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ASSISTED REPRODUCTION TECHNOLOGIES

Perinatal outcomes in singleton and twin ICSI pregnancies following hysteroscopic correction of partial intrauterine septa

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Abstract
Purpose To investigate the perinatal outcomes of patients with clinical pregnancies from ICSI treatments who had previously undergone hysteroscopic surgery to correct partial intrauterine septa and compare them to outcomes of patients with no intrauterine anomalies.
Method A retrospective observational analysis of 2024 ultrasound confirmed pregnancies from ICSI treatments performed between January 2005 and June 2012. The patients were grouped according to their intrauterine status, and subgrouped according to the number of fetal hearts observed; singleton control (n=1128), twin control (n=566), singleton septum (n=217) and twin septum (n=113). The primary outcomes analyzed were miscarriage, preterm, very preterm, stillbirth, vanishing twin and live delivery rates, as well as low birth weight and very low birth weight rates.
Result(s) The live birth rate (89,9 %) in the singleton control subgroup was non-significantly higher than the live birth rate (85,3 %) in the septum subgroup, with a RR of 1,05 (p=0, 0583, 95 % CI 0,9943–1,1182) for live birth. In contrast the live birth rate (91,3 %) in twin control subgroup was significantly higher than the live birth rate (84,1 %) in the septum subgroup, with a RR 1,09 (p=0,0282, 95 % CI 0,9988–1, 1819). Non-significantly, higher miscarriage and stillbirth rates were the main contributors to the reduced live birth rates. The singleton and twin septum subgroups also had higher rates of premature and very premature delivery and LBWs and vLBW, especially in the singleton septum subgroup.
Conclusion(s) The hysteroscopic correction of intrauterine septa may not eliminate all risks for premature delivery.

Keywords Hysteroscopy · Partial intrauterine septum · Miscarriage · Preterm delivery · Live birth

Capsule While hysteroscopic correction of partial septa may significantly reduce adverse perinatal outcomes, some losses most probably attributable to the pre-existance of intrauterine septa may persist, especially in cases of twin pregnancy.

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Introduction

The septate uterus is the most common of the intrauterine anomalies. The abnormality develops during embryogenesis, when the partition between the two fused Müllerian ducts does not get completely resorbed, resulting in a fibro-muscular septal structure that can partially or completely divide the uterine cavity into two parts [1, 2]. The reported prevalence of intrauterine anomalies has varied widely (10–20 %), due to the different diagnostic imaging modalities and classification systems used, and the differences in the patient populations examined and reported on (i.e., women with normal fertility, unexplained or primary infertility, and recurrent pregnancy loss) [3]. The general agreement is, however, that the prevalence is highest in women with recurrent pregnancy loss and long-term infertility. The myometrium of an intrauterine septum generally has a structure different from that of normal intrauterine myometrium [1, 2, 4, 5]. The altered myometrial structure provides fibromuscular and vascular conditions that may negatively affect the support required for an ongoing or term pregnancy [1]. In many cases, the presence of an intrauterine septum may even be associated with cervical incompetence, and if so, this will further complicate pregnancies from progressing to term [1]. These intrauterine changes have been reported to

reduce uterine function and performance significantly, resulting in increased rates of implantation failure, pregnancy loss, preterm delivery, adverse fetal presentations, and ultimately long-term infertility [6–10].

The prevalence, significance and often asymptomatic nature of intrauterine septa makes the deliberate screening of women presenting with infertility for intrauterine anomalies an essential part of patient fertility management in ART [1, 2, 11]. A patient screening process with a presumed >90 % accuracy in the diagnosis and classification of genital tract anomalies has been suggested to include the following procedures: a gynecological examination, a 2D ultrasound examination, a sono-hysterographic (sono-HG) examination, and a diagnostic hysteroscopy [1]. However, while the improvements in the technologies used for visualization have helped to significantly increase the diagnostic accuracy, the clinical interpretation of examinations has remained troublesomely inconsistent. The reason for the inconsistency has been leveled at the lack of appropriate and consensual classification systems [11–15]. The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) in recognition of this problem have recently developed an improved classification system, using a DELPHI procedure to obtain scientific consensus for its formulation [15].

There is now evidence to suggest that even a small, arcuate class of septum cannot be regarded as an harmless abnormality [7, 9]. Women with small intrauterine septa have been reported to have impaired reproductive outcomes similar to those of women with large intrauterine septa [7, 9]. Therefore, based mainly on the observational evidence available, hysteroscopic surgery has been recommended for all infertile women diagnosed with intrauterine septa, irrespective of size [2, 6, 8, 9]. Fortunately, the low risk profile (i.e., side effects and complications) of hysteroscopic surgery mitigates the adoption of such a liberal therapeutic approach in ART.

