Frequency of Uterine Malformation among Women in a Restricted Gene Pool Community

A retrospective cross-sectional study in La Crete, Canada

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Objective: This random retrospective cross-sectional study was done to determine the incidence of uterine malformation in 4 groups of women desiring to conceive during their reproductive years, all of them living in La Crete, a community in Northern Alberta, Canada, with endogamous marriage practices in a 500 year old restricted gene pool.

Methods: During 2003-2006, eight hundred women, suspected of having uterine malformation, were scanned using 2-D abdominal and transvaginal sonography (TVS). A sub-group of 156 patients was identified with suspected uterine malformations and referred for further diagnostic investigation, including MRI, 3-D sonography, hysterosalpingography, hysteroscopy and laparoscopy. This group included 30 women without previous pregnancies (Group 1), 31 women with previous pregnancies and live births (fertile) (Group 2), 40 women with live births and more than 2 miscarriages (Group 3) and 55 women with recurrent miscarriages (infertile) (Group 4).

Results: The overall frequency of uterine malformations was recorded at 19.5% in La Crete women. Ninety five women with recurrent or some miscarriages had more uterine malformation than the other groups. The incidence in Groups 3 and 4 (infertile) was 60.8% and 39.2% in the fertile Groups 1 and 2. The p < 0.01 was significant at 95% confidence interval.

Conclusion: This study has provided new insights into the increasing number of uterine malformations in the population of La Crete.  It was 19.5%, 5.5 times higher than that of the general population of (0.1% to 3.5%). This might indicate an increase in uterine malformations among women in a restricted gene pool community. A combination of TVS, hysterosalpingography, 3-D sonography and MRI are necessary for the precise classification of uterine malformations.
Uterine malformations are not rare, but may be increasingly related to consanguinity. The finding of uterine malformation is more frequent in patients with recurrent miscarriages, especially women with septated, unicornuate, or didelphys uteri.

**Key words:** Uterus; Abnormalities; Gene pools, Restricted; Canada

**Advances in Knowledge**

This study contributes to advances in knowledge as it shows that communities which practice endogamous marriages can see an increase of certain anomalies such as uterine malformation. We can then educate these communities to practice a wider choice of marriage partners in order to lower the genetic risk linked to recurrent miscarriages.

**Application to Patient Care**

The application to patient care is in the knowledge gained by researchers and doctors that can be applied both to the correct diagnosis of uterine malformation and to the management of patients with these abnormalities. Doctors and sonographers can use this study to improve skills in the difficult diagnosis of unicornuate uteri. The ability to diagnose uterine malformation has been improved by new imaging techniques.

**Conflict of interest declaration**

The author acknowledges no commercial affiliation or financial conflict of interest.

Little, if any, information exists in the literature regarding incidences of uterine malformation in restricted gene pool communities. Such information would be invaluable to the gynaecologists and other health care professionals involved in the care of these patients. La Crete is a small town located 56 km southeast of High Level in Northern Alberta, Canada. The estimated population of La Crete is 3,000, almost 100% of Mennonite origin from a German background and speaking Low German. The entire population is descendent from only 26 different families, who arrived in Canada in 1500s. These 26 families have been sharing genetic material for over 500 years. In fact, marriages outside these 26 known families are estimated to occur in La Crete in only less than 1% of cases. Their religion does not allow first or second cousin marriages, though occasionally they do marry fourth or fifth cousins.

Uterine malformation consists of a group of congenital anomalies of the female genital system. They are the result of four major problems in the development or fusion of Mullerian or paramesonephric ducts during fetal life. It is important to diagnose uterine malformation as it is related to miscarriage and infertility. Some Mullerian defects do not hinder normal reproductive outcomes. In this study, only those women with two or more pregnancy losses were defined as infertile. The incidence of Mullerian defects in the general population is not accurately known since they are asymptomatic unless discovered accidentally, or in relation to pregnancy complications. Generally, 0.1 to 3.5% is the number accepted by many authors and these numbers differ according to each type of malformation.

Almost all structural uterine malformations are due to errors of development occurring in very early pregnancy. Embryologically in the female fetus, the fused caudal ends of the two Mullerian (paramesonephric) ducts form the uterus, cervix and upper vagina, whereas the un-fused cranial ends form the paired fallopian tubes. Different types of fusion may occur including malformation of either or both the uterine body and uterine cavity, with subsequent impaired reproductive performance. Such malformations affect negatively the reproductive performance of the uterus leading to increasing incidence of abortion and pre-term delivery in women with uterine anomalies such as unicornuate, bicornuate, didelphys and septate uteri. This is seen clinically as an increased rate of primary infertility (failure to conceive), or more often as an increase rate of early pregnancy loss (impaired implantation and early development). Later in pregnancy, unsuspected uterine malformations may present as impaired intrauterine fetal growth due to abnormal placenta tion, or abnormal fetal positioning related to mechanical factors in the shape of the uterine cavity. Labour, delivery, and third stage problems may occur related to incoordinate uterine muscular activity. A didelphys uterus is a very rare anomaly, 1 in 1 million,
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and can be up to 1 in 25 million in pregnancies with twins. It can lead to pregnancy failure. \(^{17}\)

