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Original Article

# Uterine Septum and Other Müllerian Anomalies in a Recurrent Pregnancy Loss Population: Impact on Reproductive Outcomes

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**ABSTRACT** **Study Objective:** To study the impact of Müllerian anomalies on reproductive outcomes in a recurrent pregnancy loss (RPL) population and to evaluate the effect of surgical correction of uterine septum on the odds of achieving live birth in RPL patients with a septate uterus.

**Design:** A retrospective cohort study.

**Setting:** A specialized RPL clinic at a tertiary center.

**Patients:** RPL patients with ≥ 2 pregnancy losses before 20 weeks' gestation who attended a specialized RPL clinic.

**Intervention:** We aimed to assess the association between a possible risk factor (Müllerian anomalies) and reproductive outcomes and that between having surgery for septate uterus and achieving a live birth.

**Measurements and Main Results:** The primary outcome is live birth rate in RPL patients with Müllerian anomalies compared with those without; secondary outcome measures include rates of full-term live birth, preterm live birth, first and second trimester pregnancy loss, and stillbirth. After adjusting for patient age at the initial RPL visit, the number of pregnancy losses, and the presence of any other abnormal RPL investigation, the odds of achieving live birth were on average 49.4% lower for patients with a septate uterus than those without Müllerian anomalies (odds ratio, 0.51; 95% confidence interval, 0.30−0.86) in the studied cohort (n = 377). A subanalysis of 72 patients with septate uterus demonstrated a higher likelihood of live birth in those who underwent septum resection (46/72; 63.9%) than those who elected to go for expectant management (26/72; 36.1%), yet this study was underpowered to establish a significant difference (52.2% vs 34.6%; p = .22).

**Conclusion:** In RPL patients, having a septate uterus significantly decreased the chances of achieving live birth. Patients with septate uterus who received hysteroscopic septum division had a higher tendency to achieve more live births than those who elected expectant management. However, our study was underpowered to detect a statistically significant difference. Journal of Minimally Invasive Gynecology (2023) 00, 1−9. © 2023 AAGL. All rights reserved.

*Keywords:* Live birth; Hysteroscopic metroplasty; Reproductive outcomes; Septum resection; Septate uterus

[1] The first and second authors contributed equally to the work.

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Request for data collected for the study can be made to the corresponding author and will be considered on an individual basis in accordance with the internal regulations of the health authority.

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Recurrent pregnancy loss (RPL) is a stressful clinical disorder that affects 1% to 2% of couples [1]. Although controversial in its definition, the American Society for Reproductive Medicine (ASRM) considers RPL as the loss of ≥ 2 clinically identified pregnancies [2], whereas RPL is defined as ≥ 2 pregnancy losses from conception to 24 weeks' gestation by the European Society of Human Reproduction and Embryology (ESHRE) [1]. The Royal College of Obstetricians and Gynecologists describes recurrent miscarriage as the loss of ≥ 3 first trimester pregnancies [3].

Furthermore, RPL can be classified as either primary or secondary. Where primary RPL refers to repeated losses without a previous ongoing viable pregnancy beyond 24 weeks' gestation, secondary RPL is described as repeated losses among patients who have experienced at least one pregnancy that led to a delivery after 24 weeks' gestation [1].

The widely accepted etiologies of RPL are parental chromosomal abnormalities, endocrinological disorders such as thyroid dysfunction, immunologic disorders such as antiphospholipid antibody syndrome, and anatomic uterine abnormalities. However, 50% of RPL cases remain unexplained [4]. Anatomic uterine abnormalities can be congenital (Müllerian) or acquired (e.g., intrauterine adhesions, fibroids, and polyps), with the former consisting of a complex group of anomalies frequently involving the uterus, vagina, and urinary tract [5]. Müllerian anomalies are prevalent in 5.5% of the general fertile population and more so in high-risk groups such as patients with miscarriages (24.5%) and infertility (8.0%) history, in which septate uterus is the most predominant anomaly [6]. Müllerian anomalies potentially associated with RPL include septate uterus, bicornuate uterus, unicornuate uterus, and uterus didelphys [7].

As part of a complete workup, RPL patients should have an anatomic evaluation of their uterus [1,2]. A variety of modalities are currently used to detect uterine abnormalities. The highly sensitive and specific transvaginal 3-dimensional sonography (3D-US) can discriminate between a septate uterus and a bicornuate uterus [8]. When 3D-US is not available or tubal patency is questioned, the cavity can be assessed using magnetic resonance imaging (MRI), sonohysterography, or hysterosalpingography (HSG) [1,9,10]. Hysteroscopy allows direct visualization of the uterine cavity and can often be performed in an office setting under local anesthesia, as required [11].

