

Original Research

Pregnancy Outcome of Infertile Patients with Uterine Malformation after Hysteroscopic and Laparoscopic Surgery

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Abstract

Background: Uterine malformations can be divided into the dysmorphic uterus (U1); septate uterus (U2); bicornuate uterus (U3); hemi-uterus (U4) and hypoplastic uterus (U5) with clinical significance ranging from mild to severe. This study aims to investigate whether different types of uterine malformations in infertile patients who have undergone hysteroscopic and laparoscopic surgery are associated with different pregnancy outcomes. **Methods:** This is a retrospective study of patients with uterine malformations and infertility admitted to the Department of Gynecology of Peking Union Medical College Hospital between January 2003 and December 2020. Patients were followed through 31 October 2021. Those lost to follow-up or who had not tried to become pregnant were excluded. Fertility outcomes included pregnancy rate, live birth rate and miscarriage rate. Fertility outcomes among patients experiencing different uterine anomalies were compared using one-way analysis of variance (ANOVA). **Results:** A total of 161 patients were included, of whom 62 (38.5%) had no other infertility-related factors except a uterine malformation. The rate of concomitant endometriosis (36.0%) was significantly higher than among the non-specific infertile population ($p < 0.05$). One hundred seventeen patients achieved a total of 151 pregnancies postoperatively. The total pregnancy rate was 77.5%, and the live birth rate was 73.4%. The pregnancy and miscarriage rates in patients with uterine septum with a single cervix were 76.0% and 15.5%, respectively; 75.0% and 37.5% among patients with unicornuate uterus with a single cervix; 88.9% and 9.5% among patients with uterine septum with a double cervix; 100% and 25% among patients with uterus duplex with double cervix; and 50% and 25% among patients with bicornuate uterus with a single cervix. Patients were grouped into either the septum group or the unicornuate uterus group dependent on the ability to enlarge the uterine cavity by surgery. The pregnancy rates for the two groups were 78.1% and 80.6%, respectively, with no significant difference noted ($p = 0.599$), although there was a significant difference in the miscarriage rate (14.4% vs. 33.3%) ($p = 0.002$). **Conclusion:** This retrospective analysis can help to illustrate differences in pregnancy outcomes of different types of uterine malformations although it lacked a proper control group. The non-obstructive uterine malformation may not be a dominant cause of infertility, and the volume of the uterine cavity may be a key factor leading to first-trimester miscarriage, rather than an important causative factor for infertility.

Keywords: uterine malformation; infertility; pregnancy outcome

1. Introduction

The Müllerian ducts are first identifiable at approximately six weeks of gestation, when they begin to elongate caudally and cross the metanephric ducts medially to meet in the midline [1]. The lateral and/or vertical fusion defects at 6–20 weeks gestation lead to a congenital uterine anomaly (CUA), with a morphological disorder but approximately normal fertility potential [2].

The prevalence of specific CUAs in affected patients can vary substantially depending on the specific population studied and the methodology used to identify the abnormalities [3]. In a literature review analyzing infertile and fertile patients with CUAs, the frequencies of specific anomalies were: septate (35%), bicornuate (26%), arcuate (18%), unicornuate (10%), didelphys (8%), and agenesis (3%) [4]. According to the European Society of Human Reproduction and Embryology (ESHRE) and European Society for Gynecological Endoscopy (ESGE) [5] classification

(2013) of female genital malformations, uterine malformation can be divided into the dysmorphic uterus (U1); septate uterus (U2); bicornuate uterus (U3); hemi-uterus (U4); and hypoplastic uterus (U5) with clinical significance ranging from mild to severe. Apart from U5, these patients often present with increased adverse pregnancy outcomes, such as miscarriage or premature delivery, although they have the potential to maintain a pregnancy to term [6].