In our previous study, involving infertile women with partial intrauterine septa, the primary outcomes reported on were implantation and pregnancy. The results from that study showed, that infertile women who had their partial septa corrected prior to having treatment by ICSI had reproductive outcomes similar to women with no intrauterine anomalies [6]. In this, follow-up study we analyzed the effect of hysteroscopic surgery to correct partial intrauterine septa on the perinatal outcomes.

Materials and methods

Patients

This retrospective observational study was conducted at a private ART clinic (Antalya IVF, Turkey; www.antalyatupbebek.com.tr) with Institutional Ethics committee approval (reference no. 444/2014) and patient consent to the use of non-identifying data in research studies. The pre-treatment consultation notes, operation notes, and in vitro procedure reports of the selected patients with clinical pregnancies from ICSI treatments performed between January 2005 and June 2012 were reviewed and analyzed. A pregnancy was assessed to be clinical if an ultrasound examination after the 7th week of gestation revealed a fetal sac with a normal fetal heart activity. Only clinical pregnancies were included in the study to limit pregnancy losses that were more related to embryo factors, such as embryo blastomere quality and embryo euploidy [16], rather than uterine factors.

The first patient cycle extraction based on clinical pregnancy delivered a primary study population of 2966 patient cycles (Fig. 1). If one or more of the following were found in the notes and reports of the patient cycles, the cycles were excluded from the study: all required data was not recorded, >2 fetal heartbeats were observed, fetal reductions or terminations were performed, other intrauterine anomalies were found, a partial intrauterine septum was corrected at another surgical unit, a partial intrauterine septum was not corrected, and monochorionic or empty sac pregnancies. The secondary study population that resulted from this exclusion process was further conditioned to eliminate all duplicate patient cycles; only the 1st treatment cycle following hysteroscopic surgery and only the 1st treatment cycle for a patient (control patients) in the study period was selected. This extraction and selection process provided a final sample population of 2024 patient cycles (Fig. 1), which was then grouped into patients with no intrauterine anomalies (control group; $n=1694$) and patients with corrected partial intrauterine septa (septum group; $n=330$). These two groups were further divided into singleton pregnancy (singleton control $n=1128$ and singleton septum $n=217$) and twin pregnancy (twin control $n=566$ and twin septum $n=113$) subgroups.

Diagnosis

At first infertility consultations, patient uterine cavities were examined by transvaginal ultrasound and a follow-up sono-HG examination was performed if there was any evidence to suggest the presence of an intrauterine abnormality. A partial septate diagnosis was made based on intrauterine myometrium thickness measurements of the fundal (Fm) and cornual (Cm) regions [5, 11]. If the Fm was <11 mm and the difference between Fm and Cm was <5 mm the uterus was diagnosed to be normal. All patients diagnosed with a partial septate uterus (>11 mm; Fm and >5 mm; Fm-Cm) were offered hysteroscopic surgery as an option to improve their fertility.

