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Original Article

Single Euploid Embryo Transfer Outcomes after Uterine Septum Resection

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ABSTRACT **Study Objective:** To study pregnancy outcomes after single euploid embryo transfer (SEET) in patients who underwent prior uterine septum resection to those with uteri of normal contour, without Müllerian anomalies or uterine abnormalities including polyps or fibroids, and without a history of prior uterine surgeries.

Design: Retrospective cohort study.

Setting: Single academic affiliated center.

Patients: 60 cycles of patients with prior hysteroscopic uterine septum resection who underwent an autologous SEET between 2012 and 2020 were used as the investigational cohort. A 3:1 ratio propensity score matched control cohort of 180 single euploid embryo transfer cycles from patients without a history of uterine septa were used as the control group.

Interventions: No interventions administered.

Measurements and Main Results: Pregnancy, clinical pregnancy loss, ongoing clinical pregnancy, and live birth rates in patients with a history of uterine septum resection compared with matched patients without Müllerian anomalies or uterine surgeries.

Patients with a prior uterine septum had significantly lower rates of chemical pregnancy (58.33% vs 77.2%, p = .004), implantation (41.67% vs 65.6%, p = .001), and live birth (33.33% vs 57.8%, p = .001) per transfer. No statistical difference in clinical pregnancy loss rates was found when comparing septum patients with controls (8.33% vs 7.8%, p = .89).

Conclusion: Patients with a history of hysteroscopic resection who undergo in vitro fertilization are more susceptible to suboptimal clinical outcomes compared with patients with normal uteri. Early pregnancy loss rates in patients with a uterine septum are higher than in those without; however, after resection, the rates are comparable. Patients born with septate uteri require assessment of surgical intervention prior to SEET, and to optimize their reproductive outcomes. Journal of Minimally Invasive Gynecology (2024) 00, 1−6. © 2024 AAGL. All rights reserved.

Keywords: Hysteroscopy; Septoplasty; Single euploid embryo transfer; Uterine septum

Müllerian anomalies can include individual or multiple variant features resulting from abnormal embryologic development of the reproductive system. As these anomalies vary in presentation and can be asymptomatic, they are often not identified until individuals are faced with poor pregnancy outcomes or infertility [1]. This also limits the ability to quantify the true prevalence of anomalies in the general population. The uterine septum is the most common Müllerian anomaly and has been associated with early pregnancy loss, preterm labor, and lower rates of successful pregnancy in patients who undergo assisted reproductive technology treatment [2]. Historically, there have been discrepancies in the definition of the uterine septum and its architecture. These inconsistencies make it difficult to evaluate the interplay between pregnancy outcomes and the uterine septum. The 2021 American Society for Reproductive Medicine Müllerian Anomalies Classification (MAC 2021) has provided a system for categorizing the developmental differences in uteri, with the goal of enhancing

The other authors declare that they have no conflict of interest.

This study has been presented at the American Society for Reproductive Medicine, 2022. Poster presentation.

Data will be made available to the editors of the journal for review or query upon request.

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communication between providers and researchers, as well as improving clinical care [2]. While other systems from the American Fertility Society and the European Society of Human Reproduction and Endocrinology exist, the new system's standardization will help guide physicians in identifying and classifying an array of Müllerian anomalies.

Patients presenting with infertility have a higher incidence of uterine septa when compared with the general population [3]. Therefore, understanding the role a septum has on a patient's ability to conceive is paramount. The strongest evidence regarding poor pregnancy outcomes for patients with uterine septa is related to early pregnancy loss. While there have yet to be randomized control trials on the topic, several retrospective studies have shown women with a septate uterus experience a higher rate of first-trimester early pregnancy loss compared with women without septa [3−5]. Despite being small and observational, those studies have demonstrated hysteroscopic uterine septum resection to improve clinical pregnancy rates in patients with infertility and decrease the chance of early pregnancy loss [4,6].

The objective of this study was to evaluate pregnancy outcomes in patients with a history of a uterine septum resection undergoing a single euploid embryo transfer (SEET) as compared with patients undergoing SEET with uteri of normal contour, without müllerian anomalies and without a history of prior uterine surgeries. Single euploid embryo transfers provide a clearer assessment of pregnancy outcomes by reducing the risk of aneuploidy, which is recognized as a major factor contributing to failed cycles. Single euploid embryo transfer outcomes, including chemical pregnancy, implantation, live birth, and early pregnancy loss, were compared in the postresection septum cohort versus a control cohort.

