What is the best time to perform intracytoplasmic sperm injection/embryo transfer cycle after hysteroscopic surgery for an incomplete uterine septum?

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Objective: To determine whether there is an optimal time period to perform intracytoplasmic sperm injection (ICSI)/embryo transfer cycle after hysteroscopic resection of an incomplete uterine septum.
Design: A retrospective cohort study.
Setting: Private infertility clinic.
Patient(s): A total of 282 women, who had undergone an ICSI/embryo transfer cycle after hysteroscopic resection of an incomplete uterine septum (from May 6, 2003 to January 1, 2006).
Intervention(s): One hundred thirty-three patients (group A) underwent an ICSI/embryo transfer cycle within 9 weeks after hysteroscopic resection of an incomplete uterine septum, 93 patients (group B) underwent an ICSI/embryo transfer cycle between 10 and 16 weeks after hysteroscopic resection of an incomplete uterine septum, and 56 patients (group C) underwent an ICSI/embryo transfer cycle more than 17 weeks after hysteroscopic resection of an incomplete uterine septum.
Main Outcome Measure(s): Peak E_2 levels, total recombinant FSH dosage, MII oocytes retrieved, number of embryos transferred, number of grade 1 embryo transferred, pregnancy rate (PR; positive hCG), clinical PR (positive fetal cardiac activity), implantation rate, and first trimester miscarriage rate.
Result(s): Pregnancy rates were 52.6%, 52.6%, and 46.4% for groups A, B, and C, respectively. Clinical PRs were 45.8%, 43.1%, and 41.1% for groups A, B, and C, respectively. Implantation rates were 21.1%, 17.6%, and 22.1% for groups A, B, and C, respectively. First trimester miscarriage rates were 6.4%, 7.9%, and 5.1% for groups A, B, and C, respectively. There were no significant differences in the etiology of infertility, age, length of infertility, previous spontaneous abortion rates, length of septum, peak serum E_2 concentration, total recombinant FSH dosage, total number of MII oocytes retrieved, number of embryos transferred, number of grade 1 embryos transferred, PRs, clinical PRs, implantation rates, and first trimester miscarriage rate between the three groups.
Conclusion(s): Starting an ICSI/embryo transfer cycle just after the hysteroscopic procedure does not result in any impairment in implantation rate or PR compared to those started 10 or more weeks after the operation. (Fertil Steril® 2008;90:2112–5. ©2008 by American Society for Reproductive Medicine.)

Key Words: Hysteroscopy, uterine anomaly, septum, ICSI

Congenital abnormalities of the Müllerian ducts are relatively common and contribute to the problems of infertility, recurrent pregnancy loss, and poor pregnancy outcome (1–3). Müllerian anomalies are encountered with a prevalence of 2%–3% in fertile women and 3% in infertile women, although less than half have clinical symptoms (4–6).

Lack of resorption of the midline septum between the two Müllerian ducts results in defects that range from a slight midline septum to a complete division of the endometrial cavity. The current classification criteria for Müllerian anomalies are dependent on subjective definitions rather than quantified measurements or cutoff values (7). A precise definition of the so-called incomplete septum (or subseptum) based on strict quantification measurements is lacking in the literature. A previous study reported the diagnosis and measurement of an incomplete septum using transvaginal sonohysterography in a nonselected infertile population (8).

Among the different types of structural uterine anomalies, the septate uterus is the most common (9, 10) and associated with the poorest reproductive outcome, with fetal survival rates of 6%–28% and a high rate of spontaneous miscarriages (>60%) (1, 2, 11). Septa have also been claimed to be an

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etiologic factor for infertility. Decrease in sensitivity of the endometrium covering the septa to preovulatory changes may be the cause of infertility (12).

The septate uterus is also the type of Müllerian anomaly that is most amenable to simple hysteroscopic treatment. Hysteroscopic metroplasty has been shown to be a safe, simple, and expeditious method of treating the septate uterus (13). The results are comparable to those achieved with the abdominal approach. Many IVF centers now recommend removal of the septum before assisted reproductive treatment (ART) to reduce the possibility of miscarriage (9). In a recent study, it has been shown that hysteroscopic correction of an incomplete uterine septum before IVF improves pregnancy outcome (14).

Hysteroscopic approach has been the preferred method for the treatment of the septate uterus since 1974 after its first introduction (15). But it is usually advised to delay attempts at pregnancy for at least two cycles. The purpose of this retrospective cohort study is to determine whether delaying intracytoplasmic sperm injection (ICSI)/embryo transfer after hysteroscopic uterine septum resection is justified, and whether there is an optimum time to wait.

