A comparative study of the morphology of congenital uterine anomalies in women with and without a history of recurrent first trimester miscarriage

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BACKGROUND: The true impact of congenital uterine anomalies on reproductive outcomes is unknown. The aim of this study was to examine differences in the morphology of uterine anomalies found in women with and without a history of recurrent miscarriage. METHODS: A total of 509 women with a history of unexplained recurrent miscarriage and 1976 low risk women were examined for the presence of congenital uterine anomalies by three-dimensional ultrasound. The anomalies were classified according to the American Fertility Society classification. In addition, the size of fundal distortion (F) and the length of the remaining uterine cavity (C) were measured to calculate a distortion ratio (F/F+C). The findings were compared with the measurements obtained in low risk women with an incidental finding of uterine anomaly. RESULTS: In all, 121 anomalies were detected in the recurrent miscarriage group and 105 in low risk women. There was no significant difference in relative frequency of various anomalies or depth of fundal distortion between the two groups. However, with both arcuate and subseptate uteri, the length of remaining uterine cavity was significantly shorter (P<0.01) and the distortion ratio was significantly higher (P<0.01) in the recurrent miscarriage group. CONCLUSION: The distortion of uterine anatomy is more severe in congenital anomalies, which are found in women with a history of recurrent first trimester miscarriage.

Key words: congenital uterine anomalies/recurrent miscarriage/three-dimensional ultrasound

Introduction
Congenital uterine anomalies have been implicated as a cause of adverse pregnancy outcomes (Acien, 1993; Raga et al., 1997). Women with a history of infertility or miscarriage are, therefore, often offered surgery in an attempt to restore uterine anatomy and improve the prognosis for future pregnancies (Pellicer, 1997). The reported prevalence of congenital uterine anomalies in women with recurrent pregnancy loss varies between 6 and 38% (Makino et al., 1992a; Clifford et al., 1994; Acien, 1996). This wide variation is likely to reflect differences in the diagnostic criteria and techniques used for diagnosis. Although most authors subscribe to the American Fertility Society Classification of Uterine anomalies (American Fertility Society, 1988), the final diagnosis is based on the subjective impression of the clinician performing the test. So far, no published study has investigated the reproducibility of different tests used in routine clinical practice for the diagnosis of uterine anomalies.

Most studies of uterine anomalies have been performed on women with either a history of infertility or recurrent pregnancy loss. However, little is known about the prevalence and reproductive implications of uterine anomalies in the general population. In the absence of such data, it is difficult to be certain whether uterine anomalies are indeed a major cause of recurrent pregnancy loss. We have recently reported on the prevalence and morphological characteristics of uterine anomalies detected on screening low risk women using three-dimensional ultrasound (Jurkovic et al., 1997; Woelfer et al., 2001). In this study, we have used the same technique and diagnostic criteria to investigate women with recurrent pregnancy loss. The aim of the study was to investigate the prevalence and severity of uterine anomalies in women with recurrent pregnancy loss and then to compare the results to the findings in low risk women.

Materials and methods
A total of 522 consecutive women with a history of recurrent miscarriage was prospectively recruited from the Recurrent Miscarriage Clinics at St Mary’s and King’s College Hospitals, London, between August 1997 and January 2001. All women were screened for the presence of antiphospholipid antibodies and both partners had peripheral blood karyotyping. All women also underwent a transvaginal ultrasound scan as a part of the investigations into the causes of recurrent pregnancy loss. The inclusion criteria were a
history of three or more consecutive unexplained pregnancy losses before 14 weeks gestation. The control group consisted of 2034 pre-menopausal women without a history of infertility of recurrent miscarriage who were referred for an ultrasound scan for a variety of indications unrelated to reproductive outcomes. Exclusion criteria in both groups of women were an ongoing pregnancy, presence of uterine fibroids distorting the uterine cavity, previous hysterectomy or myomectomy and inadequate visualization of the uterine cavity. The study was approved by the Research Ethics Committees of both institutions, and informed consent was obtained for the trial from all participants.