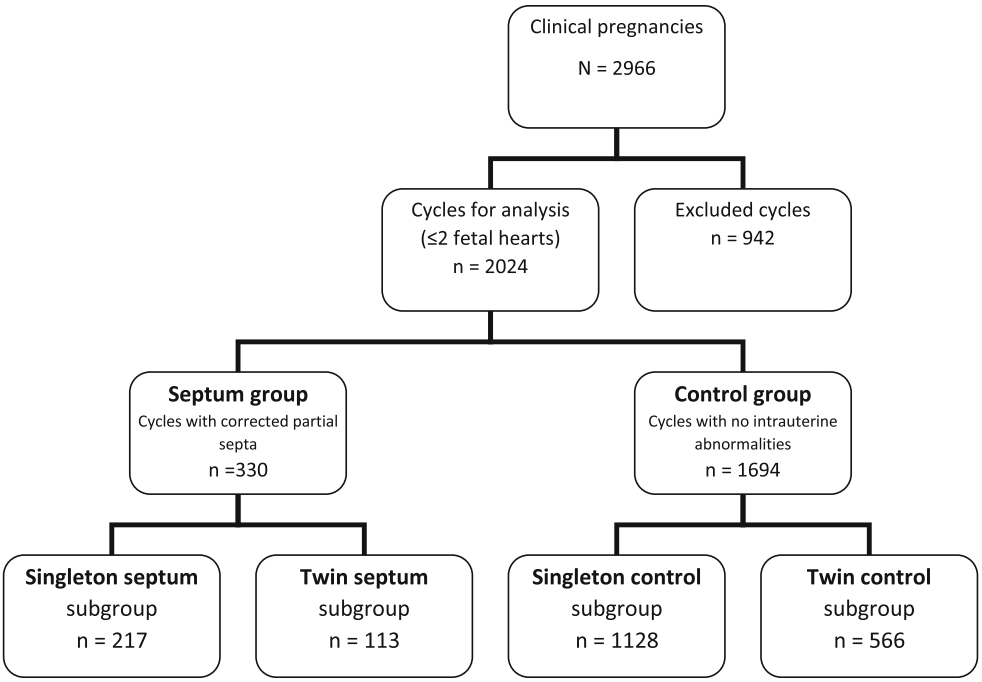

Fig. 1 The flow chart of patient cycle selection and grouping for comparative analysis

Partial intrauterine septum correction

Three clinicians with fertility specializations performed all the hysteroscopic surgeries and all the ART treatments during the study period. Hysteroscopic procedures were scheduled for the early proliferation phase of patients' menstrual cycles, to ensure a thin endometrium and the absence of bleeding. The procedures were performed under general anesthesia, with misoprostol (200 g Cytotec; Searle, UK) given vaginally 2 h before the start of the procedures. The hysteroscopic surgeries were performed using a 26 French resectoscope (Karl Storz, Tuttlingen, Germany) and a monopolar, 90° angled, cutting knife electrode. During the procedures, the cervixes were dilated and the uterine cavities distended, using a 5 % mannitol solution (Resectisol, Eczacıbası-Baxter) with manually applied pressure to the flow system. The cutting knife electrode was used at a power setting of 50 W. Electro-incisions to the septum were made equidistantly between the anterior and posterior uterine wall and went up high to the uterine fundus until the area between the tubal ostia was in a straight line. When completed the intrauterine pressure was decreased and any bleeding points electro-desiccated. One month following surgery, patients had a follow-up ultrasound examination to re-measure the intrauterine myometrial dimensions. Patients with a Fm <11 mm and Fm-Cm <5 mm, had their treatment records annotated with the term 'corrected partial intrauterine septum' and patients in whom the dimensions were still outside what was considered normal had their treatment records annotated with the term 'modified partial intrauterine septum

Assisted reproductive treatment

The patients who had hysteroscopic surgery had their ICSI treatment cycles scheduled to start at least 2 months after the date the surgery [17]. Short GnRH antagonist protocols were used for all controlled ovarian stimulations (COSs). All oocytes were inseminated using intracytoplasmic sperm injection (ICSI) [18]. Luteal phase support was started on the day of the oocyte pick-up (OPU) procedure, which consisted of the daily administration of E2 (Estrofem, Novo Nordisk, 2 mg BD) and P4 (Crinone, Merck Serono, 8 % BD). Luteal phase support was maintained until the 9th week of gestation, if the day 14 βhCG concentration exceeded 30 IU/mL. Prior to 2009, all embryo transfers were performed on day 2 of embryo culture (<4 embryos/transfer). After 2009, all embryo transfers were performed on day 3 or day 5 (<3 embryos/transfer).

Outcomes and statistics

Pregnancy was defined as a day 14 βhCG serum concentration of >30 IU/mL. A clinical (ongoing) pregnancy was defined as a pregnancy where ultrasound revealed at least one gestational sac with cardiac activity after the 7th week of gestation. Live birth was defined as a delivery of a live infant after the 20th week of gestation, surviving for at least 7 days. The delivery of a singleton or twin pregnancy was counted as one live birth. Miscarriage was defined as the spontaneous loss of a clinical pregnancy before the 20th week of gestation. Preterm delivery was defined as a delivery of a live infant prior to 37 weeks and very preterm as a delivery prior to 32 weeks.

Stillbirth was defined as a delivery of a deceased infant after 22 weeks. Low birth weight (LBW) was defined as the delivery of a live infant with a weight of less than 2500 g and very low birth weight (vLBW) with a weight of less than 1500 g. All obstetric care was provided by obstetricians who operated independently of Antalya IVF, but with full knowledge of the origins and nature of the pregnancies.