Materials and Methods

Study Design

This retrospective, single academic center study included autologous SEET cycles from January 1st, 2012 to December 31st, 2020. Patients were assigned to the septum cohort if they had a history of a uterine septum and underwent at least one hysteroscopic resection of septum prior to autologous SEET. The septum cohort was identified by querying the electronic medical record for diagnoses, billing codes, or free text related to patient history of uterine septum. Using natural language processing within the electronic medical record, the septum cohort was identified using the following keywords: septum, uterine septum, septoplasty, and septum resection. Patient infertility diagnoses of septum, uterine anomaly, uterine factor, and Müllerian anomaly were used to further compile the septum cohort. Patients were excluded from the septum cohort if they had a history of any prior uterine surgery other than septum resection (hysteroscopy, myomectomy, polypectomy, cesarean section, dilation and curettage, evacuation of retained products of conception, cold knife cone, loop electrosurgical excision procedure) or presence of any other uterine factor infertility diagnosis (fibroid, endometrial polyp, another Müllerian anomaly, Asherman's syndrome). Cases of patients harboring chromosomal rearrangements, using donor gametes, undergoing preimplantation genetic testing for monogenic defects, using mosaic embryos or unscreened embryos for transfer, unknown pregnancy outcomes, and missing or irresolvable data were excluded from the analysis.

A 3:1 ratio propensity score matched the control cohort, included SEET cycles of patients without a history of uterine septa, prior uterine surgery, or the presence of any uterine factor infertility diagnoses. Cycles were matched by age, antimullerian hormone (AMH), and body mass index (BMI).

This retrospective study was approved by the Institutional Review Board at Icahn School of Medicine at Mount Sinai, with a waiver of consent for retrospective analysis of deidentified data.

Participants and Procedures

Patients were designated as part of the septum or control cohort based on the above criteria. Demographic and cycle information included age, age at the time of embryo creation, BMI, gravidity, parity, AMH, number of prior early pregnancy losses, duration of infertility at presentation, endometrial thickness at the time of embryo transfer, day of embryo biopsy, embryo grade (poor, fair, good), and infertility diagnoses. For septum patients, further data was gathered regarding their septum. If documented, data on prior uterine septum imaging performed, the length of the septum, and the number of septum resection surgeries performed were reviewed in each chart.

For standardization and per typical clinical practice, every SEET in this study was performed in a synthetic preparation cycle. For each patient, the uterine cavity was prepared with micronized oral estradiol (Estrace, Teva Pharmaceuticals, Parsippany, NJ, USA) 2 mg twice daily for 4 days, then 2-mg 3 times daily. After a minimum of 12 days of estradiol administration, transvaginal ultrasonography was performed to assess endometrial thickness. When an adequate thickness was achieved, typically at least 8 mm, 50 mg of intramuscular progesterone in oil (Watson Pharma Inc., Parsippany, NJ, USA) was administered daily. For all clinical cases, thawing and transfer of the embryos were carried out on the sixth day of progesterone supplementation, regardless of the day of embryo development at the time of cryopreservation. Euploid embryos with the highest morphological grade were selected for transfer [7]. For patients who underwent more than one SEET, each cycle was analyzed individually.

Outcome Measures

The primary outcome was live birth rate per transfer (defined as live birth at > 24 wk gestation divided by

Table 1

Demographics and cycle characteristics of septum resection and control cohorts

Variables	Prior septum (n = 60 cycles)	Controls (n = 180 cycles)	p value
Age (yrs), mean ± SD	36.6 ± 3.8	36.7 ± 3.6	.91
BMI (kg/m^2), mean ± SD	24.1 ± 4.7	23.9 ± 4.1	.72
Gravidity, mean ± SD	1.6 ± 1.2	1.1 ± 1.2	.002*
Parity, mean ± SD	0.3 ± 0.5	0.3 ± 0.6	.59
Duration of infertility (mo), mean ± SD	18.2 ± 16.0	12.9 ± 11.8	.02*
Number of prior early pregnancy losses, mean ± SD	1.1 ± 1.1	0.2 ± 0.70	<.001*
Endometrial thickness at transfer (mm), mean ± SD	8.8 ± 1.7	9.9 ± 2.2	<.001*
High quality embryo (%)	89.40	91.1	.59
Diagnosis of patients (%) (number of patients)			
Male factor	17.1 (6)	19.4 (30)	.75
Tubal factor	11.4 (4)	4.5 (10)	.12
Diminished ovarian reserve	11.4 (4)	16.2 (25)	.48
Ovulatory dysfunction	8.6 (3)	14.3 (22)	.38
Unexplained	2.9 (1)	25.3 (39)	.003*
Genetic	5.7 (2)	5.8 (8)	.98
Recurrent pregnancy loss	28.6 (12)	7.1 (11)	<.001*
Endometriosis	8.6 (3)	3.2 (5)	.16
Using donor sperm	2.9 (1)	1.9 (3)	.74
Embryo cryopreservation	2.9 (1)	1.9 (3)	.74