Numerous classification systems have been developed to characterize Müllerian anomalies; the American Fertility Society (AFS) classification developed in 1988 was perhaps one of the most extensively used ones [12]. In 2013, ESHRE and the European Society for Gynecological Endoscopy established a more recent classification that is primarily based on uterine anatomy [13]. In 2021, the ASRM released the new Müllerian anomalies classification (MAC) [7]. Keeping the 1988 AFS classification's simplicity and maximizing its recognizability were the key goals of the ASRM Task Force on MAC [7].

Congenital uterine abnormalities are associated with a number of obstetric complications such as second trimester pregnancy loss, preterm labor, and fetal malpresentation, yet their role in early pregnancy losses is still controversial [14]. The prevalence of Müllerian anomalies, especially septate uteri, is lower in secondary RPL patients (4.6%) than those with primary RPL (9.0%) [15].

There is no evidence that surgery for unicornuate, bicornuate, or didelphic uterus improves reproductive outcomes in RPL population; although a septate uterus is amenable to surgical correction, its value is controversial [2]. ASRM reported that resection of uterine septum might be more beneficial and should be pursued in RPL patients [2], yet ESHRE recommended that hysteroscopic septum resection in RPL patients should still be evaluated in the context of trials [1]. To this end, our study aimed to (1) provide a deeper understanding of how Müllerian anomalies classified according to the MAC 2021 affect reproductive outcomes in a RPL population compared with those without Müllerian anomalies and (2) to evaluate the effect of surgical correction of uterine septum on live birth rate in RPL patients with a septate uterus.

## Materials and Methods

### *Baseline Assessment at the RPL Program*

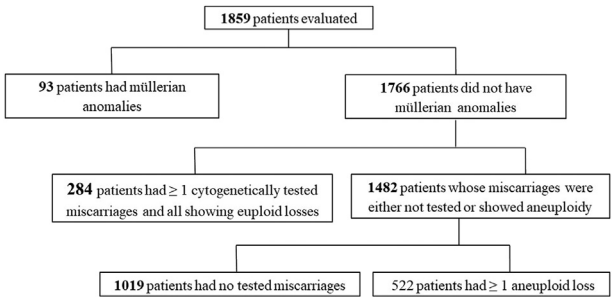
The RPL program at British Columbia (BC) Women's Hospital and Health Center is the only high-volume tertiary care center in the province, receiving referrals from across BC, and provides specialized care for RPL patients representing multiethnic groups. Patients with ≥ 2 pregnancy losses from conception until 20 weeks' gestation are eligible for referrals to the clinic. All patients were evaluated and treated according to the ASRM recommendations for RPL [2]. A comprehensive history was taken, and a thorough physical examination was performed. The standard of care in the RPL clinic included the following investigations: parental karyotyping, antiphospholipid antibodies testing, uterine cavity assessment, and endocrine evaluation. Other investigations were performed only when indicated, such as testing for inherited thrombophilias, serum prolactin test, oral glucose tolerance test, and endometrial biopsy. Patients were screened for Müllerian anomalies using 2-dimensional pelvic ultrasound, HSG, and office hysteroscopy. All suspected Müllerian anomalies were definitively diagnosed and classified via 3D-US or MRI.

### *Study Cohort*

This is a retrospective cohort study of RPL patients seen at BC Women's Hospital and Health Center RPL clinic from January 2012 to March 2021. The study was approved

**Fig. 1**

Flowchart of eligible patients and their follow-up. Flowchart demonstrates the included and excluded patients in the study.




by the University of British Columbia and BC Women's Hospital Ethics Committee (H21-0125).

RPL was defined as ≥ 2 pregnancy losses before 20 weeks' gestation. RPL patients with Müllerian anomalies classified according to the MAC 2021 [7] were included in the Müllerian anomalies group. RPL patients with no evidence of Müllerian anomalies were included in the non-Müllerian anomalies group if they had at least one of their previous miscarriages cytogenetically tested; all the tested miscarriages should be euploid losses. After a detailed retrospective chart review of 1859 patients, 377 patients were included in the study; 93 patients (24.7%) were included in the Müllerian anomalies group and 284 patients (75.3%) in the non-Müllerian anomalies group. Fig. 1 depicts the flowchart of the study population.