All calculated rates were based on the number of clinical pregnancies in each group or subgroup. MedCalc version 13.0.6 was used for statistical analysis and to obtain the confidence intervals and risk ratios (RR). Descriptive statistics were presented as the mean and standard deviation for continuous data and as percentages for the categorical data. The independent samples *t*-test was used to compare the means, and the chi-square or Fisher exact test was used for to determine statistical significance between percentages. $P<0.05$ was considered to be significant. Receiver operating characteristic (ROC) curves were calculated using ∑SigmaPlot 12,5, and used to determine whether age (miscarriage, preterm delivery and live birth) and years of infertility (live birth) could accurately discriminate specific perinatal outcomes.

Results

The comparative analysis was performed on treatment cycles with clinical pregnancies from the 7694 ICSI cycles performed during the period January 2005 to June 2012. The ICSI treatments during the study period resulted in an overall pregnancy rate of 47,1 % (n=3627; βhCG≥30 IU) and clinical pregnancy rate of 38,6 % (n=2966; >7-week fetal heart). Two thousand and twenty four clinical pregnancy cycles from the 2966 clinical pregnancies obtained were included in the final analysis, and in 330 (11,1 %) of these cycles, the patients had hysteroscopic surgery to correct partial intrauterine septa prior to their successful ICSI treatments (Fig. 1). The patient demographics and potential confounding factors of the cycles included in the comparative subgroups are presented in Tables 1 and 2. The infertility etiology classifications obtained for each of the 4 pregnancy subgroups formed were found to be statistically similar, with the major etiologies having the following approximate proportions; male factor 40 %, unexplained 20 %, anovulatory 10 % and tubal 10 %. The mean female BMIs (≈25 kg/m^2) in the 4 pregnancy subgroups were also statistically similar. Patients who had hysteroscopic surgery to correct partial intrauterine septa prior to achieving clinical pregnancies were however, on average older and had on average longer periods of infertility compared to patients who had no intrauterine anomalies (Tables 1 and 2). ROC calculations for age (miscarriage, preterm delivery and live birth) and years of infertility (live birth) showed that both were at best only poor in predicting the noted perinatal outcomes.

Singleton subgroup comparative analysis

The perinatal outcomes for the two singleton subgroups, control and septum, are presented in Tables 3 and 4. In the control subgroup a live birth rate of 89,9 % was obtained compared to the 85,3 % live birth rate obtained in the in the septum subgroup. The RR for live birth in the control subgroup was 1054 (p=0,0583, 95 % CI: 0,9943–1,1182). The mean gestational age of live births in the control subgroup was 0,5 weeks longer (p=0,0001) than for live births in the septum subgroup. However, this difference was not evident in the mean live birth weights (3162,6±508,9 vs 3168,5±632,7 g; p=0,8808) between the two subgroups. The higher live birth rate in the control subgroup was as a result of a non-statistically lower miscarriage rate (8,5 vs 10,6 %; p=0,3889) and a lower post-20 week loss rate, the latter indicated in part by the non-statistically lower stillbirth rate (1,4 vs 2,3 %; p=0,5062) in the control subgroup. Overall, the timing of losses between the two subgroups were not dissimilar (p=0,904) with the majority of losses in both occurring in the 1st and early 2nd trimester. In the control subgroup 86,8 % (99/114) and in the septum subgroup 87,5 % (28/32) of the losses occurred before 23 weeks of gestation. Infant morbidity and mortality are

Table 1 Comparison of demographical variables of the singleton control and singleton septum subgroups

	Control subgroup (n=1128)	Septum subgroup (n=217)	p-value
Age (yrs) mean±std (range)	30,6±4,95 (18,0–43,2)	32,5±4,94 (21,0–42,9)	<0,0001
Infertility (yrs) mean±std (range)	4,69±3,81 (0,16–19,0)	5,54±4,54 (0,30–18,5)	0,0036
BMI (kg/m^2) mean±std (range)	25,2±4,77 (16,0–46,8)	25,7±5,34 (16,0–50,0)	0,1659
Male (%)	40,9	42,5	0,7164
Unexplained (%)	20,3	23,7	0,2993
Endometriosis (%)	2,36	1,60	0,6580
Anovulatory (%)	10,2	11,3	0,7151
DOR (%)	3,93	1,60	0,1342
Tubal (%)	9,11	12,4	0,1681
Other (%)	13,25	7,0	0,0139

The subgroups were statistically compared using the independent samples *t* test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

Table 2 Comparison of the demographical variables of the twin control and twin septum subgroups

