Reproductive impact of congenital Müllerian anomalies

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This retrospective longitudinal study was undertaken in order to determine the incidence and reproductive impact of uterine malformations on women desiring to conceive during their reproductive years. A total of 3181 patients in whom the morphology of the uterus was ascertained by hysterosalpingography (HSG) and laparoscopy/laparotomy during the years 1980–1995 was included in the study. The population analysed included fertile, infertile and sterile patients. The overall frequency of uterine malformations was 4.0%. Infertile patients (6.3%) had a significantly \( P < 0.05 \) higher incidence of Müllerian anomalies, in comparison with fertile (3.8%) and sterile (2.4%) women. Septate (33.6%) and arcuate (32.8%) uteri were the most common malformations observed. Each malformation was individually analysed in fertile and infertile patients, in order to ascertain its actual reproductive impact. The performance of the unicornuate and didelphys uterus was similar with a chance of having a living child of 37–40%. The reproductive potential of the bicornuate uterus showed a live birth rate of 62.5% and the septate uterus showed a live birth rate of 62%. In all these abnormalities, early miscarriages (25–38%) and preterm deliveries (25–47%) were quite common. The arcuate uterus presented a live birth rate of 82.7%. It is concluded that uterine anomalies are relatively frequent in fertile women, and more frequent in infertile patients. Nevertheless, fertile patients with normal reproductive performance do exist, and Müllerian defects can permit an absolutely normal obstetric outcome. The reproductive performance of the unicornuate and didelphys uterus was poor, while that of the septate and bicornuate uteri was better than expected. The arcuate uterus had no impact on reproduction.

Key words: incidence/Müllerian defects/reproductive performance/uterine malformations

Introduction

Müllerian duct malformations delineate a miscellaneous group of congenital anomalies that result from arrested development, abnormal formation, or incomplete fusion of the mesonephric ducts. In many patients, uterine congenital anomalies have been related with infertility, recurrent pregnancy loss, prematurity and other obstetric complications which increase perinatal morbidity and mortality rates (Green and Harris, 1976; Heimonen et al., 1982; Golan et al., 1989), whereas in others, these uterine malformations are asymptomatic (Simón et al., 1991).

The true incidence of uterine anomalies in the general and in the infertile population is not accurately known, albeit several pieces of evidence indicate that they are not uncommon. The frequency varies according to the source from one out of 10 to one out of 1600 patients (Green and Harris, 1976; Heimonen et al., 1982; Golan et al., 1989). The discrepancy between reports is due to the inaccuracy of the diagnostic methods employed, the lack hitherto of a uniform system of classification and because many of these defects are asymptomatic and therefore remain undiagnosed. Recently, Simón et al. (1991) found the incidence of uterine anomalies in a fertile population to be 3.2%.

The introduction of the vaginal probes in conventional gynaecological screening has improved the diagnosis of such malformations even before a woman attempts to become pregnant. In addition, new ambulatory endoscopic surgical methods have been developed for congenital Müllerian anomalies, perhaps increasing the number of unnecessary surgical corrections, since the actual impact on reproduction of each Müllerian defect is not well defined (Acien, 1997; Donnez and Nisolle, 1997; Jacobsen and DeCherney, 1997; Pellicer, 1997). Therefore, the aim of the present study was to establish the actual incidence and reproductive performance of the different types of uterine malformations in women willing to conceive during their reproductive life in order to define which abnormalities are related to a poor prognosis and which should be surgically corrected (if possible) before trying to conceive.

Materials and methods

We carried out a retrospective study of 3181 patients in whom a hysterosalpingography (HSG) and a laparoscopy/laparotomy were performed at our Institutions (Instituto Valenciano de Infertilidad and Hospital Clínico Universitario) during the years 1980–1995. Thus, in this retrospective study the correct morphology of the uterus was ascertained by HSG and laparoscopy/laparotomy (investigating both the uterine cavity and the external uterine contour). The study population was divided into three groups.

Fertile population \( (n = 1289) \)

Patients with normal reproductive outcome (mean age 37 years, range 32–42) who were treated at the family planning clinic and underwent a tubal sterilization by three different techniques: laparoscopic bilateral
occlusion (n = 891); bilateral tubal ligation by Pomeroy's technique or fimbriectomy at the time of Caesarean section (n = 183); or tubal occlusion immediately after delivery by minilaparotomy or periumbilical boarding (n = 215). Five months after surgery all patients underwent HSG to check tubal patency.

**Infertile population (n = 868)**

Patients attending the fertility clinic due to infertility problems ranging from recurrent spontaneous abortion to preterm delivery. Only couples with two or more consecutive pregnancy losses were defined as infertile (Harger et al., 1983). Mean age in this group was 28 years (range 24–34).