All data were collected from records housed on the Research Electronic Data Capture platform as well as patients' electronic and paper charts. The extracted data included sociodemographic characteristics of the studied population, obstetric history, results of RPL investigations and interventions, and reproductive outcomes of pregnancies conceived after the initial RPL clinic visit. Imaging reports for evaluation of the uterine cavity using techniques such as 2-dimensional pelvic ultrasound, 3D-US, sonohysterography, HSG, MRI, and hysteroscopy, along with laparoscopic operative reports, were carefully verified. Müllerian anomalies were characterized and classified based on physical examination and radiologic findings according to the MAC 2021 system [7] using the interactive tool provided by the ASRM (https://connect.asrm.org/education/asrm-mac-2021?ssopc=1).

### *Uterine Septum Surgery*

For patients with partial or complete septate uterus (endometrial cavity with fundal indentation > 1.0 cm), surgical vs expectant management counseling was provided. Operative reports for both previous surgical correction and that after their presentation to the RPL clinic were reviewed for those who opted for surgical management. Detailed information about the surgery was collected. At our RPL program, hysteroscopic septum division was performed by gynecologists with expertise in reproductive surgery and with advanced training in minimally invasive surgery. Using the Wolf Surgical Hysteroscopy Set, the septum was divided using cold scissors. For septa where the upper part was muscular, hysteroscopic division was performed using a right-angled bipolar electrosurgical loop. Normal saline was used as a distension media. Patients with septate uterus electing to proceed with expectant management were offered supportive care, and once pregnant, they received serial assays for serum beta human chorionic gonadotropin and ultrasonography follow-ups until 10 weeks' gestation. Subsequently, patients were referred to their primary care providers for ongoing care. An Excel worksheet (Microsoft Corp., Redmond, WA, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA) were used for data consolidation.

### *Outcome Measures*

The primary outcome was live birth rate. Secondary outcomes included rates of preterm birth, full-term birth, first and second trimester pregnancy loss, and stillbirth.

We evaluated both the primary outcome and secondary outcomes for study aim 1 (i.e., the impact of Müllerian anomalies on reproductive outcomes), whereas we evaluated only the primary outcome for study aim 2 (i.e., the benefits of surgical correction of the uterine septum).

Live birth rate was defined as the rate of delivery of a fetus, after 20 completed weeks of gestation and with any evidence of life [16]. Preterm birth rate was defined as the rate of a live birth with < 37 completed weeks of gestation [17]. Full-term birth rate was defined as the rate of live birth with at least 37 completed weeks of gestation [17]. First trimester pregnancy loss rate was defined as the rate of pregnancy loss within the first 12 6/7 weeks' gestation [18]. Second trimester pregnancy loss rate was defined as the rate of pregnancy loss between 13 and 20 weeks' gestation [18]. Stillbirth rate was defined as the rate of death of a fetus after 20 completed weeks of gestation and before delivery [16].

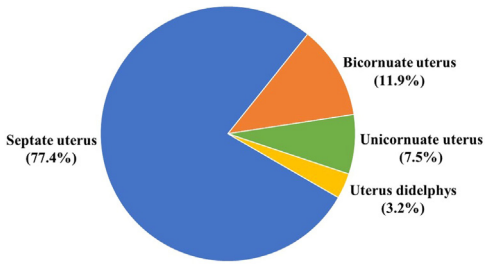
### *Statistical Analysis*

Statistical analyses and data visualizations were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two groups were identified: the Müllerian anomalies group and the non-Müllerian anomalies group.

Kruskal-Wallis and Fisher's exact tests were performed to detect baseline imbalance between the 2 groups in numeric and categorical variables, respectively. Logistic regression was used to model the effects of having a Müllerian anomaly on the primary outcome (achieving live birth) controlling for statistically significant and clinically important confounding variables. The same parsimonious adjusted model was applied to analyze secondary outcomes

**Fig. 2**

Distribution of Müllerian anomalies among the studied cohort. Illustration of the percentages of different anomalies in the studied cohort.




(full-term live birth, preterm live birth, first trimester pregnancy loss, second trimester pregnancy loss, and stillbirth).

The association between hysteroscopic septum division and achieving a live birth in patients with septate uterus was assessed using Fisher's exact test. A p value <.05 was considered significant.

Missing values were treated as a separate category only in Fisher's exact tests of the baseline clinical and sociodemographic characteristics. For other analyses, missing values were dropped.