MATERIALS AND METHODS

Patients who were candidates for IVF procedures underwent sonohysterography. In our center it is a standard practice to perform ICSI on all couples rather than IVF. During examination with sonohysterography, if the difference between the fundal midsagittal myometrial thickness and the cornual myometrial thickness was more than 5 mm (8, 14), a diagnostic hysteroscopic examination was performed. If an incomplete septum was detected, hysteroscopic septal incision was performed using a resectoscope. The percentage of patients who needed hysteroscopic metroplasty is 13.5% in patients who were candidates for ICSI. Concomitant laparoscopy was added only in cases to complete the diagnostic workup in patients with infertility and to treat any coexisting pelvic pathology, including proximal tubal occlusion of hydrosalpinxes. In other cases, ultrasonographic guidance was used during hysteroscopic metroplasty.

The study group included 282 infertile women who had undergone hysteroscopic resection for an incomplete uterine septum and then underwent ICSI/embryo transfer cycles (from May 6, 2003 to January 1, 2006). The study was approved by the institutional ethical committee.

Hysteroscopic metroplasty was performed with a hysteroscope (Karl Storz, Tuttlingen, Germany) whose surgical sheath had an outer diameter of 9 mm. The uterine cavity was distended with 5% mannitol (Resectisol; Eczacıbası/Baxter, Istanbul, Turkey). The endocervical canal, uterine cavity, and endometrium were inspected methodically. Then the incision of the incomplete septum was started with a monopolar electric resectoscope (Karl Storz). The incision was performed equidistant between the anterior and posterior uterine walls and extended up to the fundus, but not into the fundal myometrium with an L-type electrode attached to the resectoscope. A prophylactic antibiotic of 0.5 mg of cefazoline (Sefazol; Mustafa Nevzat, Istanbul, Turkey) was used, but postoperative hormonal therapy was not added. Sonohysterography was repeated postoperatively when the patients were entered into the ICSI program. If the examination reveals normal findings, the ICSI program was started.

The ICSI/embryo transfer cycles were performed after administration of luteal GnRH agonist (LA; Lucrin daily; Abbott, Istanbul, Turkey) and recombinant gonadotropins (Gonal F; Serono, Bari, Italy or Puregon; Organon Oss, Holland) for controlled ovarian hyperstimulation (COH). Embryos were transferred on day 2. The grading criteria for embryos were based on cell number, evenness of blastomeres, and the amount of fragmentation. Embryo quality was graded from 1 (best quality) to 4 (worst quality), as described previously (16).

The patients were divided into three groups. Group A included 133 women having an ICSI/embryo transfer cycle within 9 weeks after hysteroscopic resection for an incomplete uterine septum.

Group B included 93 women having an ICSI/embryo transfer cycle between 10 and 16 weeks after hysteroscopic resection for an incomplete uterine septum.

Group C included 56 women having an ICSI/embryo transfer cycle more than 17 weeks after hysteroscopic resection for an incomplete uterine septum.

The clinical outcomes including pregnancy rates (PR; positive hCG), clinical PRs (positive fetal cardiac activity) and implantation rates, and first trimester miscarriage rates were compared between the three groups.

Statistical Analysis

Etiology of infertility, age, percentage of patients more than 37 years of age, length of infertility, previous spontaneous abortion rate, length of septum, percentage of patients with more than a 10-mm septum, antral follicle count, day 3 FSH, peak E_2 levels, total recombinant FSH dosage, MII oocytes retrieved, number of embryo transferred, number of grade 1 embryos transferred, PR (positive hCG), clinical PR (positive fetal cardiac activity), implantation rate, and first trimester miscarriage rate were compared between the groups.

Analysis of variance (ANOVA) and χ^2 test were used for statistical comparisons. $P<.05$ was considered statistically significant. Statistical calculations were performed using Sigmastat for Windows, version 3.0 (Jardel Scientific Corporation, San Rafael, CA).

RESULTS

There was no statistically significant difference in cause of infertility of the study groups (Table 1). Furthermore, there was no statistically significant difference in age, percentages of patients more than 37 years of age, length of infertility, previous spontaneous abortion rates, length of septum,

TABLE 1

Etiology for infertility.

	Group A (≤9 weeks)	Group B (10–16 weeks)	Group C (≥17 weeks)
No. of patients	133	93	56
Tubal factor (%)	11.2	16.1	7.1
Male factor (%)	31.5	29.1	39.4
Ovulatory (%)	4.9	6.4	5.6
Unexplained (%)	15.7	22.5	18.2
Multifactorial (%)	31.5	22.5	32.1

Note: All *P* values are not significant.

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percentage of patients with more than a 10-mm septum, total number of antral follicles, day 3 FSH, peak E_2 level, dosage of recombinant FSH used, total number of MII oocytes retrieved, number of embryos transferred, and number of grade 1 embryos transferred between groups A, B, and C (Table 2).