	Control subgroup (n=566)	Septum subgroup (n=113)	p-value
Age (yrs) mean±std (range)	29,3±4,64 (18,8–43,1)	31,7±4,88 (21,3–41,8)	<0,0001
Infertility (yrs) mean±std (range)	4,52±3,60 (0,16–22,0)	5,36±4,49 (0,50–17,5)	0,0306
BMI (kg/m^2) mean±std (range)	25,2±4,69 (15,0–42,5)	25,60±4,33 (17,0–41,0)	0,4023
Male (%)	42,1	43,3	0,8954
Unexplained (%)	20,4	22,1	0,7794
Endometriosis (%)	2,65	1,92	0,9020
Anovulatory (%)	10,5	8,7	0,6840
DOR (%)	5,30	3,85	0,6840
Tubal (%)	8,65	11,5	0,4344
Other (%)	10,5	8,65	0,6722

The subgroups were statistically compared using the independent samples t test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

perinatal outcomes closely associated with preterm delivery and LBWs. The preterm (14,2 vs 24,7 %; p=0,0004) and very preterm (1,8 vs 8,8 %; p<0,0001) delivery rates were both significantly lower in the control subgroup, with RRs of 0, 58 (95 CI: 0,4319–0,7674) and 0,21 (95 % CI: 0,1112–0, 3969), respectively (Table 4). The LBW rates were not significantly different (7,5 vs 8,8 %,p=0,6326) between the two singleton subgroups, but the vLBW rate was significantly lower (0,68 vs 2,58 %, p=0,0387) in the control subgroup.

Twin subgroup comparative analysis

The perinatal outcomes for the two twin subgroups, control and septum, are presented in Tables 5 and 6. In the control subgroup a live birth rate of 91,3 % was obtained, compared to the 84,1 % live birth rate obtained in the septum subgroup. The RR for live birth in the control subgroup was 1087 (p=0, 0282; 95 % CI: 0,9988–1,1819). In contrast to what was found in the singleton analysis, there was no statistical difference in the mean gestational age of live births (35,6 vs 35,3 weeks, p= 0,6990) in the twin analysis. The mean birth weights (2386,3 ±561,7 vs 2384,4±625,0 g, p=0,9743) of live deliveries in the twin analysis were also non-significantly different. The higher live birth rate in the control subgroup was also as a result of a non-statistically lower miscarriage rate (5,3 vs 8,0 %, p=0, 3735) and a lower post-20 week loss rate. In the twin subgroups, as in the singleton analysis, the latter was indicated in part by the lower stillbirths rates (4,2 vs 7,1 %, p=0,2904) in the control subgroup. In the twin analysis the timing of losses were dissimilar, although not significantly (p=0,795). In the control subgroup the majority of losses occurred in the 1st and early 2nd trimester (86,8 %, 99/144), while in the septum subgroup equal numbers of losses occurred in the 1st (33, 3 % 6/18), early 2nd (33,3 % 6/18) and late 2nd (33,3 %

Table 3 Comparison of the perinatal outcomes obtained in the singleton control and singleton septum subgroups

	Control subgroup (n=1128)	Septum subgroup (n=217)	p-value	RR (95 % CI)
Mean age (yrs) mean±std	30,6±4,95	32,5±4,94	<0,0001	
Miscarriage rate[a] (<20 weeks) % (n)	8,5 (96/1128)	10,6 (23/217)	0,3889	0,8030 (0,5331 to 1,2604)
Delivery rate (≥20 weeks) % (n)	91,5 (1032/1128)	89,4 (194/217)	0,3889	1,0234 (0,9743 to 1,0749)
Live birth rate[b] % (n)	89,9 (1014/1128)	85,3 (185/217)	0,0583	1,0544 (0,9943 to 1,1182)
Stillbirth rate[c] (>22 weeks) % (n)	1,42 (16/1128)	2,3 (5/217)	0,5062	0,6156 (0,2279 to 1,6628)
Mean gestational age of live births (weeks) mean±std (range)	37,8±1.53 (29–43)	37,3±2,30 (28–40)	0,0001	
Mean live birth weight (grams) mean±std (range)	3162,6±508,9 (770–5300)	3168,5±632,7 (900–4800)	0,8808	

The subgroups were statistically compared using calculated risk ratios, independent samples t test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

[a] Miscarriage was defined as the spontaneous loss of a clinical pregnancy before the 20th week of gestation

[b] Live birth was defined as a delivery of a live infant after the 20th week of gestation, surviving for at least 7 days

[c] Stillbirth rate, is the rate of delivery, where the infant was delivered still born after 22 weeks of gestation