## Results

A total of 377 patients were included in the analysis: 93 patients (24.7%) comprising the Müllerian anomalies group and 284 patients (75.3%) constituting the non-Müllerian anomalies group. Septate uterus was the most prevalent anomaly in the Müllerian anomalies group (72/93 [77.4%]), of whom 22 patients had an arcuate uterus (endometrial cavity with fundal indentation of < 1.0 cm), 48 patients had a partial septate uterus (endometrial cavity with fundal indentation > 1.0 cm), and 2 patients had a complete septate uterus (endometrial cavity divided by fundal indentation dividing endometrial cavity extending from fundus through cervix). Uterus didelphys (3/93 [3.2%]) was the least common (Fig. 2).

### *Baseline Clinical and Sociodemographic Characteristics of the Studied Population*

Patients in the Müllerian anomalies group were slightly younger (34.0 years) than those in the non-Müllerian anomalies group (34.8 years) at the time of their first presentation to the RPL clinic; however, this difference was not significant (p = .075). Patients in the Müllerian anomalies group experienced significantly more pregnancy losses than those in the non-Müllerian anomalies group (3.60 ± 1.34 vs 3.40 ± 1.55; p = .046), respectively. Patients in the non-Müllerian group had more frequent abnormal results of other RPL investigations than those in the Müllerian group, at 54.6% and 39.8%, respectively (p = .002). Other sociodemographic characteristics including ethnicity, alcohol consumption, current smoking status, and drug use history were comparable between the 2 groups (p >.05) (Table 1).

### *Impact of Müllerian Anomalies on Reproductive Outcomes*

Having a septate uterus was associated with 51.3% decreased odds of achieving a live birth outcome in RPL patients regardless of patients' surgical correction status (unadjusted odds ratio [OR], 0.49; 95% confidence interval [CI], 0.29−0.82). Other Müllerian anomalies examined including bicornuate uterus, unicornuate uterus, and uterus didelphys did not demonstrate statistical significance in the unadjusted analyses (Table 2).

After adjusting for patient age at the initial RPL clinic visit, number of pregnancy losses, and the presence of any other abnormal RPL investigation, the odds of achieving a live birth were on average 49.4% lower for a patient with a septate uterus than someone without Müllerian anomalies (OR, 0.51; 95% CI, 0.30−0.86). Holding else the same, bicornuate uterus, unicornuate uterus, and uterus didelphys trended toward a decreased odds of achieving a live birth but the associations were not statistically significant (OR, 0.74; 95% CI, 0.22−2.50; OR, 0.85; 95% CI, 0.18−3.90; OR, 0.28; 95% CI, 0.03−3.10), respectively.

Likewise, a sensitivity analysis by excluding patients with arcuate uterus (n = 22) demonstrated that having a septate uterus in RPL patients is associated with a decreased odds of achieving a live birth (OR, 0.52; 95% CI, 0.30 −0.90; p = .019).

In terms of secondary outcomes, patients with a septate uterus also had significantly decreased odds of achieving full-term live birth compared with patients without Müllerian anomalies (OR, 0.50; 95% CI, 0.29−0.85) after controlling for the maternal age at the initial RPL clinic visit, number of pregnancy losses, and presence of any other abnormal RPL investigation. However, the impact of having a septate uterus on other secondary outcomes including first and second trimester pregnancy loss, preterm birth, and stillbirth was inconclusive (Fig. 3).

### *Probability of Achieving Live Birth in RPL Patients with Septate Uteri Who Underwent Surgical Correction*

Among the 72 patients with septate uteri, 46 patients (63.9%) received hysteroscopic division of their septa, whereas 26 patients (36.1%) did not undergo surgical management. Among the 46 patients treated with surgery, 24 (52.2%) had at least one successful live birth, whereas only 9 of the 26 patients (34.6%) who did not undergo surgical management achieved live birth. Although those who underwent septum division were approximately 1.5 times more likely to achieve a live birth outcome than those who did not undergo surgical management, the subanalysis was underpowered to establish a difference in live birth proportions between the 2 approaches (p = .218).