** Sterile population (n = 1024)**

Patients also attending the fertility clinic due to failure to achieve pregnancy for >2 years. Mean age was 31 years (range 23–35). All patients included in the two latter groups had diagnostic HSG and laparoscopy performed during the infertility work-up.

The uterine malformations were grouped in accordance with the American Fertility Society (1988) classification, which divides the anomalies into classes with similar clinical features, therapeutic options and prognoses. Patients with type I abnormalities (hypoplasia/agenesia) have no reproductive potential and therefore were excluded from this study. The data on the reproductive outcome were documented as follows: number of gestations, early miscarriages (defined as up to 13 weeks of pregnancy), late miscarriages (14–22 weeks), term deliveries (37–42 weeks), preterm deliveries (if occurred before week 37 of gestation), ectopic pregnancies and live births (newborn alive after 7 days). All pregnancies achieved in this series were in women who had not undergone corrective surgery or prophylactic cervical cerclage.

**Statistical analysis**

This was performed using the $\chi^2$ test. The analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA); $P < 0.05$ was considered to be statistically significant.

**Results**

Table I shows that the overall frequency of uterine defects was 4.0%. The distribution of each anomaly among fertile, infertile and sterile patients is also shown in Table I. Infertile patients had significantly ($P < 0.05$) increased frequency of Mullerian anomalies (6.3%) compared with fertile (3.8%) and sterile (2.4%) women.

The incidence of each particular type of anomaly has been also analysed from the data shown in Table I. A septate uterus was present in 43 out of the 128 malformations identified (33.6%) and the arcuate in 42/128 (32.8%). These were the most common malformations and appeared significantly ($P < 0.05$) more frequently than the remaining anomalies. The bicornuate uterus was observed in 26/128 (20.3%). When the distribution of uterine malformations was separately considered, infertile women had an increased incidence of bicornuate uterus. In keeping with this concept, the ratio septate:bicornuate uterus was 4:1 in the fertile population while it represented almost 1:1 in the infertile group. The diethylstilboestrol (DES)-exposed uterus was very uncommon in our population (0.8%).

We further addressed the issue of the reproductive outcome of each type of malformation by analysing the fertile and infertile populations. Among sterile patients, reproductive outcome was overwhelmingly determined by sterility in 20 out of the 25 presenting with uterine anomalies, so this group was excluded. There was a male factor in 10 cases (40%), bilateral tubal occlusion in four (16%), and endometriosis in six (24%) cases. Thus, sterility was due to other causes in 80% of the couples, irrespective of the presence of a uterine abnormality.

Table II shows the prognosis of the unicornuate uterus (n = 8). In these patients, a total of 16 pregnancies was recorded. Five of them achieved term; there were four preterm deliveries, and the remaining seven cases were pregnancy losses. Didelphys uteri (n = 8) carried 15 pregnancies, from which only three went to term. There were seven preterm deliveries and five more pregnancy losses before week 20. The bicornuate uteri (n = 26) had a total of 56 pregnancies; 26 were term pregnancies, 14 preterm deliveries, two late miscarriages and 14 early abortions. The septate uterus (n = 43) was the most

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**Table I. Incidence of uterine malformations among patients willing to conceive during reproductive age.**

<table>
<thead>
<tr>
<th>Type of malformation</th>
<th>Fertile (n = 1289)</th>
<th>Infertile (n = 868)</th>
<th>Sterile (n = 1024)</th>
<th>Total (n = 3181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II Unicornuate</td>
<td>2 (0.2)</td>
<td>5 (0.6)</td>
<td>1 (0.1)</td>
<td>8 (0.3)</td>
</tr>
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<tr>
<td>a</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>b</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>c</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>d</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>III Didelphys</td>
<td>1 (0.1)$^c$</td>
<td>6 (0.7)$^b$</td>
<td>1 (0.1)</td>
<td>8 (0.3)$^c$</td>
</tr>
<tr>
<td>IV Bicornuate</td>
<td>5 (0.4)$^c$</td>
<td>16 (1.9)$^d$</td>
<td>5 (0.5)$^c$</td>
<td>26 (0.7)$^c$</td>
</tr>
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<td></td>
</tr>
<tr>
<td>a</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>b</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>V Septate</td>
<td>20 (1.5)</td>
<td>17 (2)</td>
<td>6 (0.6)</td>
<td>43 (1.4)$^b$</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>a</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>b</td>
<td>16</td>
<td>11</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>VI Arcuate</td>
<td>21 (1.6)</td>
<td>9 (1.0)</td>
<td>12 (1.1)</td>
<td>42 (1.3)$^b$</td>
</tr>
<tr>
<td>VII Diethylstilboestrol</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Total</td>
<td>49 (3.8)$^c$</td>
<td>54 (6.3)$^b$</td>
<td>25 (2.4)$^c$</td>
<td>128 (4.0)</td>
</tr>
</tbody>
</table>

$^a$Roman numerals indicate classification of malformation (American Fertility Society, 1988).