Of the multiple adverse pregnancy outcomes that most often attract attention is recurrent miscarriage, traditionally defined as three or more miscarriages, continuous or no miscarriage, occurring before 20 weeks of gestation, that is, before the fetus is viable [7]. The incidence of uterine anatomic abnormalities in women who experience recurrent pregnancy loss (RPL) ranges from 15% to 42%. Congenital uterine abnormalities are associated with 7% to 28% of RPL [8–12]. These consist mainly of septate uteruses and, to a lesser extent, of arcuate or bicornuate uteri. Although



the pathophysiology of this disorder interfering with early pregnancy development is not fully understood, a hypothesis has been developed. Septal miscarriage may be the result of insufficient embryo implantation. In addition, under the influence of estradiol and progesterone, uterine contractility and/or endometrial physiological factors changes in the endometrial, especially the destruction of vascular endothelial growth factor [13].

We conducted a retrospective analysis of infertility patients with uterine malformations who had undergone hysteroscopic and laparoscopic surgery in Peking Union Medical College Hospital to ascertain the frequencies of specific CUAs in infertile patients and their fertility outcomes after metroplasty. We believe that this might provide a better understanding of fertility prognosis in this specific population.

2. Methods

A total of 3257 cases between January 2003 and December 2020 were retrieved from the medical record database of Peking Union Medical College Hospital using “infertility” + “hysteroscopy” + “laparoscopy” as the index words. Adding “uterine malformation” as the appended search term identified 196 of these patients. Their records were collected and with follow-up by telephone of reproductive outcomes up to 31 October 2021.

This study conformed to the guidelines explained in the Declaration of Helsinki and was approved (S-K1373) by the ethics committee of Peking Union Medical College Hospital (PUMCH, Beijing, China). A waiver for the requirement of informed consent from the patients whose records were analyzed was granted by the Chair of the Committee on the grounds of being a minimal-risk study.

Uterine malformation was diagnosed by ultrasound and intraoperative findings, including uterine septum with single cervix; unicornuate uterus with single cervix; uterine septum with double cervix; uterus duplex with double cervix; and bicornuate uterus with the single cervix. Exclusion criteria were a normal uterus and other uterine malformations, such as uterine dysplasia and unclassified uterine deformities.

The primary outcome measures were the postoperative pregnancy rate and live birth rate; the secondary outcome measures included the miscarriage rate (miscarriage occurring within 28 weeks of pregnancy) and persistent pregnancy rate (gestation of at least 20 weeks). The mode of conception and delivery were also considered and analyzed. The pregnancy rate was calculated using the number of patients trying to conceive as the denominator. In contrast, the abortion, continuing pregnancy and live birth rates were calculated using the actual number of pregnancies as the denominator.

SPSS 21.0 statistical software (IBM SPSS Inc., Chicago, IL, USA) was used for analysis. Measurement data were expressed as mean $\pm$ standard deviation (mean $\pm$ SD) with one-way analysis of variance (ANOVA) used

for multi-group comparison; enumeration data were represented by rate (%), and comparison was performed using Pearson χ^2 or Fisher tests, with $p < 0.05$ indicating statistical significance.

3. Results

3.1 Basic Information

A total of 196 infertile patients with uterine malformations were admitted to the Department of Obstetrics and Gynecology of Peking Union Medical College Hospital between 1 January 2003, and 31 December 2020, accounting for 5.9% of the total number of infertile patients (3298) diagnosed and treated by hysteroscopy and laparoscopy during this period (Fig. 1).

The types of uterine malformations included 120 cases (61.2%) of the uterine septum with single cervix with patients' average age 30.38 ± 4.14 years; 38 cases (19.4%) of unicornuate uterus with single cervix with patients' average age 31.64 ± 4.11 years; 22 cases (11.2%) of uterine septum with double cervix with patients' average age 29.67 ± 4.50 years; 10 cases (5.1%) of uterus duplex with double cervix with patients' average age of 30.73 ± 4.39 years; and 6 cases (3.1%) of bicornuate uterus with single cervix with patients' average age 34.33 ± 8.66 years. There was no statistical difference in age between patients with different uterine malformations.

