age, controlled ovarian stimulation which was meticulously managed, choosing a TQ or GQ blastocysts, or preferring frozen ET for all patients. Also, while the studies of Di Spiezio et al., Uyar et al., and Boza et al., included both patients with unexplained infertility and patients with a history of repeated miscarriages, our study group was more homogeneous and included only primary infertile patients and not including patients with recurrent pregnancy loss.[11,17,18] This difference may also be a causal factor for better reproductive outcomes than many other studies.

Besides notable improvements in reproductive outcomes, our complication rates were also much lower compared to the literature. Only 1 ectopic pregnancy, 2 retained placentas, and 1 perinatal death related to premature rupture of membrane at 23 weeks of gestation were noted as the complications in our series. Fernandez et al. reported 5 ectopic pregnancies, 1 severe hemorrhage and 5 cervical incompetence in 48 women who underwent metroplasty.[13] Di Spiezio et al. reported 8 episodes of retained placenta after delivery and 1 intrauterine fetal death in the postoperative period of 214 women.[11] In a systematic review that included 6 research articles, 98 cases with surgical complications were reported. These were 39 cases of cervical incompetence, 56 mild synechiae, 2 postoperative infections, and one postoperative bleeding.[25] We did not observe any surgical complication such as adhesion formation, perioperative bleeding, or the need for a second operation.

Retrospective design of the study may be considered as a limitation, but we shared our 10 years of experience as a case-controlled study including 78 patients with a dysmorphic uterus. Furthermore, the homogeneity of the groups, the quality of transferred blastocysts and the exclusion of various confounding factors on reproductive outcomes such as maternal age are strengths of the study.

Conclusion

In the present study, we documented similar reproductive outcomes such as IR, CPR and LBR with the eSBT FET cycle, in patients who underwent hysteroscopic metroplasty compared to normal uterine cavity. But that women who conceive with a dysmorphic uterus are at higher risk for first- and second trimester pregnancy losses and preterm birth. As a result, pregnancies in these patients should be monitored more closely and it is important to inform the patients in this direction. Because of the scarce number of randomized controlled trials and the heterogeneity of the data (i.e. patient population, diagnostic criteria, and procedure details), further randomized controlled studies are needed to solve the complexity of this anomaly and to help a clear follow-up of reproductive outcomes after the procedure.

Author Contributions

Concept, Design and Writing –U.H.; Data – G.U.; Supervision –K.S.

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FROZEN-THAWED EMBRYO TRANSFER CYCLE OUTCOMES OF PATIENTS WITH DYSMORPHIC UTERUS FOLLOWING HYSTEROSCOPIC METROPLASTY: CASE-CONTROLLED STUDY IN A SINGLE IVF CENTER

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Disclosure statement

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Table 1. Demographic characteristics and laboratory values of the groups

	Study group (n=78)	**Control group (n=379)**	**P value**
Age, (years)	34.2 ± 4.3	33.9 ± 3.7	NS
Duration of infertility, (years)	5.3 ± 0.4	4.2 ± 0.6	NS

BMI, (kg/m²)	24.7 ± 3.5	23.0 ± 4.7	NS
AMH level, (ng/ml)	2.6 ± 2.5	2.4 ± 2.3	NS

Abbreviations: SD = standart deviation, BMI = body mass index, AMH= anti-mullerian hormone, NS = not significant

Table 2. FET cycles' characteristics and reproductive results in the groups

	Study group (128 cycles)	Control group (481 cycles)	P value
IR, (%)	81 (63.2%)	312 (64.8%)	NS
CPR, (%)	73 (57.0%)	265 (55%)	NS

LBR, (%)	51 (39.8%)	194 (40.3%)	NS
Term delivery rate	39/51 (76.5%)	173/194 (89.1%)	**0.03**
Preterm delivery rate	12/51 (23.5%)	21/194 (10.9%)	**0.03**
Pregnancy Losse rate, (%)	31 (24.2%)	108 (22.4%)	NS
Clinical pregnancy losses (before or after 12 weeks of gestation)	22 (27.1%)	61 (19.5%)	NS
Biochemical pregnancy losses	9 (7.0%)	47 (9.7%)	NS
Multiple pregnancy rate, (%)	3 (3.7%)	20 (3.4%)	NS
Endometrial preparation, (%)			
Natural (modified or true natural)	64 (50%)	237 (49.3%)	NS
Artificial (estrogen replacement therapy)	64 (50%)	244 (50.7%)	NS
Endometrial thickness (mm)	8.9 ± 1.4	10.1 ± 1.7	**<0.001**
Mean number of frozen blastocysts per patient	5.8 ± 3.6	5.28 ± 4.4	NS
Number of frozen-thawed blastocysts per cycle	1.3 ± 0.6	1.2 ± 0.5	NS

Abbreviations: IR: implantation rate, CPR: clinical pregnancy rate, LBR: live birth rate, FET: frozen-thawed embryo transfer, PGT-A: Preimplantation genetic testing for Aneuploidy, ET: embryo transfer, TQ: top quality, GQ: good quality, NS: not significant. Data are expressed as mean ± SD or percentages (n) as appropriate,

Figure 1: Hysterosalpingography of a dysmorphic uterus before and after metroplasty

Figure 2: 3D ultrasound of a dysmorphic uterus before and after the surgery

figure 1

177x179mm (72 x 72 DPI)