In addition, there was no difference in the PR, the clinical PR, the implantation rates, and first trimester miscarriage rates between groups A, B, and C (Table 1). Pregnancy rates were 52.6%, 52.6%, and 46.4% for groups A, B, and C, respectively. Clinical PRs were 45.8%, 43.1%, and 41.1% for groups A, B, and C, respectively. Implantation rates were 21.1%, 17.6%, and 22.1% for groups A, B, and C, respectively. First trimester miscarriage rates were 6.4%, 7.9%, and 5.1% for groups A, B, and C, respectively.

DISCUSSION

Among congenital uterine abnormalities, the septate uterus is associated with the highest incidence of reproductive failure and obstetric complications, including first and second trimester recurrent miscarriage, premature delivery, abnormal fetal presentation, intrauterine growth retardation (IUGR), and infertility.

The role of metroplasty in patients with primary infertility remains controversial (17, 18). Some investigators

TABLE 2

Demographic features and clinical outcomes.

	Group A (≤9 weeks)	Group B (10–16 weeks)	Group C (≥17 weeks)
No. of patients	133	93	56
Age (y)	32.1 ± 0.4	31.9 ± 0.5	33.4 ± 0.7
Age >37 y (%)	14.2	12.9	19.2
Length of infertility (y)	6.8 ± 0.6	7.2 ± 0.6	7.7 ± 0.7
Previous spontaneous abortions (%)	12.9	16.8	16.7
Length of septum (mm)	8.4 ± 0.4	8.1 ± 0.6	8.7 ± 0.7
Septum >10 mm (%)	13.6	11.8	14.5
Antral follicle count	15.9 ± 1.7	17.8 ± 1.8	17.9 ± 2.4
Day 3 FSH (IU/L)	7.1 ± 1.9	6.9 ± 1.8	7.3 ± 1.9
FSH ampules	49.5 ± 1.7	51.9 ± 2.2	52.2 ± 3.1
Peak E_2 levels	2,263.2 ± 142.1	2,131.2 ± 175.3	1,895.4 ± 223.5
MII oocytes retrieved	10.8 ± 0.6	11.9 ± 0.6	10.5 ± 1.1
Embryos transferred	3 ± 0.1	3.1 ± 0.1	2.7 ± 0.2
G_1 embryos transferred	2 ± 0.2	2.1 ± 0.2	2 ± 0.2
Pregnancy rate (%)	52.6	52.6	46.4
Clinical pregnancy rate (%)	45.8	43.1	41.1
Implantation rate (%)	21.1	17.6	22.1
1st trimester miscarriage rate (%)	6.4	7.9	5.1

Note: All *P* values are not significant.

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recommend treatment in this situation, but others do not (19). However, with the introduction hysteroscopic surgery, removal of the septum is usually recommended whenever it is diagnosed, not only because of its possible beneficial effect on fecundity but also because of the potential benefits of reduced rates of miscarriage and preterm labor if these women conceive (20, 21). Therefore, many IVF centers now recommend removal of the septum before ART to reduce the possibility of miscarriage (9). In accordance a recent study has shown that hysteroscopic correction of an incomplete uterine septum before IVF improves the pregnancy outcome (14).

Surgical correction of septate uterus traditionally was performed by transabdominal metroplasty, which required a long postoperative interval before conception (3–6 months) (13). During this procedure, the full thickness of the uterine fundus was damaged and it was associated with a significant risk of scar rupture. This mode of therapy dictates that the mode of delivery in a subsequent pregnancy must be by cesarean section.

Since the first introduction of the hysteroscopic approach for the treatment of septate uterus in 1974 (15), hysteroscopic metroplasty has become an outstanding tool for the treatment of the septate uterus. This method has universally replaced transabdominal metroplasty. Although hysteroscopic excision of uterus septum leaves an injured area within the endometrial cavity, it is rapidly covered by nearby healthy endometrium. Mencaglia and Tantini (17) have shown healing of the injured area within 1 month by doing postoperative hysteroscopy 1 month after surgery.

At present, to our best knowledge, there is no data regarding when to start an ICSI cycle in patients having hysteroscopic surgery for complete or incomplete septate uterus. Although it is usually recommended to try attempts at pregnancy more than 2 months after hysteroscopic metroplasty, there are no evidence-based studies supporting this claim. The results of our study show that starting an ICSI/embryo transfer cycle just after the hysteroscopic procedure does not result in any impairment in implantation or PR compared to those started 10 or more weeks after the operation.

Therefore, if an ICSI/embryo transfer cycle is planned after hysteroscopic resection of an incomplete uterine septum, there is no reason to delay attempts at starting the cycle.

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