Values are significantly different ($P < 0.05$).
common malformation and therefore more pregnancies \(n = 145\) were registered in these patients. The outcome was as follows: 75 carried a fetus to term, 21 ended prematurely, nine were late abortions, three resulted in ectopic pregnancies, and as many as 37 were early pregnancy losses. The arcuate uteri \(n = 42\) carried 110 pregnancies. A total of 86 went to term, five were preterm, two late abortions, three ectopic pregnancies and 14 early miscarriages. Finally, we registered a single DES-exposed uterus which provided three early pregnancy losses, but this particular case was excluded from the analysis because of the single and isolated occurrence in our population.

**Discussion**

Congenital Mullerian defects are a fascinating clinical problem encountered by obstetricians. The true incidence in the general population is hard to determine for two main reasons: most data are derived from studies of patients presenting with reproductive problems, and accurate diagnosis and complete assessment of the uterine morphology has not always been performed. In addition an analysis of the reproductive performance of the malformed uteri needs to take into account not only those presenting with reproductive failures, but also those asymptomatic with normal reproductive outcome. To this end, we have collected the results of women who at some point decided to stop their reproductive life and therefore completed a reproductive cycle, plus those patients who had reproductive problems and attended an infertility clinic. This report of more than 3000 cases is far from being representative of the general population but we believe is more appropriate than previous reports in an attempt to calculate the incidence of Mullerian defects and their reproductive potential.

In this study we have confirmed that the frequency of uterine malformations in fertile patients is 3.8\%. In a previous report from our group based on half of the population analysed herein, we described the presence of uterine abnormalities in 3.2\% of the cases (Simón et al., 1991). In that study, we demonstrated that the reproductive performance of malformed uteri in women subjected to tubal sterilization was exactly the same as that of patients with normal uteri, thus providing the scientific basis for the assumption that some Mullerian defects have normal reproductive outcome (Simón et al., 1991). In the present study, we did not evaluate the obstetric outcome of the malformations in comparison with normal pregnancies; our goal was to re-evaluate the incidence since we believe that the normal reproductive history of some malformed uteri is unquestionable.

The sterile group showed the lowest incidence (2.4\%) of uterine malformations and only eight of them (6.2\% of all uterine anomalies) presented with primary sterility and no other associated problem. This disagrees with previous reports (Nickerson, 1977), that have found a high incidence of uterine malformations in patients with no obvious cause of primary sterility, but agrees with others (Heinonen and Pystynen, 1983) who maintain that sterility in these women is generally caused by extrauterine factors, and in fact patients with congenital uterine malformations undergoing in-vitro fertilization (IVF) and embryo transfer have a good pregnancy rate (Marcus et al., 1996).

It is also worth mentioning the strict criteria followed to select patients for this study. For many years, the reproductive consequences associated with the diagnosis of Mullerian anomalies were based on inaccurate diagnosis performed by incomplete analysis of uterine morphology, so the majority of bicornuate uteri identified by HSG were actually septate (Buttram and Gibbons, 1979). Only patients undergoing HSG and laparoscopy/laparotomy were included in this study. This may explain the apparent discrepancy of having similar numbers of infertile and sterile couples. The paradox may be explained by the fact that our protocol for study of the recurrent aborters was much more strict than for sterile women, resulting in a lower rate of completed work-up in the latter. The assessment and diagnosis of uterine defects unfortunately needs invasive techniques, although new non-invasive techniques such as three-dimensional ultrasound (Raga et al., 1996) are encouraging because of the ability to generate accurate images of the endometrial cavity and of the external contour of the uterus. It can also be argued that it would be difficult to assess fully the external configuration of the uterus after delivery, especially if a small incision has been performed. However,
this was also of concern to us, and only records in which a morphological description of the internal genitalia was provided, were included in the study.

The American Fertility Society (1988) classification of uterine malformations was employed in this study. Class I abnormalities were not documented because our data collection was based on women desiring a pregnancy during their reproductive span while class I defects are more often seen in paediatric and endocrine clinics because of primary amenorrhoea. In addition, exposure to DES was very seldom documented in the Spanish population, but this observation is not relevant because it is an induced malformation dependent on the use of a medication in a given country. When class I and class VII uteri are thus ruled out, it was observed that septate and arcuate uteri represented ~66% of the malformations, while the bicornuate, didelphys and unicornuate uteri constituted the remaining 33%. This picture is of clinical interest because of the fact that the former malformations can be easily managed by hysteroscopy, while the latter need more complicated procedures (Pelosi and Pelosi, 1996) or have no surgical solution. It is helpful to know that most of the uterine anomalies can be treated successfully and easily. The question is still whether a given malformation should be operated upon. The answer depends on the obstetric history of a particular patient and the general prognosis of a given malformation. Therefore, the second aim of the study was to analyse individually the reproductive performance of each type of Müllerian defect.