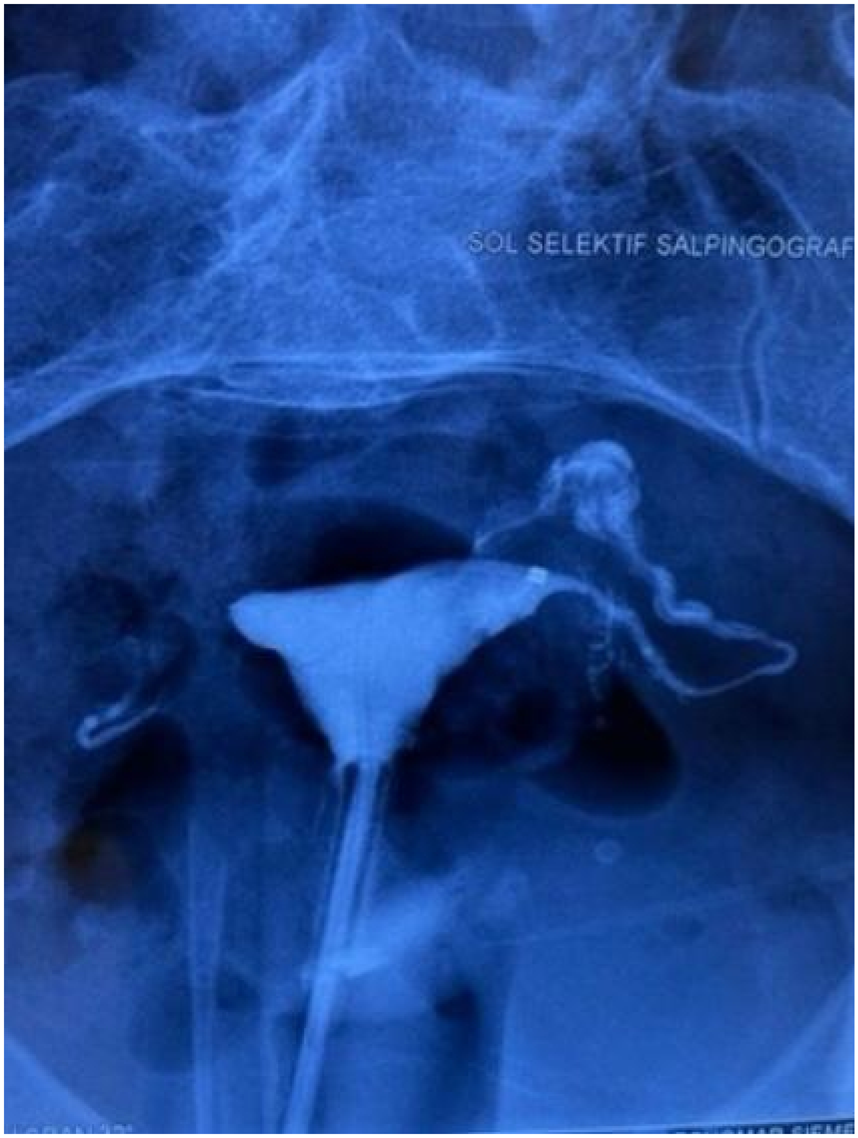

figure 2

149x199mm (72 x 72 DPI)

figure 3

125x182mm (72 x 72 DPI)

Table 1. Demographic characteristics and laboratory values of the groups

	Study group (n=78)	Control group (n=379)	P value
Age, (years)	34.2 ± 4.3	33.9 ± 3.7	NS
Duration of infertility, (years)	5.3 ± 0.4	4.2 ± 0.6	NS
BMI, (kg/m^2)	24.7 ± 3.5	23.0 ± 4.7	NS
AMH level, (ng/ml)	2.6 ± 2.5	2.4 ± 2.3	NS

Abbreviations: SD = standart deviation, BMI = body mass index, AMH= anti-mullerian hormone, NS = not significant

Table 2. FET cycles' characteristics and reproductive results in the groups

	Study group (128 cycles)	Control group (481 cycles)	P value
IR, (%)	81 (63.2%)	312 (64.8%)	NS
CPR, (%)	73 (57.0%)	265 (55%)	NS
LBR, (%)	51 (39.8%)	194 (40.3%)	NS
Term delivery rate	39/51 (76.5%)	173/194 (89.1%)	**0.03**
Preterm delivery rate	12/51 (23.5%)	21/194 (10.9%)	**0.03**
Pregnancy Losse rate, (%)	31 (24.2%)	108 (22.4%)	NS
Clinical pregnancy losses	22 (27.1%)	61 (19.5%)	NS
(before or after 12 weeks of gestation)			
Biochemical pregnancy losses	9 (7.0%)	47 (9.7%)	NS
Multiple pregnancy rate, (%)	3 (3.7%)	20 (3.4%)	NS
Endometrial preparation, (%)			
Natural (modified or true natural)	64 (50%)	237 (49.3%)	NS
Artificial (estrogen replacement therapy)	64 (50%)	244 (50.7%)	NS
Endometrial thickness (mm)	8.9 ± 1.4	10.1 ± 1.7	**<0.001**
Mean number of frozen blastocysts per patient	5.8 ± 3.6	5.28 ± 4.4	NS
Number of frozen-thawed blastocysts per cycle	1.3 ± 0.6	1.2 ± 0.5	NS

Abbreviations: IR: implantation rate, CPR: clinical pregnancy rate, LBR: live birth rate, FET: frozen-thawed embryo transfer, PGT-A: Preimplantation genetic testing for Aneuploidy, ET: embryo transfer, TQ: top quality, GQ: good quality, NS: not significant. Data are expressed as mean ± SD or percentages (n) as appropriate,

fidure 4

109x174mm (72 x 72 DPI)