Midline uterine defect size is correlated with miscarriage of euploid embryos in recurrent cases

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Objective: To compare subsequent pregnancy outcomes after two or more miscarriages in patients with and without congenital uterine anomalies.

Design: Case-control study.

Setting: Nagoya City University Hospital.

Patient(s): A total of 42 patients with a bicornuate or septate uterus and 1528 with normal uteri.

Intervention(s): No surgery.

Main Outcome Measure(s): The cumulative success rate for birth, abnormal chromosome karyotype rate in aborted concepti, and the predictive values of the height of the defect/length of the remaining uterine cavity ratio (D/C ratio).

Result(s): Of the total of 1676 patients, 54 (3.2%) had congenital uterine anomalies; 25 (59.5%) of the 42 patients with a bicornuate or septate uterus had a successful first pregnancy after examination, while this was the case for 1096 (71.7%) of the 1528 with normal uteri. There was no difference in the cumulative live-birth rate (78.0% and 85.5%) within the follow-up period. However, the rates for an abnormal chromosome karyotype in aborted concepti in cases with and without uterine anomalies were 15.4% (two of 13) and 57.5% (134 of 233), respectively, with the latter being significantly higher. The D/C ratio in the miscarriage group was also significantly greater than that for the live-birth group.

Conclusion(s): Congenital uterine anomalies have a negative impact on reproductive outcome in couples with recurrent miscarriage and are associated with further miscarriage with a normal embryonic karyotype. The D/C ratio was found to have a predictive value for further miscarriages in recurrent cases. (Fertil Steril 2010;93:1983–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: Bicornuate uterus, congenital uterine anomaly, recurrent miscarriage, septate uterus

Established causes of recurrent miscarriages are antiphospholipid antibodies (aPL), uterine anomalies, and chromosomal abnormalities in the embryo (1–3). Abnormal chromosomes in either partner, particularly translocations, are also risk factors (4). Regarding uterine anomalies, Raga et al. reported that patients (6.3%, 54 of 868; \( P < .05 \)) with a history of two or more miscarriages had a significantly elevated incidence of Mullerian anomalies compared with fertile (3.8%, 49 of 1289) and sterile (2.4%, 25 of 1024) cases (2). The frequency of congenital uterine anomalies has been reported to be between 1.8% and 37.6% in women with a history of recurrent miscarriage, the variation largely depending on the methods of selection and criteria for diagnosis (5–7).

Thus, affected patients are offered surgery in an attempt to restore the uterine anatomy (8–16). The conclusion is that operations can increase successful pregnancies, but to our knowledge there have been no prospective studies comparing pregnancy outcomes between cases with and without surgery in patients with a history of recurrent miscarriage. Lee et al. reported a preoperative pregnancy loss rate of 77.4%, a 18.2% miscarriage rate, and a 77.3% uncomplicated delivery rate after hysteroscopic septum resection (14). However, it is inappropriate to simply make comparisons before and after surgery because the miscarriage rate before examination might be 100% but the subsequent success rate is never 0. The subsequent live-birth rate is expected to be 72% in recurrent miscarriage patients without abnormal chromosomes in either partner (17) and decreases with the number of previous miscarriages (3).

Information concerning the prognosis in women with congenital uterine anomalies with a history of recurrent miscarriage is limited. The present study was therefore conducted to assess the subsequent live-birth rate, comparing pregnancy outcome between cases with and without bicornis or septum in individuals with a history of recurrent miscarriage.

PATIENTS AND METHODS

We conducted a case-control study. We studied 1676 patients with a history of two or more (2–12) consecutive miscarriages whose subsequent pregnancies were ascertained at least once in our medical records. Hysterosalpingography (HSG), chromosome analysis for both partners, determination of aPL,
including lupus anticoagulant and β2-glycoprotein I dependent antiphospholipid antibodies (18), and blood tests for hyperthyroidism, diabetes mellitus, and hyperprolactinemia were performed for all patients before subsequent pregnancy. All patients were examined between 1986 and 2007 at Nagoya City University Hospital.

Laparoscopy/laparotomy and/or magnetic resonance imaging (MRI) were performed to ascertain the type of anomaly (investigating both the uterine cavity and the external uterine contours) in accordance with the American Fertility Society classification of Mullerian anomalies (19–21). Tompkin’s index was used to distinguish between arcuate uterus and mild septate or bicornuate uterus (22). A Tompkin’s index >25% was the criterion for septate or bicornuate uterus. Patients desiring surgical treatment before subsequent pregnancies underwent a Jones metroplasty, Strassman metroplasty, or hysteroscopic transcervical resection (TCR; 8–10).