Telephone follow-up was undertaken to enquire about postoperative pregnancy outcomes up to October 31, 2021. Thirty-five patients (17.9%) were lost to follow-up, including 18 cases (52.9%) of uterine septum with single cervix, twelve cases (32.4%) of unicornuate uterus with single cervix, four cases (11.8%) of the uterine septum with double cervix, and 1 case of uterus duplex with double cervix. Ten of the remaining 161 patients had not attempted pregnancy and were excluded from the birth outcome statistics.

3.2 Pregnancy Outcome

Table 1 indicates the postoperative pregnancy outcome of patients with 5 different types of uterus malformation. One hundred and fifty-four pregnancies resulted in 113 live births. The live birth rate was 73.4% with an average gestational age of (38.0 ± 1.4) weeks (32–42) weeks. The *in vitro* fertilization and embryo transfer (IVF-ET) rate was 44.2% (68/154). The cesarean section rate was 71.7% (81/113). In total, the 151 pregnancies resulted in 29 miscarriages, and the overall miscarriage rate was 18.8%. The miscarriage rate of patients with unicornuate uterus with a single cervix was 37.5%, double that among patients with uterine septum with a single cervix (15.5%). Two of the miscarriages (both uterine septum with single cervix) occurred at 22 and 26 weeks of gestation, respectively; the remaining miscarriages occurred during the first trimester. The median gestational age of patients undergoing an abortion was 10 weeks + 3 days (7–22 weeks). The miscarriage rate among patients with unicornuate uterus with sin-