**Table 1**

Basic clinical and sociodemographic characteristics of the studied cohort (n = 377)

| Variable | Müllerian anomalies group (n = 93) | Non-Müllerian anomalies group (n = 284) | p value* |
|---|---|---|---|
| Age at the initial RPL clinic visit (yr) | 34 ± 4.22 | 34.9 ± 4.49 | .075 |
| Number of pregnancy losses | 3.61 ± 1.34 | 3.40 ± 1.55 | .046 |
| Ethnicity | | | .561 |
| Asian | 30 (32.3%) | 76 (26.8%) | |
| Caucasian | 43 (46.2%) | 132 (46.5%) | |
| Other (Latino, Indigenous, African American, Pacific Islander, and Middle Eastern) | 7 (7.50%) | 20 (7.00%) | |
| Missing | 13 (14.0%) | 56 (19.7%) | |
| Alcohol consumption (drink/wk) | | | .395 |
| 0 | 44 (47.3%) | 127 (44.7%) | |
| 1−4 | 44 (47.3%) | 127 (44.7%) | |
| 5−15 | 3 (3.24%) | 18 (6.34%) | |
| > 15 | 1 (1.08%) | 1 (0.37%) | |
| Missing | 1 (1.08%) | 11 (3.89%) | |
| Current smoking | | | .647 |
| No | 85 (91.4%) | 256 (90.1%) | |
| Yes | 7 (7.52%) | 19 (6.70%) | |
| Missing | 1 (1.08%) | 9 (3.20%) | |
| Drug use history | | | .891 |
| No | 76 (81.7%) | 224 (78.9%) | |
| Yes | 13 (14.0%) | 46 (16.2%) | |
| Missing | 4 (4.30%) | 14 (4.90%) | |
| Abnormal RPL investigation | | | .002 |
| One or more | 37 (39.8%) | 155 (54.6%) | |
| None | 56 (60.2%) | 127 (44.7%) | |
| Not tested | 0 | 2 (0.70%) | |
| Maternal karyotype | | | .031 |
| Abnormal | 0 | 4 (1.40%) | |
| Normal | 75 (80.6%) | 190 (66.9%) | |
| Not tested | 18 (19.4%) | 90 (31.7%) | |
| Paternal karyotype | | | .241 |
| Abnormal | 1 (1.08%) | 3 (1.06%) | |
| Normal | 54 (58.06%) | 139 (48.94%) | |
| Not tested | 38 (40.86%) | 142 (50.0%) | |
| Antiphospholipid antibody serology | | | .415 |
| Positive | 3 (3.20%) | 14 (4.90%) | |
| Negative | 76 (81.7%) | 240 (84.5%) | |
| Not tested | 14 (15.1%) | 30 (10.6%) | |
| Uterine cavity assessment for acquired uterine anomalies | | | .001 |
| Abnormal | 10 (10.8%) | 62 (21.8%) | |
| Normal | 83 (89.2%) | 207 (72.9%) | |
| Not assessed | 0 | 15 (5.30%) | |
| Serum TSH level (mIU/L) | | | .585 |
| > 2.5 | 25 (26.9%) | 90 (31.7%) | |
| 2.5 or less | 63 (67.7%) | 183 (64.4%) | |
| Not tested | 5 (5.40%) | 11 (3.90%) | |
| Serum TPO antibody level (IU/mL) | | | .459 |
| > 35.0 | 8 (8.60%) | 33 (11.6%) | |
| 35.0 or less | 57 (61.3%) | 182 (64.1%) | |
| Not tested | 28 (30.1%) | 69 (24.3%) | |
| Serum HbA1c level (%) | | | .330 |
| ≥ 6.5 | 0 | 0 | |
| < 6.5 | 53 (57.0%) | 178 (62.7%) | |
| Not tested | 40 (43.0%) | 106 (37.3%) | |
| Inherited thrombophilia testing | | | .029 |
| Abnormal | 1 (1.08%) | 13 (4.58%) | |
| Normal | 15 (16.12%) | 75 (26.41%) | |
| Not tested | 77 (82.8%) | 196 (69.01%) | |

HbA1c = hemoglobin A1C; RPL = recurrent pregnancy loss; TPO = thyroid peroxidase; TSH = thyroid stimulating hormone.
Data are reported as mean ± standard deviation for numeric variables and count (percent) for categorical variables.
* Kruskal-Wallis or Fisher's exact tests as appropriate.

**Table 2**

Impact of Müllerian anomalies on achieving live birth

| | Unadjusted OR | | Adjusted† OR | |
|---|---|---|---|---|
| Effect of different types of Müllerian anomalies* | Estimate | (95% CI) | Estimate | (95% CI) |
| Having a septate uterus (n = 72) | 0.49 | (0.29−0.82) | 0.51 | (0.30−0.86) |
| Having a bicornuate uterus (n = 11) | 0.69 | (0.21−2.3) | 0.74 | (0.22−2.5) |
| Having a unicornuate uterus (n = 7) | 0.77 | (0.17−3.5) | 0.85 | (0.18−3.9) |
| Having a uterus didelphys (n = 3) | 0.29 | (0.026−3.2) | 0.28 | (0.03−3.1) |

CI = confidence interval; OR = odds ratio; RPL = recurrent pregnancy loss.