Table 4 Comparison of adverse perinatal parameter outcomes obtained in the singleton control and singleton septum subgroups

	Control subgroup (n=1032)*	Septum subgroup (n=194)*	p-value	RR (95 % CI)
Preterm delivery rate[1] (<37 weeks) % (n)	14,2 (147/1032)	24,7 (48/194)	0,0004	0,5757 (0,4319 to 0,7674)
Very preterm delivery rate[1] (<32 weeks) % (n)	1,84 (19/1032)	8,76 (17/194)	<0,0001	0,2101 (0,1112 to 0,3969)
Low birth weight rate[2] (<2500 g) % (n)	7,5 (77/1032)	8,8 (17/194)	0,6326	0,8515 (0,5152 to 1,4071)
Very low birth weight rate[2] (<1500 g) % (n)	0,68 (7/1032)	2,58 (5/194)	0,0387	0,2632 (0,08439 to 0,8207)

The rates were calculated as per confirmed pregnancy or delivery, groups were statistically compared using calculated risk ratios, independent samples t test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

*The number of patient cycles with a delivery after 20 gestation weeks

[1] Preterm delivery was defined as a delivery of a live infant prior to 37 weeks and very preterm as a delivery prior to 32 weeks

[2] Low birth weight (LBW) was defined as the delivery of a live infant with a weight of less than 2500 g and very low birth weight with a weight of less than 1500 g

6/18) trimester. In both subgroups, however, all pregnancy losses occurred before 26 weeks (<32 weeks, very preterm). These losses were as result of miscarriages, stillbirths and combinations of vanishing twins and stillbirths. The vanishing twin is a phenomenon where one of the implantations of a twin pregnancy spontaneously reduces after 8 weeks of gestation. The vanishing twin rates was non-significantly lower (18,4 vs 21,2 %, p=0,6990) in the control subgroup. The number of vanishing twin cycles that resulted in preterm delivery was 25 (24,0 %) in the control subgroup and 5 (20,8 %) in the septum subgroup (p=0,997), with 5 and 1 of the vanishing twin cycles resulting in a total pregnancy loss respectively. Another rate describing the differences in functional capacity of uteruses in the two subgroups was the live twin delivery rate, with a higher rate (72,3 vs 63,7 %, p= 0,0870) achieved in the control subgroup.

Preterm delivery and LBW outcomes for the two twin subgroups are presented in Table 6. In the twin subgroup analysis only the very preterm delivery rates (9,7 vs 20,2 %, p=0, 0036) were significantly different, with a RR of 0,481 (95 % CI: 0,3029–0,762) for very preterm delivery in the control twin subgroup. Difference in preterm delivery rates was most probably masked by the predisposition of all twin pregnancies to be delivered preterm (<37 weeks), which may also have affected the birth weight outcomes, as both LBW (39,9 vs 40, 4 %, p=0,9826) and vLBWs (6,3 vs 8,7 %, p=0,5174)

Table 5 Comparison of the perinatal outcomes obtained in the twin control and twin septum subgroups

	Control subgroup (n=566)	Septum subgroup (n=113)	p-value	RR (95 % CI)
Mean age (yrs) mean±std	29,3±4,64	31,7±4,88	<0,0001	
Miscarriage rate[a] (<20 weeks) % (n)	5,3 (30/566)	8,0 (9/113)	0,3735	0,6655 (0,3249 to 1,3631)
Delivery rate (≥20 weeks) % (n)	94,7 (536/566)	92,0 (104/113)	0,3735	1,0289 (0,9713 to 1,09)
Live birth rate[b] % (n)	91,3 (517/566)	84,1 (95/113)	0,0282	1,0865 (0,9988 to 1,1819)
Live twin delivery rate[c] % (n)	72,3 (409/566)	63,7 (72/113)	0,0870	1,1341 (0,9779 to 1,3153)
Stillbirth rate[d] (>22 weeks) % (n)	4,2 (24/566)	7,1 (8/113)	0,2904	0,5989 (0,2761 to 1,2991)
Vanishing twin rate[e] % (n)	18,4 (104/566)	21,2 (24/113)	0,5626	0,8651 (0,5827 to 1,2845)
Mean gestational age of live births (weeks) mean±std (range)	35,6±2,4 (25–40)	35,5±3,0 (27–41)	0,6990	
Mean live birth weight (grams) mean±std (range)	2386,3±561,7 (760–3845)	2384,4±625,0 (850–4000)	0,9743	

The subgroups were statistically compared using calculated risk ratios, independent samples t test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