BMI = body mass index; SD = standard deviation.
* Statistically significant.

number of transfers). Secondary outcomes included chemical pregnancy rate (defined as a positive beta-human chorionic gonadotropin (bHCG) per transfer), biochemical pregnancy loss rate (defined as a positive bHCG with a subsequent drop in bHCG prior to identification of clinical pregnancy per transfer), implantation rate (defined as intrauterine pregnancy with ultrasound showing gestational sac per transfer), and early pregnancy loss rate (defined as clinical pregnancy loss after detection of an intrauterine pregnancy with cardiac activity per transfer).

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Continuous data was reported as mean ± standard deviation (SD) or median (interquartile range) as appropriate with Clopper-Pearson binomial 95% confidence intervals (CIs). Comparative statistics were performed using chi-square and student's *t* test where appropriate.

A multivariate regression analysis fitted with a generalized estimating equation (GEE) was performed on the primary outcome of live birth and secondary outcomes of implantation and clinical pregnancy loss. Analysis was conducted controlling for age, number of prior early pregnancy losses, duration of infertility, BMI, endometrial thickness, day of embryo biopsy, and quality of embryo. Variables were chosen based on their physiologic plausibility of impacting the outcome. GEE was used to account for the presence of individual patients with multiple cycles. Adjusted odds ratio (aOR) for all cycle outcomes in the septum cohort and control cohort were reported**.** A sample size of 61 cycles per group was calculated for our study to be able to detect a 25% difference in live birth rates, with an 80% power and an alpha = 0.05.

Results

After applying the inclusion and exclusion criteria and performing propensity score matching based on age, BMI, and AMH, a total of 60 SEET cycles in 35 patients with a uterine septum were matched to 180 SEET cycles in 154 control patients. Demographic and cycle variables are presented in Table 1. Average age of patients in septum cohort was 36.66 ± 3.82 years, and in control cohort was 36.72 ± 3.60 years. Average BMI was 24.12 ± 4.76 kg/m^2 in septum cohort and 23.90 ± 4.14 kg/m^2 in control cohort. Septum patients were found to have higher gravidity at time of presentation for fertility treatment (1.68 ± 1.21 vs 1.11 ± 1.24, p = .002), but a similar parity (0.33 ± 0.57 vs 0.38 ± 0.65, p = .59). Compared with the control cohort, septum patients had a longer duration of infertility at initial consultation (18.2 ± 16 months vs 12.9 ± 11.8 months, p = .02). We also found that septum patients had a significantly higher number of prior early pregnancy losses or spontaneous abortions (SAB) at time of treatment (1.11 ± 1.16 vs 0.29 ± 0.70, p <.001) when compared with controls. The quality of the embryos was similar in both cohorts, with the

Table 2

Single euploid embryo transfer outcomes between groups

Outcomes:	Prior septum (%)	Controls (%)	p value
Chemical pregnancy rate	58.3	77.2	.004
Biochemical pregnancy rate	16.6	11.7	.75
Implantation rate	41.6	65.6	.001
Early pregnancy loss rate	8.3	7.8	.89
Live birth rate	33.3	57.8	.001

majority being considered top quality (control 91.1% vs septum 89.4%, p = .59). Many of the infertility diagnoses were similar between groups (Table 1). The majority of patients who underwent prior septum resection had a diagnosis of recurrent pregnancy loss. According to a chart review of patients with prior septum resection, the majority of patients had 1 prior surgery for their septum (n = 32). Two patients had 2 prior surgeries, and one patient had 3 prior surgeries.