Two-dimensional ultrasound was used first to screen for congenital uterine anomalies. Uterine anomalies were suspected when there was evidence of duplication of uterine cavity or when the interstitial portion of either Fallopian tube could not be seen. All women with suspected anomalies were then examined by three-dimensional ultrasound (Combison 530 3-D Voluson, Kretztechnik, Zipf, Austria). In order to obtain three-dimensional ultrasound images, the uterus was visualized in the longitudinal plane. A three-dimensional ultrasound volume was then generated by the automatic sweep of the mechanical transducer. The acquired volumes were in the shape of a truncated cone with the depth of 4.3–8.6 cm and a vertical angle $\alpha = 90^\circ$. The volumes were immediately stored on removable hard disk cartridges (Magneto-Optic 3.0\', 640 MB; Olympus Optical Co., Hamburg, Germany). The analysis of uterine morphology was then performed online using the technique of planar reformatted sections with the interstitial portions of the Fallopian tubes as reference points (Jurkovic and Aslam, 1998). In all cases, the ultrasound operator was aware of the clinical diagnosis of the woman being examined.

Congenital uterine anomalies were classified in accordance with the modified American Fertility Society Classification (Woelfer et al., 2001). In addition, in each case of arcuate and subseptate uterus a distance was measured between the midpoint of the line joining the two internal tubal ostia and the distal tip of fundal indentation or uterine septum. Further measurements were then taken from this point to the level of the internal os, this measurement representing the length of the unaffected uterine cavity. The degree of distortion of uterine architecture was then quantified by the ratio $F/F+C$, where $F$ was the length of the uterine septum or depth of fundal indentation in arcuate uteri, and distortion ratio. Pearson’s $r$-test was used to compare the mean ages of the women and septum length or depth of fundal indentation, in arcuate uteri, and distortion ratio. Student’s $t$-test was used to compare relative proportions of various types of uterine anomalies between control and recurrent miscarriage groups. The Mann–Whitney test for non-parametric data was used to compare the differences in proportions of women who had been pregnant, first

Both operators were also tested for the intra-observer variability of measurement. The mean differences for measurements of $F$ were $-0.157$ mm (95% limits of agreement from $-2.54$ to $2.23$ mm) and $0.277$ mm (95% limits of agreement from $-2.13$ to $2.69$ mm) for operators R.S. and B.W. respectively. The mean differences for measurement of $C$ were $0.138$ mm (95% limits of agreement from $-2.87$ to $3.02$ mm) and $0.110$ (95% limits of agreement from $-1.91$ to $2.13$ mm) for operators R.S. and B.W. respectively.

A database file was set up using Microsoft Excel for Windows (Redmond, WA, USA) to facilitate data entry and retrieval. Statistical analysis was performed using SPSS for Windows (Version 6.0; SPSS, Inc., Chicago, IL, USA). Student’s $t$-test was used to compare the mean of the women and septum length or depth of fundal indentation, in arcuate uteri, and distortion ratio. Pearson’s $r$-test was used to compare relative proportions of various types of uterine anomalies between control and recurrent miscarriage groups. The Mann–Whitney test for non-parametric data was used to compare the differences in proportions of women who had been pregnant, first

Table I. Demographics of women with uterine anomalies included in the final data analysis

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Recurrent miscarriage</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>32.4 (18–48)</td>
<td>34.9 (21–45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total no. of women who were pregnant in the past (%)</td>
<td>56 (53.3)</td>
<td>121 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total no. of pregnancies</td>
<td>126</td>
<td>491</td>
<td></td>
</tr>
<tr>
<td>No. of pregnancies per woman (mean and range)</td>
<td>1.26 (0–9)</td>
<td>4.0 (3–11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First trimester miscarriage (%)</td>
<td>37 (29.4)</td>
<td>411 (83.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second trimester miscarriage (%)</td>
<td>9 (7.1)</td>
<td>35 (7.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pre-term labours (%)</td>
<td>14 (11.1)</td>
<td>9 (1.8)</td>
<td>0.423</td>
</tr>
<tr>
<td>Live births (%)</td>
<td>68 (53.9)</td>
<td>36 (7.3)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Figure 1. A coronal view of a septate uterus demonstrating the normal outer uterine contour. The length of the septum ($F$) is measured between its distal tip and the midpoint of the line adjoining tubal ostia. The length of the residual uterine cavity ($C$) was measured between the distal tip of the septum and the internal os.
Results