[a] Miscarriage was defined as the spontaneous loss of a clinical pregnancy before the 20th week of gestation

[b] Live birth was defined as a delivery of a live infant after the 20th week of gestation, surviving for at least 7 days

[c] Live twin delivery rate, is the rate of delivery, where delivered alive and survived for at least 7 days

[d] Stillbirth rate, is the rate of delivery, where at least one of the infants was delivered still born after 22 weeks of gestation

[e] Vanishing twin rate, is the rate of live delivery, where one gestation spontaneously reduced

Table 6 Comparison of adverse perinatal parameter outcomes obtained in the twin control and twin septum subgroups

	Control subgroup (n=536)*	Septum subgroup (n=104)*	p-value	RR (95 % CI)
Preterm delivery rate[1](<37 weeks) % (n)	60,3 (323/536)	59,6 (62/104)	0,9891	1,0108 (0,8507 to 1,2011)
Very preterm delivery rate[1] (<32 weeks) % (n)	9,7 (52/536)	20,2 (21/104)	0,0036	0,4805 (0,3029 to 0,762)
Low birth weight rate[2] (<2500 g) % (n)	39,9 (214/536)	40,4 (42/104)	0,9826	0,9886 (0,7657 to 1,2765)
Very Low birth weight rate[2] (<1500 g) % (n)	6,3 (34/536)	8,7 (9/104)	0,5174	0,7330 (0,3625 to 1,4821)

The rates were calculated as per confirmed pregnancy or delivery, groups were statistically compared using calculated risk ratios, independent samples t test for means and Fisher's exact test and Chi square test for percentages, $p<0.05$ being significant

*The number of patient cycles with a delivery after 20 gestation weeks

[1] Preterm delivery was defined as a delivery of a live infant prior to 37 weeks and very preterm as a delivery prior to 32 weeks

[2] Low birth weight (LBW) was defined as the delivery of a live infant with a weight of less than 2500 g and very low birth weight with a weight of less than 1500 g

deliveries were non-significantly different between the two subgroups.

Discussion

In our clinical pregnancy follow-up study, we analyzed the perinatal outcomes of singleton and twin pregnancies in patients who had hysteroscopic surgery to correct partial intrauterine septa prior to conception and compared them to singleton and twin pregnancy outcomes in patients with no intrauterine anomalies. The septum patients in our study were older (≈2 years) and had longer periods of involuntary infertility (≈0,85 years) than the control patients. Although both these factors are known to contribute significantly to the probability of pregnancy and perinatal outcomes [19], no strong association with any of the primary perinatal outcomes in our study could be statistically confirmed. The live birth rates per confirmed clinical pregnancy in the control patient (singleton and twin) were approximately 90 %, while the live birth rates in the septum patients with singleton and twin pregnancies were 4,6 and 7,2 % lower, respectively. The mean birth weights of live infants born were not significantly different between the septum and the control patients, with differences ranging between 1,9 and 5,9 g. This lack of difference is encouraging outcome, as it showed that fetal growth was not restricted in the septum patients relative to the control patients and, therefore, did not add to the risks of infant morbidity and mortality in the septum patients [19].

In the review by Homer et al. [2], studies investigating the in vivo time-to-pregnancy outcomes in septate patients who had surgical treatment and those who had no treatment were analyzed. A meta-analysis calculated a mean miscarriage or pregnancy loss rate of 88 % and a term delivery rate of only 3 % in patients who had no surgical treatment. In patients who had surgical treatment the calculated pregnancy loss rate was 14 %, only, and the term delivery rate increased to 80 %, showing a significant improvement in the reproductive performance of operated patients. In support of these findings, a study by Ban-Frangez, et al. [20], showed abortion rates in ART singleton pregnancies to be similar to those of the 'in vivo' studies. The abortion rate in the before surgery group was significantly higher than in their normal controls (≈80 vs 20 %), for women with a small as well as a large septum. After surgery, the abortion rate in both groups reduced to the same level as that observed in women with no intrauterine anomalies. In another study by Tomazevic et al. [9], the authors investigated live birth outcomes from ART treatments and observed live births per pregnancy of approximately 20 % before surgery in women with both small and large septa, compared to live birth rates of 74–83 % in normal controls. After surgery, the observed live birth rates in both septa groups were comparable to the live birth rates in women with normal uteruses. All these studies describe reproductive outcomes in broad terms (i.e., pregnancy, abortion, and live birth). According to these terms and rates, the data from our study confirms that hysteroscopic surgery to correct a partial intrauterine septum does significantly improve reproductive outcomes. The live birth rate (85,3 %) and mean gestational age of live births (37,3 weeks) obtained in septum patients with singleton pregnancies was non-significantly lower than in the control patients. Even though the live birth rate in the septum patients with twin pregnancies was a high 84,1 %, it was significantly lower than in the control patients. Although SET has significantly reduced the incidence of multiple pregnancy in ART over the last decade, we included the twin pregnancy analysis in our study, as SET has not been universally implemented [18].