* Modeled as a single variable with 4 categories.

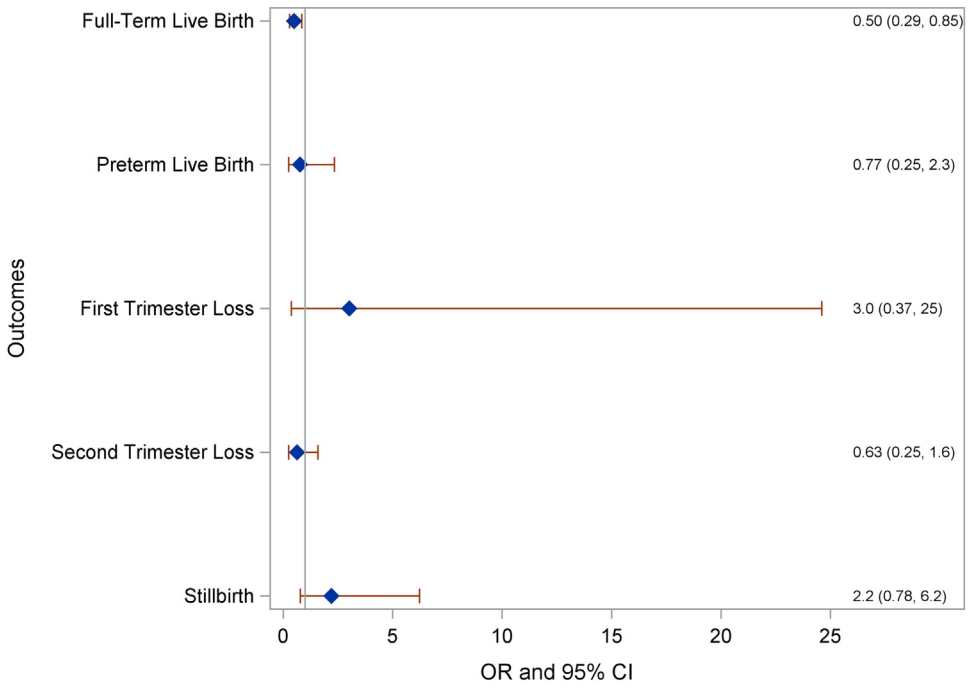
† Adjusted for age at the initial RPL clinic visit, number of pregnancy losses, and having any other abnormal RPL investigation.

## Discussion

Many studies have investigated the impact of Müllerian anomalies, specifically septate uterus, on reproductive outcomes as well as the benefit of hysteroscopic septum resection in enhancing the reproductive outcomes and reported conflicting evidence [1,2,19,20]. In this study, we evaluated the effects of congenital uterine anomalies on the reproductive performance of women with a history of RPL and the benefits of surgical correction of septate uterus on achieving live birth. There are various classification systems for Müllerian anomalies and each system has its pros and cons. There is no agreement on which system should be used. In addition, there is no head-to-head comparisons of the impact of the different systems on the diagnosis and management of patients. In this study, we adopted the most recent classification system (MAC 2021). We strongly recommend standardizing the definitions and classifications of the Müllerian anomalies, which would indeed be beneficial to promote better understanding, communication, and comparison of findings across different studies.

**Fig. 3**

Adjusted ORs for the secondary outcomes among RPL patients with septate uteri. Adjusted OR estimates and 95% CIs for the secondary outcomes among RPL patients with septate uteri compared with those in the non-Müllerian anomalies group, controlling for age at the initial RPL clinic visit, number of pregnancy losses, and having any other abnormal RPL investigation, regardless of patients' surgical status. CI = confidence interval; OR = odds ratio; RPL = recurrent pregnancy loss.



### *Impact of Having a Müllerian Anomaly on Reproductive Outcomes*

In the present study, we observed a significant association between having a septate uterus and decreased odds of achieving a full-term live birth. Moreover, although there was a trend toward decreased odds of live birth among other congenital uterine anomalies including bicornuate uterus, unicornuate uterus, and uterus didelphys, this trend was not statistically significant. Moreover, having a septate uterus did not have significant consequences on other reproductive outcomes such as first and second trimester pregnancy loss, preterm birth, and stillbirth. When evaluating basic characteristics of the studied cohort, we found that the number of pregnancy losses in patients with Müllerian anomalies was statistically significantly higher than patients without Müllerian anomalies (3.6 $\pm$ 1.34 vs 3.4 $\pm$ 1.55; p = .046), respectively.