A total of 509 women with a history of recurrent miscarriage was included in the final data analysis. Thirteen women (2.6%) were excluded: three were found to have submucous fibroids, which were significantly distorting the uterine cavity, and nine women had an irregular uterine cavity following previous uterine surgery. An additional patient with the diagnosis of an arcuate uterus tested positive for antiphospholipid antibodies and therefore she was also excluded from the final data analysis. Of the 509 women who were included in the final analysis, 388 (76.2%) had a normal uterus and uterine anomalies were diagnosed in 121 (23.8%) (Table I). In the control group, satisfactory three-dimensional ultrasound images were obtained in 1976 women (97.1%) with 43 women being excluded due to the presence of submucous fibroids, 11 due to the presence of an intrauterine contraceptive device and four women were excluded due to an irregular uterine cavity following myomectomy. A conclusive diagnosis of congenital uterine anomaly was made in 105 (5.3%) women.

The most common anomalies in both groups were arcuate and subseptate uterus, which accounted for >90% of cases (Table II). There was no significant difference in the relative proportions of congenital uterine anomalies in the two groups of women. Morphological characteristics of uterine anomalies in women with recurrent miscarriage were compared with the control group. Depth of fundal indentation, in arcuate uteri, and septum length, in subseptate uteri, were not significantly different between the two groups of women. However, in both arcuate and subseptate uteri, the length of the normal uterine cavity was significantly shorter and the degree of distortion of the uterine cavity was significantly higher in women with a history of recurrent miscarriage (Table III). In order to eliminate a potential effect of parity on uterine morphology, comparisons were also performed in the cohort of nulliparous women only. This revealed similar results except that the depth of fundal indentation in arcuate uteri in the recurrent miscarriage group was significantly greater compared with that in low risk women (Table IV).

Discussion

In this study, congenital uterine anomalies were found in 23.8% of women with recurrent miscarriage. The most common anomaly, however, was the arcuate uterus, whilst major anomalies were present in 6.9% of women. Previous studies of women with a history of recurrent early pregnancy loss have shown a variable prevalence of congenital uterine anomalies. In one study (Clifford et al., 1994), major uterine anomalies were found in 23.8% of women with recurrent miscarriage. The most common anomaly, however, was the arcuate uterus, whilst major anomalies were present in 6.9% of women. Previous studies of women with a history of recurrent early pregnancy loss have shown a variable prevalence of congenital uterine anomalies.
anomalies were found in nine out of 500 cases (1.8%). Another large screening study of 1200 Japanese women found major anomalies in 4.6% of women (Makino et al., 1992a), whilst in a study of 55 women (Tulppala et al., 1993), major uterine anomalies were found in four cases (7.2%). The prevalence of major uterine anomalies in our study is broadly in agreement with these previous studies, which used invasive diagnostic techniques to detect uterine anomalies. The lower prevalence reported by Clifford et al. (1994) may be explained by the low sensitivity of two-dimensional transabdominal ultrasound for the diagnosis of congenital uterine defects.

The potential significance of uterine anomalies in the context of recurrent pregnancy loss cannot be established without comparisons with the low risk population. In a previous screening study of 1022 low risk women, we found major congenital uterine anomalies in 2.3% of cases (Jurkovic et al., 1997), which is comparable with the prevalence of 1.7% in this series. Similar results have been reported by others who have used a combination of invasive tests to screen for uterine anomalies in women undergoing tubal sterilization. One study (Ashton et al., 1988) found major anomalies in 1.9% of cases using hysterosalpingography and hysteroscopy, whilst Simon et al. (1991) reported the prevalence of 3.2% using a combination of laparoscopy and hysterosalpingography. A recent study (Byrne et al., 2000), using transabdominal two-dimensional ultrasound to screen for anomalies, found prevalence of only 0.4% in 2065 low risk women. Similar to the study by Clifford et al. (1994), this low prevalence is likely to be the reflection of the poor sensitivity of transabdominal two-dimensional ultrasound for the diagnosis of uterine anomalies.