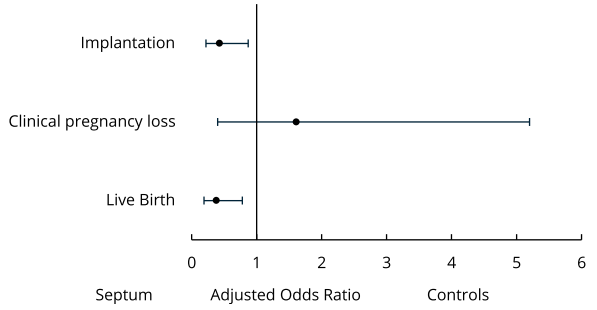
On univariate analysis, chemical pregnancy rates between groups were significantly different, with the septum cohort having lower rates of chemical pregnancy (septum 58.3% vs control 77.2%, p = .004). Biochemical pregnancy loss rates were similar between the septum cohort and control cohort (16.7% vs 11.7% vs p = .75). Implantation rates and live birth rates were significantly different as well (septum 41.6% vs control 65.6%, p = .001 and septum 33.3% vs control 57.8%. p = .001, respectively). Early pregnancy loss rates were similar between the 2 groups, with patients with prior septum resection having an 8.3% early pregnancy loss rate and the control group having a 7.8% rate. These results are shown in Table 2.

After adjusting for age, number of prior early pregnancy losses, duration of infertility, BMI, endometrial thickness, day of embryo biopsy, quality of embryo, and multivariate regression analysis fitted with GEE showed that SEET in patients with prior septum resection had significantly lower odds of live birth (aOR = 0.38, 95% CI 0.19−0.78) compared with controls. Secondary outcomes of implantation rate and clinical pregnancy loss rate were assessed using multivariate regression analysis fitted with GEE. Analysis showed that the septum cohort had significantly lower odds of implantation (aOR = 0.43, 95% CI 0.22−0.87). SEET cycles in patients with prior septum resection and controls had no significant difference in odds of clinical pregnancy loss (aOR = 1.61, 95% CI 0.4−5.2) compared with controls. These results are represented in Chart 1.

Data on prior uterine septum imaging performed, the length of the septum, and the number of septum resection surgeries performed were reviewed in each chart. It was found that these variables were inconsistently documented, and therefore, additional subanalyses based on these characteristics were unable to be performed. However, patients at our practice routinely undergo uterine cavity assessment

Chart 1

Comparison of single euploid embryo transfer outcomes in patients with prior septum resections versus controls. Odds ratio (95% confidence interval).



by 3D ultrasound and/or saline sonogram prior to SEET to ensure no clinically significant uterine abnormality is present. Generally, a remaining septum greater than 1.0 cm with a leading angle < 90 degrees at the fundus is considered clinically significant. Hence, all patients were presumed to have normal-appearing uterine cavity prior to transfer.

Discussion

Patients with Müllerian anomalies, in particular uterine septa, are at risk of having pregnancy complications [2]. Guidance from medical providers can lower their risk of early pregnancy loss. Many patients with a uterine septum and poor pregnancy history are offered surgical resection of the uterine septum by hysteroscopy. Intervention by surgical resection restores normal anatomy to the uterine cavity, with the goal of increasing pregnancy success and decreasing pregnancy complications [8,9]. However, it is important to acknowledge the potential for an unintended effect of damage to the uterine cavity through hysteroscopic septum resection. This must be weighed against the goal of improving the uterine cavity. No patients in the septum or control cohorts within this study had a uterine septum at the time of SEET. Thus, the impact of septum resection versus those without resection cannot be compared directly within this study. While good quality data on whether to perform septum resection in the general population is limited, it has been associated with improved clinical pregnancy rates in patients with infertility [2].

On review of patient history prior to treatment, patients with a history of uterine septum had a longer duration of infertility and a higher number of early pregnancy losses. This is in comparison to a control cohort of an infertile population without Müllerian anomalies or uterine factors. This finding is consistent with the literature regarding patients with uterine septa and their increased risk of early pregnancy loss [5,8].

Our study focused on patients who underwent hysteroscopic septum resection and subsequently had a single

euploid embryo transfer. Results showed the prognosis for patients with a history of uterine septum remains suboptimal despite resection. When compared with an infertile patient population without Müllerian anomalies or prior uterine surgeries, there were lower odds of pregnancy, implantation, and live birth following SEET in the septum resection population. This is in contrast to results from Abuzeid et al and Tomaževič et al, which both showed similar pregnancy and live birth rates between patients with prior septum resection and controls [9,10]. However, these studies included patients with arcuate uteri in the septum groups and involved the fresh transfer of multiple untested embryos at variable stages of development, practices that are no longer considered standard.