All pregnancy outcomes of 1676 patients were examined. Patients with at least one kind of aPL were treated with low-dose aspirin and heparin combined therapy. Gestational age was calculated from basal body temperature charts. Ultrasound was performed once or twice a week from 4 to 8 weeks’ gestation. Dilation and curettage was performed on all patients diagnosed with miscarriage, and the karyotypes of aborted conceptions were determined with the use of a standard G-banding technique. The study was approved by the Research Ethics Committee at Nagoya City University Medical School.

In the present study, [1] the prevalence of clear congenital uterine malformations such as septate uterus, bicornuate uterus, unicornuate uterus, and didelphys was examined; [2] the first pregnancy outcome after systematic examination for recurrent miscarriage was determined for both septate and bicornuate uterus cases, comparing patients with or without anomalies; [3] all pregnancy outcomes after systematic examination were also assessed, and the final live-birth rate/patient was calculated; [4] abnormal karyotype rates for aborted conceptuses at the first miscarriage after the ascertainment of uterine abnormalities were also compared between patients with and without congenital uterine anomalies; [5] the height of the defect/length of the remaining uterine cavity (D/C) ratios were calculated in cases with bicornuate and septate uterus and compared between miscarriages and live birth at the subsequent first pregnancy. We also ascertained whether the D/C ratio has predictive value for further miscarriage in recurrent miscarriage cases.

The analysis was carried out using the SAS system (SAS Institute Inc., Cary, NC) with receiver operating curve (ROC) analysis and logistic regression. \( P < .05 \) was considered statistically significant.

RESULTS
Baseline Characteristics

One thousand six hundred seventy-six patients became pregnant after systematic examination for recurrent miscarriages. Of this total, 54 (3.2%) had congenital uterine anomalies, 38 with partial bicornis unicoli, 10 with a septum, five with a unicornis, and one with a didelphys. None of them had hypoplasia/agenesis or diethylstilbestrol (DES) drug-related anomalies. Two patients with a septate uterus and a bicornuate uterus also had translocations in either partner. The 94 patients who had structural chromosome abnormalities, including 73 translocations, in either partner, were excluded from the analysis.

One thousand five hundred twenty-eight patients had neither congenital uterine anomalies nor an abnormal chromosome karyotype in either partner; 75 patients exhibited persistent aPL and were treated with low-dose aspirin and heparin combined therapy.

One of the two patients with bicornuate uteri underwent a Jones metroplasty, and the other underwent a Strassman metroplasty (8, 9). One patient with a septum also received a Jones metroplasty, and hysteroscopic TCR was performed for the other four patients with septate uteri.

We compared pregnancy outcomes between 42 patients with septate or bicornuate uterus not undergoing surgery and 1528 patients without uterine anomaly. We found no differences in baseline characteristics between the two groups (Table 1).

Pregnancy Outcome

Subsequent pregnancy outcomes are summarized in Table 2. Twenty-five of the 42 patients with a septate or bicornuate uterus (59.5%) treated without any kind of surgery had a successful outcome, while this was the case for 1096 (71.7%) of the 1528 without congenital uterine anomalies at the subsequent first pregnancy \( (P = .084) \). Four of five patients with a septate uterus and 21 of 37 patients with a bicornuate uterus gave birth to live babies. There was one case with a bicornuate uterus who suffered from uterine rupture in the first trimester because of the limited capacity.

One patient received surgery after further miscarriage. Thus, 32 (78.0%) of 41 patients and 1307 (85.5%) of 1528 patients with and without uterine anomalies could cumulatively have a live baby within the follow-up period \( (P = .006) \). Live-birth rates of patients with congenital uterine anomalies tended to be lower both at the first pregnancy after ascertainment and cumulatively. Final live-birth rates/person are also shown in Table 2.

Furthermore, rates for an abnormal chromosome karyotype in aborted conceptuses in cases with and without uterine anomalies were 15.4% (two of 13) and 57.5% (134 of 233), respectively, at the first pregnancy after ascertainment of uterine anomalies, the difference being highly significant \( (Fisher’s exact probability test, P = .006) \).