In accordance with our results, a recent systematic review and meta-analysis of observational studies revealed that septate uterus in patients with RPL or infertility was associated with lower live birth (OR, 0.21; 95% CI, 0.12−0.39) [21]. Our data are also in line with Sugiura-Ogasawara et al [22] who demonstrated that RPL patients (≥ 2 consecutive miscarriages) with Müllerian anomalies typically had decreased live birth rates at the first pregnancy after diagnosis as well as lower cumulative live birth rates. According to another meta-analysis, the OR for miscarriage was 0.45 (95% CI, 0.22−0.90) [23]. Similarly, Saravelos et al [14] compared patients with Müllerian anomalies and RPL (≥ 3 consecutive miscarriages) with patients with unexplained RPL and observed that patients with septate and bicornuate uterus had substantially increased rates of second trimester miscarriages. Venetis et al [24] concluded in their meta-analysis of 25 studies using the 1988 AFS classification that spontaneous miscarriage rate was significantly higher in patients with congenital uterine anomalies, particularly in women with septate, unicornuate, and bicornuate uteri. In a recent meta-analysis, patients with Müllerian anomalies were found to be at a higher risk of preterm birth (OR, 3.89; 95% CI, 3.11−4.88) than those without anomalies based on the ESHRE-European Society for Gynecological Endoscopy definition [25]. The disagreement with our findings can be explained by the different MAC systems used in the different studies and differences in the studied population. There could also be contribution from our sample size with respect to some secondary outcomes, for example, preterm live birth, stillbirth, and first and second trimester miscarriages that we studied in which the sample statistics might deviate from the corresponding population parameters.

### *Value of Hysteroscopic Division of Uterine Septum*

Septate uterus constitutes a clinical challenge for physicians to care for patients with this congenital uterine defect, and the efficacy of its hysteroscopic resection is still debatable. In the present study, we found that RPL patients who underwent hysteroscopic septum division had a higher expected live birth rate, yet the trend did not reach statistical significance probably owing to an insufficient sample size. Zlopasa et al [26] demonstrated a significantly decreased total and first trimester pregnancy loss rates among 23 patients with septate uterus and 2 patients with bicornuate uterus who underwent resectoscope metroplasty, while providing nonsignificant improvement in live birth rate. In contrast, Noventa et al [21] in their recent meta-analysis concluded that hysteroscopic septum resection could significantly improve live birth rate in RPL and infertile patients. Similarly, in one of the few prospective studies, Pang et al [27] evaluated 138 patients with partial septate uterus and found that hysteroscopic septum resection in RPL patients offered lower rates of spontaneous miscarriage and preterm birth and higher rates of pregnancy and full-term live birth. In the same line, another prospective, multicenter study demonstrated the potential for surgery to help achieve live birth in septate uterus patients experiencing RPL (≥ 2 consecutive miscarriages); the investigators found that 83 of 96 patients (86.5%) with a septate uterus who underwent surgery achieved live birth cumulatively within the follow-up duration compared with 9 of 13 patients (69.2%) with a septate uterus and did not undergo surgery [28]. Another prospective study of 36 RPL and infertile patients with complete uterine or vaginal septum established associations between surgical resection and markedly improved pregnancy outcomes in terms of spontaneous abortion and full-term delivery rates in RPL patients, but not infertile patients [29]. In an additional prospective trial enrolling 43 RPL patients with septate uteri, hysteroscopic metroplasty considerably enhanced full-term live birth rate [30]. A meta-analysis of retrospective studies comparing pregnancy outcomes after hysteroscopic metroplasty for septate uterus in RPL patients (≥ 3 losses) also revealed that patients who received surgery had noticeably better outcomes than those who did not [31].