The high incidence of early pregnancy losses found in this series was a relevant observation. Classically, it has been assumed uterine malformations are associated with late miscarriages and preterm deliveries (Green and Harris, 1976; Heinonen et al., 1982; Golan et al., 1989). However, an analysis of the 342 pregnancies registered in our records showed that 21.6% were early miscarriages, suggesting that the uterine malformations cannot only create a problem of space, but also that there might be local defects that interrupt normal early embryo development after implantation. In fact, ultrastructural alterations have been demonstrated in the endometrium localized over a septum in comparison with the endometrium from the lateral wall (Fedele et al., 1996). Thus, it seems logical to assume that embryo implantation in the septum is associated with an unfavourable pregnancy outcome and especially with early pregnancy loss. This phenomenon should be further studied, but the general agreement that early miscarriages are not associated with uterine anomalies has to be definitely discarded.

The unicornuate uterus results from normal differentiation of only one Müllerian duct. The reproductive outcome of this anomaly in our series showed that the chance of having a live birth was 43.7%. Abortion rates (43.8%) and especially early miscarriage (37.5%) were high, data consistent with previous reports (Acien, 1993). The rate of preterm delivery was also high (25%), and only 31.3% of all pregnancies went to term.

The didelphys uterus results from complete failure of the Müllerian ducts to fuse in the midline. The term delivery rate found in our study was 20% and the possibility of having a living child at home was 40%, which also means a poor reproductive performance, similar to that of the unicornuate uterus (Heinonen et al., 1982; Acien, 1993). Thus, it can be concluded that the reproductive performance of unicornuate and didelphys uteri is poor, although we have also to admit that the incidence of these defects in our population was low, and therefore the conclusions drawn cannot have the same power as those reached when other Müllerian defects were evaluated.

The bicornuate uterus results when two normally differentiated ducts partially fuse in the region of the fundus. Previously, the ratio of bicornuate to septate uteri was reported to be ~1:2 (Heinonen et al., 1982; Patton and Novy, 1988; Ludmir et al., 1990) in infertile patients and we found it to be 1:20 in fertile women (Simón et al., 1991). This report confirms that there is a trend towards an increased incidence of bicornuate uterus in the infertile population in comparison with fertile subjects. While the ratio was 1:4 in fertile patients, it increased to 1:1 in the present series of infertile women, suggesting that the reproductive potential of the bicornuate uterus is much lower than that of the septate. However, when the actual reproductive outcome of those 26 bicornuate uteri was further analysed by the results of the established pregnancies, it turned out that the chances of having a term pregnancy were >60%, with a take-home baby rate of 62.5%, percentages that compare favourably with the prognosis for the above-mentioned malformations and disagree with previous reports on a poor reproductive outcome associated with a bicornuate uterus (Green and Harris, 1976; Heinonen et al., 1982; Acien, 1993). While some reports found the poorest prognosis when the defect was partial rather than complete, we were unable to find a difference between these two types.

The septate uterus results from the failure of resorption of the medial segment of the Müllerian ducts. The septate uterus has been usually associated with the poorest reproductive prognosis, with fetal survival rates of 6–28% and a high rate of spontaneous abortion (>60%) (Green and Harris, 1976; Heinonen et al., 1982; Harget et al., 1983; Golan et al., 1989). Our results show that the prognosis is actually much better (51.7% term deliveries and live birth rate of 62%), although there is a considerable rate of miscarriage (33.8%). These data reinforce the idea that metroplasty is not absolutely necessary in these patients (Acien, 1993), although the fact that surgery can be easily performed through the hysteroscope makes the issue controversial and under continuous debate. Our present position is to operate on all patients undergoing difficult and expensive assisted reproduction procedures in order to reduce the possibility of miscarriage.

Finally, the arcuate uterus is a simple change in the uterine cavity shape with no external dimpling. As a consequence, term delivery rates were almost 80% with a live birth rate of 82.7%, and no impact on reproduction. The data disagree with previous reports in which this anomaly presented the poorest survival rates and highest abortion rates (Acien, 1993).

In conclusion, our analysis of over 3000 uteri in fertile and infertile patients has provided new insights into the reproductive potential of Müllerian malformations. We have learned that the incidence of such anomalies in the infertile population is almost twice as high as in fertile women. Unicornuate and didelphys uteri have a 20–30% chance of
carrying a pregnancy to term, which is low, and therefore surgery should be recommended in the latter. The reproductive performance of the bicornuate and septate uteri is higher than expected (live birth rate of 62%), and finally the presence of an arcuate uterus is irrelevant to the reproductive performance of women.

References

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