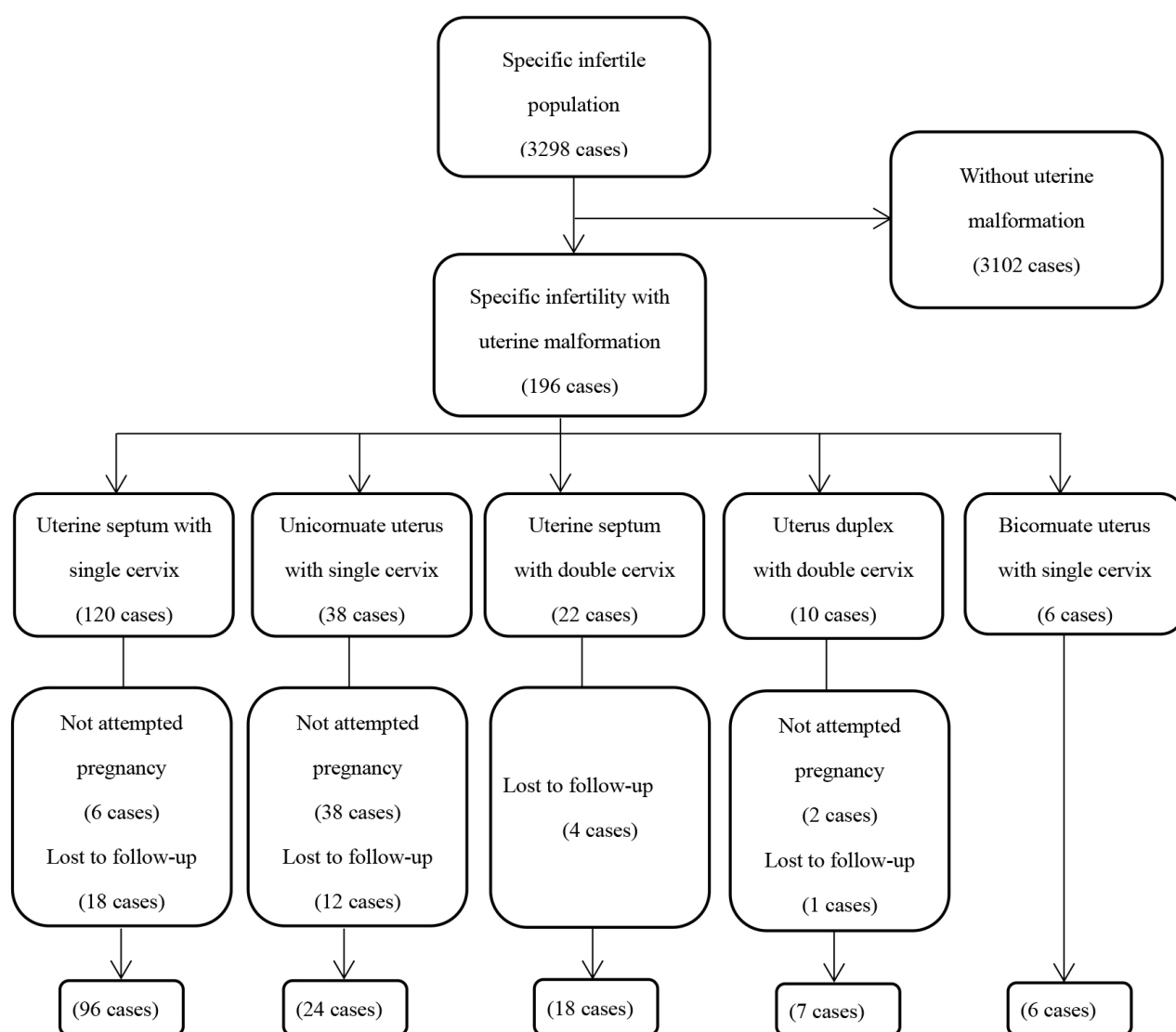


Fig. 1. The flowchart to show the enrollment of patients.

gle cervix was significantly higher than any of the other four groups ($p < 0.05$), while there were no significant differences between the other four groups in pairwise comparison ($p > 0.05$).

Based on the plasticity of the uterine cavity by surgery, the 5 types of uterine malformations were regrouped into two groups: “Septum group”, including uterine septum with single cervix and uterine septum with double cervix; and “Unicornuate group”, including unicornuate uterus with single cervix and uterus duplex with double cervix. Comparison of pregnancy outcomes between these two types is presented in Table 2. The Septum group had a significantly lower miscarriage rate and higher live birth rate than the Unicornuate group.

3.3 Infertility Factors

Data revealed that 38.5% of patients had no other significant infertility factors except a uterine malformation. The remaining 61.5% had other infertility factors, including endometriosis, fallopian tube factors, and ovulation disorders (Table 3). There were 53 cases of endometriosis; 37 in stages I & II and 16 cases in stage III. Five patients had mild adenomyosis (uneven ultrasound, thickened muscle wall, insignificant uterine enlargement).

All cases were regrouped into two groups: “Pure malformation group” & “Complex group” in order to take into account the combined impact of other infertility factors. The pregnancy rates of these two groups were 79.0% and 76.4%; the live birth rates were 71.4% and 77.3%; and the abortion rates were 20.6% and 18.2%, respectively. There was no statistical difference in any of the above indicators (Table 4).

Table 1. Comparison of postoperative pregnancy outcomes of 5 types of uterine malformation (n (%)).

Type	Trying to conceive	Actually conceived	Number of pregnancies	Miscarriage rate (<28 w)	Persistent pregnancy (≥20 w)	Live births	Assisted reproductive technology (ART)
Uterine septum with single cervix	96 (63.6)	73 (76.0)	90	14 (15.6)	75 (83.3)	70 (77.8)	42 (46.7)
Unicornuate uterus with single cervix	24 (15.9)	18 (75.0)	24	9 (37.5)*	15 (62.5)*	14 (58.3)**	15 (62.5)
Uterine septum with double cervix	18 (11.9)	16 (88.9)	21	2 (9.5)	19 (90.5)	18 (85.7)	5 (23.8)
Uterus duplex with double cervix	7 (4.6)	7 (100.0)	12	3 (25.0)	9 (75.0)	8 (66.7)	4 (33.3)
Biocornuate uterus with single cervix	6 (4.0)	3 (50.0)	4	1 (25.0)	3 (75.0)	3 (75.0)	0

Note: * $p < 0.05$, compared with the other four groups; ** $p < 0.05$, compared with the other groups apart from uterus duplex with double cervix. w, weeks.

Table 2. Comparison of pregnancy outcomes of patients with 2 major groups of uterine malformation (n (%)).