The results of these studies show that the prevalence of major congenital uterine anomalies is ~3-fold higher in women with history of recurrent miscarriage compared with the low risk population. This suggests that congenital uterine anomalies may indeed be responsible for pregnancy loss in a small proportion of women with recurrent miscarriages.

A recent literature review showed that the most common major uterine anomaly in women with recurrent pregnancy loss is subseptate uterus (Homer et al., 2000). The results of our study are similar, showing that the subseptate uterus was the most common major uterine anomaly, accounting for 77% of cases. The subseptate uterus was also the most common anomaly in low risk women, accounting for 70–90% of cases (Simon et al., 1991; Jurkovic et al., 1997; Raga et al., 1997). Subseptate uterus accounted for 84% of major anomalies found in low risk women in the present study, which is again consistent with the data from the literature.

The pathophysiology of early pregnancy loss in cases of subseptate uterus is explained by the inability of the relatively avascular septum to provide adequate blood supply to the developing embryo (Burchell et al., 1978). This view is supported by histological evaluation of the septum, which showed significantly reduced vascular supply in relation to the rest of the uterus (Nakada et al., 1989; Dabirashahi et al., 1995). If this theory is correct, then the likelihood of miscarriage caused by septal implantation should increase with the severity of the disruption of uterine morphology.

Makino et al. (1992b) tried to quantify the degree of distortion of the uterine cavity by calculating the ratio between the fundal distortion and the length of the uterine cavity on hysterosalpingography. They found no association between the severity of uterine anomaly and the number of previous miscarriages. In contrast, the results of this study showed that the degree of distortion of the uterine cavity in subseptate uterus was higher in women with recurrent miscarriage, compared with low risk women. This was mainly due to the reduced length of unaffected cavity, rather than the increased septum length. Differences between our and Makino’s study could be a result of different measurement techniques and different definition of recurrent miscarriage in their study, which included women with only two consecutive first trimester losses. Nevertheless, our results indicate that the distortion of the uterine anatomy in subseptate uterus is greater in women with recurrent pregnancy loss. This finding supports the hypothesis of septal implantation as a potential cause of miscarriage as the likelihood of septal implantation increases with an increasing ratio of septal size to functional cavity.

The prevalence of arcuate uterus in women with recurrent miscarriage was 17%, which is significantly higher compared with the prevalence of 3.2% in low risk women (Jurkovic et al., 1997). In addition, similar to the subseptate uterus, the distortion of uterine cavity was greater in women with recurrent first trimester loss. The diagnosis of arcuate uterus is difficult using conventional methods such as hysteroscopy or laparoscopy and the diagnostic criteria are far from clear (Golan et al., 1992). As a result, little is known about its prevalence and clinical significance. However, all studies report an increase in adverse reproductive outcomes, mostly second trimester loss (Tulandi et al., 1980; Acien, 1993; Raga et al., 1997; Woelfer et al., 2001). The pathophysiology of miscarriage in women with arcuate uterus remains unknown. The only therapeutic intervention that has been proposed to decrease the risk of miscarriage is the insertion of cervical suture (Golan et al., 1990). However, this intervention is unlikely to be helpful in women with a history of first trimester pregnancy loss.

This study also demonstrates the benefits of using three-dimensional ultrasound for the diagnosis of uterine abnormalities. The accuracy of three-dimensional ultrasound compared with the traditional methods for the assessment of uterine morphology has been assessed and was found to be satisfactory (Jurkovic et al., 1995; Raga et al., 1996). The main advantage of this technique is the ability to describe uterine anomalies in quantitative terms and store ultrasound volumes permanently in a form which enables further re-examination and independent evaluation of the diagnosis (Jurkovic and Aslam, 1998). This provides an opportunity to pool diagnostic information from a large number of diagnostic centres and to describe anomalies using uniform diagnostic criteria. Accumulation of such a large number of data may help to provide us with better answers in the future about the clinical significance and optimal management of many different types of uterine anomalies.
References


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