One of five patients with a unicornuate uterus succeeded in having a baby at the first pregnancy after examination, and four of five could have a baby, cumulatively. The patient with didelphys also succeeded at the first pregnancy after examination.
Predictive Value for the D/C Ratio

Mean values (SD) for the D/C ratio in the miscarriage and live-birth groups were 0.8332 (0.3974) and 0.4776 (0.2745), respectively (P = .0057, 95% confidence interval [CI]; 0.1115–0.5998). When two miscarriage cases caused by an abnormal embryonic karyotype were excluded, the value for the D/C ratio in the miscarriage group was also significantly higher than in the live-birth group (P = .0051).

Mean (SD) age and number of previous miscarriages for the 15 patients whose subsequent pregnancy ended in miscarriage and the 17 patients who experienced live births were 31.5 (3.0) versus 31.5 (3.8) and 2.76 (0.75) versus 2.72 (0.79), respectively (P = not significant). Ten patients were excluded because HSG films were not available.

The ROC curve is shown in Figure 1. From the figure, the cutoff value would be appropriate somewhere between 0.59 and 0.64, giving the sensitivity and specificity around 0.75–0.80. The area under the ROC curve, meaning the total diagnostic accuracy of the D/C ratio on live birth, was 0.808. From the logistic regression, the D/C ratio was found to be an independent risk factor on the failure of live birth after adjusting for age and previous number of miscarriages. The odds ratio for the 0.1 increment of D/C ratio was 1.42 (95% CI, 1.06–1.91).

DISCUSSION

In the present study, the live-birth rate of patients with congenital uterine anomalies tended to be lower, both at the first pregnancy after ascertainment and cumulatively, than that of patients with a normal uterus, although the differences were not significant. Congenital uterine anomalies were associated with miscarriages with a normal embryonic karyotype. Thus, congenital uterine anomalies impacted the progression of normal pregnancies.

Salim et al. earlier found no significant difference in the relative frequency of various anomalies or depth of fundal distortion as determined by three-dimensional (3D) ultrasound between women with and without a history of recurrent miscarriage, although abnormalities in uterine anatomy were more severe in women with a history of recurrent miscarriages (23). In this context, the finding in the present study that the D/C ratio is a predictor of further miscarriage in recurrent cases is clearly of interest.

However, 59.5% and 78.0% of our patients with a septate or bicornuate uterus without any kind of surgery could have a baby at the first pregnancy or cumulatively. Several studies concerning obstetric outcome after removal of a uterine septum have been reported (10–16). Lee et al. described a 77.3% uncomplicated delivery rate after hysteroscopic septum resection (14). Kormayos et al. compared pregnancy outcome after removal of septum between cases with and without a residual septum in patients with a history of two or three miscarriages and concluded that the live-birth rate in cases with no remnant was significantly higher than that in cases with a remnant (15). However, the live-birth rate for patients undergoing first hysteroscopy was 35.1% (33 of 94), and the

TABLE 1

Baseline characteristics of patients with and without congenital uterine anomalies.

<table>
<thead>
<tr>
<th></th>
<th>Patients with anomalies (n = 42)</th>
<th>Patients without anomalies (n = 1528)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.5 (3.5)</td>
<td>31.1 (4.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>31 (29)</td>
<td>31 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of previous miscarriages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17 (40.5)</td>
<td>765 (50.1)</td>
<td>.0051</td>
</tr>
<tr>
<td>3</td>
<td>18 (42.9)</td>
<td>537 (35.1)</td>
<td>.0051</td>
</tr>
<tr>
<td>4</td>
<td>7 (16.7)</td>
<td>136 (8.9)</td>
<td>.0051</td>
</tr>
<tr>
<td>5 or more</td>
<td>0</td>
<td>90 (5.9)</td>
<td>.0051</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.74 (0.77)</td>
<td>2.77 (1.12)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of previous live births</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (88.1)</td>
<td>1328 (86.9)</td>
<td>.0051</td>
</tr>
<tr>
<td>1</td>
<td>4 (9.5)</td>
<td>186 (12.2)</td>
<td>NS</td>
</tr>
<tr>
<td>2 or more</td>
<td>1 (2.4)</td>
<td>14 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.1</td>
<td>0.14 (0.37)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of previous stillbirths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (95.2)</td>
<td>1491 (97.6)</td>
<td>.0051</td>
</tr>
<tr>
<td>One or more</td>
<td>2 (4.8)</td>
<td>37 (2.4)</td>
<td>.0051</td>
</tr>
</tbody>
</table>

Note: Values are numbers (percentages) of patients unless otherwise specified.