Group	Trying to conceive	Actually conceived	Number of pregnancies	Miscarriage rate (<28 w)	Persistent pregnancy (≥20 w)	Live births
Septum group	114	89 (78.1)	111	16 (14.4)	94 (84.7)	88 (79.3)
Unicornuate group	31	25 (80.6)	36	12 (33.3)*	24 (66.7)	22 (61.1) **

Note: Compared with uterine septum group with Pearson χ^2 test, * $p = 0.002$, ** $p = 0.005$.

Table 3. Other infertility factors associated with different types of uterine malformation (n (%)).

Type	Number	EM/AM (weeks)	Fallopian tube	Ovulation disorder	Uterine factor only
Uterine septum with single cervix	102	41 (40.2)	16 (15.7)	14 (13.7)	34 (33.3)
Unicornuate uterus with single cervix	26	9 (34.6)	3 (11.5)	5 (19.2)	10 (38.5)
Uterine septum with double cervix	18	5 (27.8)	1 (5.6)	2 (11.1)	10 (55.6)
Uterus duplex with double cervix	9	3 (33.3)	2 (22.2)	0	4 (44.4)
Biocornuateuterus with single cervix	6	0	1 (16.7)	1 (16.7)	4 (66.6)
Total	161	58 (36.0)	23 (14.3)	22 (13.7)	62 (38.5)

EM/AM, Endometriosis/Adenomyosis.

Table 4. Comparison of pregnancy outcomes (n (%)).

Type	Trying to conceive	Actually conceived	Number of pregnancies	Miscarriage rate (<28 w)	Persistent pregnancy (≥20 w)	Live births
Pure uterine malformation group	62	49 (79.0)	63	13 (20.6)	47 (74.6)	45 (71.4)
Complex uterine malformation group	89	68 (76.4)*	88	16 (18.2)*	71 (80.7)*	68 (77.3)*

Note: Compared with uterine septum type group with Pearson χ^2 test, * $p > 0.05$.

4. Discussion

The prevalence of CUAs in our selected infertility population was 5.9%, and the frequencies of diverse malformations were: septate (72.4%), unicornuate (19.4%), bicornuate (3.1%), and didelphic (5.1%), which is similar to those reported in previous studies [14–16]. The natural pregnancy rate was 55.8%. The assisted reproductive technology (ART) pregnancy rate was 44.2%, which is also similar to other non-specified infertile patients [17]. The cesarean delivery rate was 71.7%. Since many women choose cesarean section voluntarily, it is difficult to infer the negative impact of abnormal uterine structure on normal delivery.

This retrospective analysis of 161 infertile patients with uterine malformations identified a postoperative pregnancy rate of 77.5% and a live birth rate of 73.4%. Both of these are encouraging and should generate confidence among patients facing these difficulties.

Among 3 relatively common types of uterine malformations, patients with uterine septum with double cervix had significantly higher pregnancy rates than patients with a unicornuate uterus and uterine septum with a single cervix. In a multicenter registered clinical trial about uterine septums, the increased incidence of the bi-cervix subtype has been noted. However, such patients' have relatively better pregnancy outcomes following transcervical resection of the septum.

Among patients with all types of uterine malformation, 38.5% had no other infertility-related factors, while the incidence of associated endometriosis (36.0%) is significantly higher than among the non-specific infertile population [17]. There is no explanation as to why non-obstructive uterine malformations increase the risk of endometriosis.

It is well documented that women with uterine malformations are prone to encounter miscarriage or premature delivery [18], of which a uterine septum is the most common [19] with a high risk of spontaneous abortion (21%–44%) and premature delivery (12%–33%) [4,20]. On the contrary, transcervical resection of the septum can significantly reduce pregnancy loss [20,21]. Some studies have proposed that a uterine septum may cause infertility (especially recurrent pregnancy loss), but the evidence is not compelling [22,23]. It is generally recognized that CUAs typically do not prevent either spontaneous conception or that following *in vitro* fertilization [24,25]. The prevalence of CUAs in patients with primary infertility is approximately the same as among inpatients with normal fertility [4]. According to our preliminary data, patients with a uterine septum and single cervix usually present with miscarriage as the chief complaint, whereas patients with uterine septum and double cervix usually present with primary infertility. It appears that the septum in the latter is generally wider.