Despite having a significantly higher number of early pregnancy losses compared with the control group, patients who underwent septum resection were found to have odds of early pregnancy loss similar to patients without a history of Müllerian anomalies or uterine surgeries after SEET [2]. These findings suggest that the correction of a uterine septum may reduce overall pregnancy loss in single euploid embryo transfers for these patients. This finding is similar to that of Ban-Frangez, et al, which showed comparable early pregnancy loss rates after in-vitro fertilization/intracytoplasmic sperm injection in patients with prior septum resection compared with controls with a normal contour uterus.

While the relationship between the uterine septum and early pregnancy loss has been described, the association with infertility is not well defined [3]. Uterine septum can be diagnosed during an infertility workup. The causation of subfertility or infertility in relationship to the uterine septum is uncertain, and there may be additional diagnoses present. This study shows lower pregnancy rates in patients with a history of uterine septum resection after a single euploid embryo transfer. These lower rates of pregnancy, implantation, and live births may be indicative of poorer fertility in these patients at baseline. These may be outcomes that cannot be recovered despite septum resection.

The major strength of this study is that it is the first study that evaluates live birth outcomes following single euploid embryo transfer in patients who had their septum resected. Using only a single euploid embryo per transfer, we were able to eliminate a significant confounder, embryonic aneuploidy, which is the major leading cause of first-trimester miscarriages [11].

Limitations of this study include its retrospective nature and heterogeneity of the available data related to individual patients' septa. Due to a lack of standardization in documentation in the medical record regarding the length and width of the septum, modality of imaging used for measurement, and timing and number of septum resections related to SEET, the impact of these factors cannot be evaluated or accounted for. Septum resection surgical information was also limited, as many of the surgeries were performed by providers outside of the study site. Because of this discrepancy, operative details regarding instruments used and any preventative measures, such as an intrauterine catheter or hormone therapy, were not uniformly documented. The size and extent of the uterine septum as well as details on the septum resection surgery, such as the use of specific instruments, energy, or preventative measures, may confound subsequent pregnancy rates and thus may be impactful and should be controlled for in future studies. Similarly, infertility diagnoses were variable and may have been multifactorial, and prior treatment was not accounted for. It is not possible to extrapolate the impact of the septum on the patient's infertility. Another limitation of our study is the small sample size in the septum resection group. Although our power analysis demonstrated that it has enough power to detect a difference in live birth rates, the sample size might be insufficient for analyzing secondary outcomes, which the study is not powered for. Conducting further multicenter studies could be beneficial to power the studies for secondary outcomes, especially miscarriage rates.

Future studies should assess prospectively and in a controlled manner the effect of septum resection on overall IVF outcomes. Such studies should be structured to collect comprehensive documentation on the architecture of the uterine septa, details of the surgical approach, and specifics regarding postoperative care. Analyzing outcomes based on these variables would reduce the effect of confounding factors and allow for more patient-specific recommendations. It would also allow for the evaluation of surgical approaches and their impact on clinical outcomes. This would provide guidance on how to optimize the surgical approach for patients with a variety of uterine septa to improve pregnancy and live birth rates to the greatest extent. Future studies should continue to use transfer of PGT-A tested euploid embryos to reduce the possibility of aneuploid embryos confounding outcomes.

Conclusion

Patients born with septate uteri require specialized approaches to assess the relative value of surgical intervention prior to undergoing assisted reproductive technology treatment and make informed choices to optimize reproductive outcomes. For those patient who undergo SEET, this study showed that the live birth rate continued to be compromised despite uterine septum resection. The absolute benefit for each patient must be assessed in a personalized fashion. This study showed the rate of clinical pregnancy loss for patients after septum resection was similar to the control group, illustrating an improvement from their baseline risk. Once pregnancy is achieved, patients who had their septum removed can expect low clinical pregnancy loss rates, similar to the general infertility population without Müllerian anomalies. Clinical pregnancy loss can result in profound grief that can continue to affect them many months after the occurrence, prolonging the time to resuming treatment and achieving a healthy pregnancy [12]. Therefore, the value of lowering the risk of clinical

pregnancy loss cannot be understated. We suggest a central focus that includes shared decision-making to be performed when counseling patients on the management of uterine septa. More standardized studies are needed to individualize care of patients with uterine septa prior to SEET to expand on these findings.

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