<table>
<thead>
<tr>
<th>Pregnancy after the ascertainment of uterine anomaly</th>
<th>Success rate per pregnancy</th>
<th>Cumulative success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With anomalies (n = 42)</td>
<td>Without anomalies (n = 1528)</td>
</tr>
<tr>
<td>First</td>
<td>25/42 (59.5)²</td>
<td>21/37 (56.8) 4/5 (80.0)</td>
</tr>
<tr>
<td>Second</td>
<td>5/9 (55.6)</td>
<td>4/8 (50.0) 2/2 (100)</td>
</tr>
<tr>
<td>Third</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>Fourth</td>
<td>4/18 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Fifth</td>
<td>3/9 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Sixth</td>
<td>0/6 (0)</td>
<td></td>
</tr>
<tr>
<td>Final follow up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Values are numbers (percentages) of couples. Success rate is defined as the live birth.

² One case underwent surgery between the first and second pregnancy after the ascertainment of an anomaly, thus this case was excluded from the cumulative analysis.

³ Comparison was performed between patients both with anomalies and with normal uterus.

⁴ Cases who could succeed in the first pregnancy were excluded from the analysis of the second and subsequent pregnancies.
cumulative live-birth rate after one or two metroplasties was 54.3% (51 of 94). Both live-birth rates were lower than that without surgery in the present study. The benefits of surgical correction (open and hysteroscopic) on pregnancy outcome have yet to be assessed in a randomized trial, but the D/C ratio might be useful in deciding who should be selected.

Limitations
In the present study, clear uterine malformations such as septate, bicornuate, or unicornuate uterus and didelphys were found in 3.2% of patients. The prevalence of clear congenital uterine anomalies in patients with a history of recurrent miscarriages has been reported to be 1.8%–20.1% with the arcuate uterus excluded (5–7) and thus higher than the 2.2% documented for fertile women (28 of 1289) (2). Minor malformations like arcuate uterus do not appear to have any impact on reproduction (2), and therefore we here excluded cases with this anomaly.

HSG is the diagnostic modality that has most often led to a tentative diagnosis of congenital anomalies (19), but when used alone it cannot distinguish between a septate and a bicornuate uterus. Thus laparoscopy has hitherto been needed for a final diagnosis. The advent of sonohysterography, MRI (20), and 3D ultrasound now allows for accurate differential diagnosis (21), although distinguishing an arcuate from a mildly subseptate or bicornuate uterus still remains difficult.

It is important to distinguish between the bicornuate uterus and the septate uterus, especially regarding the selection of surgical methods because TCR should not be performed for the former. We here ascertained the type of anomaly to study the prevalence in accordance with the American Fertility Society classification of Mullerian anomalies. Woelfer et al. proved new 3D criteria by which a bicornuate uterus can be distinguished from a septate uterus when a fundal indentation >10 mm dividing the two cornua is detectable (21). Using 3D ultrasound, it has been found that the septate uterus has the higher incidence. The criteria are useful before deciding on using TCR for the septum. It is difficult to examine the significance of the distinction between bicornuate and septate uterus because of the absence of internationally established criteria, although we have given the live-birth rate for each anomaly in Table 2. Thus we focused not on type of anomalies but rather on the D/C ratio. In addition, the sample size in the anomaly group was too small to allow any conclusion when we distinguished between the two groups.

While we examined 1676 patients who became pregnant at least one time in the present study, we failed to follow up all those who received systemic examination for causes of recurrent miscarriage at our hospital because some lived at a long distance. Some patients might become infertile after miscarriage. A prospective case-control study should therefore be conducted to compare live-birth rates between patients with and without surgery, including consideration of the infertility rate.

Conclusion
Congenital uterine anomalies have a negative impact on reproductive outcome in couples with recurrent miscarriage, being particularly associated with normal embryonic karyotype miscarriages. The height of the defect/length of the remaining uterine cavity ratio, the D/C ratio, has independent predictive value for further miscarriage in recurrent cases. Comparison of cases of anomalies with and without surgery is needed in future recurrent miscarriage studies.

REFERENCES