Nevertheless, not all studies pointed to reproductive benefits from hysteroscopic resection. For instance, using prospectively collected data of 32 patients with septate uterus and recurrent early pregnancy loss (≥ 2 pregnancy losses before 10 weeks' gestation), Whelan et al [32] found that hysteroscopic uterine septum resection did not improve subsequent live birth rate. However, this study may be limited by its small sample size. A meta-analysis evaluating pregnancy outcomes from 1589 patients with either complete or partial uterine septum showed that patients who underwent partial septum resection experienced a substantially lower odds of preterm birth than those who undertook expectant management (OR, 0.30; 95% CI, 0.11−0.79). This difference was not observed in patients with complete septum. Moreover, there was no difference in odds of having a live birth at term between the 2 groups [23]. In another meta-analysis, Krishnan et al [33] concluded that hysteroscopic resection of uterine septum had no significant effect on live birth, clinical

pregnancy, or preterm birth rates in patients having septate uterus and presenting with subfertility and/or poor obstetric history. However, the heterogenous nature may limit the comparability of this meta-analysis. A retrospective study of 257 women with septate uterus by Rikken et al [20] reported that septum resection had no effects of live births, pregnancy losses, or premature birth compared with expectant management, yet it is important to note that 2 letters to the editor were subsequently published to critique the abovementioned study by Rikken et al [20,34,35]. Rikken's research group launched an international, multicentre, open label, randomized controlled trial (RCT) called "The Randomized Uterine Septum Trial (TRUST)." As the first RCT on this topic, the TRUST aimed to evaluate whether septum resection could enhance reproductive outcomes in patients wishing to conceive. They concluded that surgical treatment offered no benefits over expectant management in those patients [19]. However, the TRUST has its own limitations including its small sample size (80 patients recruited from 10 centers over 8 years), diversity of the surgical techniques, variability in septum length (only 7 patients had a complete septum), and heterogeneity of the studied population. In addition, considerable selection bias may result from variability in septum definition and the diagnostic methods used. Consequently, it would not be accurate to extrapolate these findings to the complete septum cohort or specifically to the RPL population.

### *Strengths and Limitations of the Study*

Our study had several strengths. First, our study is unique and robust in that we selected patients with their tested miscarriages that were exclusively attributable to euploid pregnancy losses in the non-Müllerian anomalies group and adjusted for any other abnormal RPL finding when evaluating the impact of Müllerian anomalies on reproductive outcomes. Second, to the best of our knowledge, this is the first study that investigated the impact of Müllerian anomalies classified and characterized according to the most recent MAC 2021 using the ASRM interactive tool on reproductive outcomes and assessed the benefits of hysteroscopic septum resection in RPL patients with septate uterus. Third, as a tertiary care center specialized in RPL, we receive referrals from general practitioners, family physicians, gynecologists, and fertility clinics and so we can recruit a relatively large cohort of RPL patients, which may allow us to generalize our findings to this high-risk population. More specifically, we had stringent inclusion criteria according to the most updated RPL definitions [1]. Finally, the standardized care provided at our center aids in collecting patients' history, laboratory results, and diagnostic procedures, which enhance data accuracy. Thus, the studied cohort was evaluated, treated, and followed up consistently by the providers who used the same standardized investigations and management protocols throughout the study period. Moreover, data collection was based on a thorough review of paper charts and electronic medical records.

In contrast, the major limitation includes its retrospective observational nature, which limits our ability to establish causation like RCTs. Given the challenges associated with conducting RCTs in this field, cohort studies are uniquely positioned to mend this knowledge gap and answer real-life questions. An observational study similar to ours is likely the most practical method of evaluating the impact of Müllerian anomalies as well as surgery on subsequent outcomes. In addition, we were probably not adequately powered to detect statistical differences in most of the secondary outcomes, which might explain some of the discrepancies between our findings and the literature given that smaller samples are prone to being less representative of the population. Although our control group experienced exclusively confirmed euploid pregnancy loss, 17 patients in the Müllerian anomalies group had experienced aneuploid losses. We did not exclude these patients from the Müllerian anomalies group because aneuploidy is still likely a major contributor to early pregnancy losses, regardless of uterine factors. It is also not feasible to determine the ploidy status of all pregnancy losses. We ran a sensitivity analysis by excluding those patients and the results demonstrated that having a septate uterus in RPL patients is associated with decreased odds of achieving a live birth (OR, 0.46; 95% CI, 0.26−0.83).

Another limitation is the fact that we followed the patients who achieved pregnancy in the clinic only until 10 weeks' gestation and then were discharged to their primary care providers, so the live birth and second trimester loss data were not available for all patients at the time of the analysis; hence, postdischarge data could not be adequately captured. This is of particular importance because Müllerian anomalies are more associated with second trimester loss and preterm birth.

## Conclusion

The presence of a septate uterus significantly decreased the chances of achieving a live birth in the RPL population. Hysteroscopic septum division in RPL patients with septate uterus tended to result in relatively more live births than expectant management; however, a larger study with adequate power is necessary to verify this finding.

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