In our study, we were able to perform a more detailed comparative analysis of pregnancy progression and outcomes. From a previous study [21], we know that the majority of pregnancy losses in women who had intrauterine septa, and who suffered from recurrent miscarriage, occurred in the mid to late 1st trimester and early 2nd trimester of pregnancy. The data from our study corroborate these findings as the vast majority of losses appeared to occur between 7and 21 weeks

(86,8–87,5 %) in both the control and septum singleton pregnancies. However, in septum patients with twin pregnancies the loss changed significantly, with an increased number of losses occurring between weeks 22 and 26 of gestation (late 2nd trimester; 33,3 % 6/18). When analyzing both singleton and twin pregnancies the loss rates in these periods were all non-significantly higher in the septum patients, but contributed cumulatively to the lower live birth rates observed in the septum patients. In respect to patient care, our results suggest that septum patients with singleton pregnancies may require additional observational care during the period late 1st trimester to early 2nd trimester.

In the study by Tomazevic et al. [7], they observed that a hysteroscopic correction of intrauterine septa lead to reduced preterm delivery rates and very preterm delivery rates in patients with singleton pregnancies - comparable to levels in control patients. Preterm delivery is significantly associated with intrauterine septa [6–10] and can, therefore, contribute significantly to lower live birth rates [22, 23]. In our study, the relative risks of preterm delivery were still higher in the septum patients who had hysteroscopic surgery. The relative risks for preterm (RR=0,576) and very preterm delivery (RR=0, 210) were significantly lower in the singleton pregnancy control patients, while only the risk of very preterm delivery (RR=0,733) was significantly lower in the twin pregnancy control patients. The comparable risk of preterm delivery observed in our twin pregnancy have a higher risk of preterm delivery (<37 gestation weeks). The LBW outcomes observed in our study mirror the outcomes observed for premature delivery, with increased relative risks seen for vLBWs in the singleton and twin pregnancy septum patients. The increased number of premature deliveries still seen in the septum patients of our study contributed to the higher loss rates seen above 22 weeks in both the singleton (4,2 vs 1,6 %) and the twin pregnancy (8,0 vs 3,4 %) patients, and ultimately to lower live birth rates.

Although surgical technologies have improved greatly, the procedures may still induce unintentional inflammatory reactions, that may affect placentation and, thus, the peri-implantation and perinatal outcomes of subsequent conceptions [24, 25]. The data from our study shows that some patients who had hysteroscopic surgery for partial intrauterine septa may still be susceptible to a greater risk of fetal loss, possibly due to intrauterine factors that are non-correctable [1, 2, 5]. These etiologies remain largely unknown, however, studies have suggested that factors like altered intrauterine pressure dynamics and/or cervical incompetence are the most probable mechanisms underlying these losses [1, 2, 23]. A number of strategies to prevent early pregnancy loss and preterm delivery have been investigated, such as cervical cerclage, bed rest, and progesterone supplementation [26–28]. Applying the appropriate strategy prophylactically may help to reduce preterm delivery and fetal loss in patients who had surgery to correct partial intrauterine septa.

In conclusion, the results from our combined studies have confirmed the importance of performing prophylactic hysteroscopic surgery for partial intrauterine septa before the commencement of ART treatment. Even though this surgery may not restore all aspects of uterine performance, surgery will help to maximize the chances of implantation [5], and minimize the risk of pregnancy loss through miscarriage and preterm delivery. The perinatal outcome rates and patterns in patients with singleton pregnancies after hysteroscopic surgery were, however, comparable to the outcomes of controls – in contrast to the findings in the twin pregnancy group. Multiple pregnancies, therefore, should be avoided in septum patients. Based on the present finding it is suggested that all ART patients should be screened for intrauterine septa prior to treatment, using procedures that provide a more than 95 % diagnostic accuracy. Importantly, although our data is reassuring, patients with septa should still be informed that while their fertility potential will benefit significantly from surgery, they may still have a higher risk of pregnancy loss which can be reduced by applying SET.

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