According to current consensus [20], uterine malformations do not usually lead to excessive intervention by physicians unless the patient is facing unexplained infertility or repeated miscarriage. As our retrospective data demonstrated, uterine malformations accounted for 5.9% of unexplained infertility, suggesting that uterine malformations were not a dominant cause of infertility. Furthermore, based on the self-control comparison, we noticed that the natural pregnancy rate of all types of uterine malformations increased following surgery. There was no significant difference between the two groups (with/without uterine septum), which indicates that the type of uterine malformation in the cause of infertility is not relatively significant. The necessity of hysteroscopic and laparoscopic surgery is as important for infertility with uterine malformations as it is for infertility without uterine malformations [19,26].

The common characteristics of the unicornuate and bicornuate uterus are the small volume of the uterine cavity, the abnormal proportion of uterine cervical muscle and connective tissue, and poor ability to resist the uncoordinated contractions of the uterus so that miscarriage is likely to occur [14,27]. Since in a unicornuate uterus only 1 side of the fallopian tube has reproductive potential, it is speculated that pregnancy should be more difficult than in a bicornuate uterus. From our data, the natural pregnancy rate of the duplex uterus group (100.0%) was significantly higher than the unicornuate uterus group (75.5%). However, the miscarriage rates of these two groups were relatively high, 25.0% and 37.5% respectively.

Uterine malformations can be divided into two groups (uterine septum group which includes uterine septum with a single cervix and uterine septum with double cervix; and unicornuate uterus group which includes unicornuate uterus with a single cervix and bicornuate uterus with double cervix) all dependent on whether the volume of the uterine cavity can be improved [28]. The unicornuate group has a significantly higher miscarriage rate and lower live birth rate. The uterine cavity volume may be the key reason for miscarriage.

Xia *et al.* [28] reported 3 cases of unicornuate uterus in China resulting in a successful pregnancy after dilatative surgery. Subsequently, Xia *et al.* [28] analyzed the pregnancy outcomes of 33 patients with unicornuate uterus following hysteroplasty. The most noteworthy outcome was the significant decrease in the abortion rate during early pregnancy following the operation. Since there were only 14 secondary infertility cases and no control group, the level of evidence for the increased pregnancy rate was limited. We found that the pregnancy rate of patients with unicornuate uterus without volume expansion surgery was not low, although the miscarriage rate of unicornuate patients was the highest.

This study focused on the fertility outcomes of infertile patients combined with uterine malformations. Previously, a large volume of research had mainly focused on

the relationship between uterine malformations and miscarriage and pregnancy outcomes. This study provides additional information, suggesting that non-obstructive uterine malformations may not be an important cause of infertility. According to the general strategy to standardize diagnosis and treatment, the treatment outcome for such infertility patients should be viewed optimistically. This study is a retrospective analysis that only illustrates differences in pregnancy outcomes for different types of uterine malformation as it lacked a proper control group. There are limitations in this research. First, the study worked with a limited sample, and many data comparisons have no statistical differences. Second, the study did not compare women with different degrees of uterine malformation which may have an impact on live birth and miscarriage rates. Further investigations with larger sample sizes with more detailed information are required.

5. Conclusion

The study reclassified the five types of uterine malformations into two groups: the “uterine septum group” and the “unicorned uterus group”. Compared with the unicorned uterus group, the abortion rate was significantly lower and the live birth rate was significantly higher in the septum group. However, due to the limited number of cases in this study and the lack of assessment of the severity of the malformation, further exploration is needed to obtain more definitive evidence.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

SD, RC and QY designed the research study. YW performed the research and wrote the manuscript. QT, AS and ML analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study conformed to the guidelines explained in the Declaration of Helsinki and was approved (S-K1373) by the ethics committee of Peking Union Medical College Hospital (PUMCH, Beijing, China). A waiver for the requirement of informed consent from the patients whose records were analyzed was granted by the Chair of the Committee on the grounds of being a minimal-risk study.

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Conflict of Interest

The authors declare no conflict of interest.

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