Mullerian defects are associated with an increased incidence of congenital urinary tract malformation. These incidences are noted more with unicornuate and bicornuate uteri. \(^{18,19}\) In 1995, Raga reported that the overall frequency of uterine malformation was 4.0% and there was a higher incidence of miscarriages amongst patients with septated forms of uterine malformations, which was recorded at 33.6%. \(^{20}\) Recurrent abortion, i.e. consecutive abortion on three occasions, is less common and the etiology is unknown. \(^{21-25}\) Some of the associated factors include genetic factors such as thrombotic disorders, maternal medical disorders and congenital malformation of the uterus. The relative contributions of these are unknown. \(^{20-25}\) Most studies demonstrate a spontaneous miscarriage rate of 10-15%. However, the true rate of early pregnancy loss is close to 50% because of the high number of chemical pregnancies that are not recognized in the 2-4 weeks after conception. \(^{25}\) Most of these pregnancy failures are due to gamete failure. \(^{26,27}\) The term “infertility” has a specific definition, which is the inability to achieve pregnancy despite unprotected, regular and adequate intercourse over a 12 month period. It has been wrongly used in literature to describe women with recurrent abortions. \(^{7}\) 3-D sonography is very sensitive and it should be utilized for the diagnosis of uterine malformation. \(^{28}\) The unicornuate uterus is associated with poor reproductive outcomes and high abortion rates up to 22% reported in the first trimester. \(^{29}\) It is important to be precise in the diagnosis of uterine malformation as it can change the management of the treatment \(^{30}\) [see Figures 1-10].

Diagram 1: Different types of congenital uterine malformation

I Hypoplasia /agenesis uterus: It can be vaginal, cervical, fundal, tubal or combined agenesis
II Unicornuate uterus: It can be with communicating rudimentary horn, without communicating rudimentary horn, with a rudimentary horn and without cavity, without horn
III Didelphys uterus: It is with 2 vaginas, 2 cervixes, 2 cavities and 2 horns
IV Bicornuate uterus: It can be complete or partial
V Septate uterus: It can be with complete septation or partial septation (sub septus)
VI Arcuate uterus: It is like a normal uterus, but with fundal or myometrium indentation
VII This is caused by drug changes and not genetics, therefore it is not classified as a congenital uterine malformation

(Diagram reproduced with permission from the Radiological Society of North America)
with rudimentary horn, without proper cavities).

3. Failure or abnormal fusion of the ducts (didelphys or bicornuate uterus).

4. Failure of re-absorption of the midline uterine septum (septate or arcuate uterus).

**METHODS**

This was a random cross-sectional and retrospective study of 800 women in La Crete, carried out during 2003-2006. All were referred for sonographic examination for a variety of reasons such as previous miscarriages, early pregnancy, infertility, pelvic inflammatory disease, or to rule out polycystic disease. All were scanned utilizing 2-D abdominal and transvaginal sonogram (TVS). The objective was to determine the frequency of uterine malformation among women with endogamous marriage practices. The women’s mean age was 31 years. All gave informed written consent to the researcher for the study, including viewing their charts and reviewing the reports from other modalities. The Ethical Committee of the Education Counselling Service in High Level Hospital approved the study protocol in December 2003. A sub-group of 156 patients was identified with suspected uterine malformations; of these 78 (50%) belonged to four specific families; the other 50% (78 cases) belonged to the other 22 families in the community. Analysis of the patients was done according to the recurrent pregnancy loss status. All 156 women were referred for further diagnostic investigations to reach a definite diagnosis including hysterosalpingography, MRI, 3-D sonography, hysteroscopy, and laparoscopy. Each modality has its own criterion of diagnosis according to the Canadian Association of Medical Radiation Therapy and the Canadian Society of Diagnostic Medical Sonographers [Table 2]. The groups included 30 women with no previous pregnancies and live births, 40 women with previous pregnancies, live births and more than 2 miscarriages, and 55 women with recurrent miscarriages. Infertile women are those who have had two or more miscarriages.

The same sonographer preformed all the sonograms using a Philips unit (Agilent Sonos model 4500) with 3.5Mhz, 5.0 Mhz and transvaginal transducers. The morphology of the uterus was ascertained by different diagnostic procedures and was done in the Edmonton, Calgary, and Grand Prairie hospitals. These diagnostic methods were used to classify the type of uterine malformation. All the 156 women who had TVS and transabdominal sonograms were sent for hysterosalpingography (HSG). Forty of them were sent for 3-D sonography. Twenty two patients were sent to have an MRI. Sixteen were sent to have hysteroscopy and five patients had laparoscopy for the treatment of endometriosis. The uterine malformations were classified according to the degree of failure of normal development into 6 major types and according to the American Fertility Society classifications [Diagram 1].

**RESULTS**

The results of the 156 women were tabulated according to uterine malformation [Tables 1 & 2]. The overall frequency of uterine malformation in 800 women was (19.5%). It was 5.5 times higher than in the general population. Thirty women (Group 1) with out previous

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Patients</th>
<th>Early Obstetrics</th>
<th>Infertility Reason</th>
<th>Previous Miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>149</td>
<td>10</td>
<td>92</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>18.6%</td>
<td>1.2%</td>
<td>11.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>2</td>
<td>349</td>
<td>329</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>43.62%</td>
<td>41.1%</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>14</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>6.75%</td>
<td>1.7%</td>
<td>1.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>248</td>
<td>0</td>
<td>200</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>0%</td>
<td>25%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Total</td>
<td>800</td>
<td>353</td>
<td>326</td>
<td>121</td>
</tr>
</tbody>
</table>

Note: 800 women were investigated, 156 of them had malformations (19.5%). Women with 2 or more miscarriages were considered infertile.
pregnancies were diagnosed with varieties of uterine malformations, including 2 hypoplastic, 6 bicornuate, 2 septate, 4 subseptate, 4 unicornuate and 12 arcuate uteri. Thirty-one women (Group 2) with previous pregnancies and live newborns (fertile) were diagnosed with 3 hypoplastic, 6 bicornuate, 4 septate, 6 subseptate, 2 unicornuate and 10 arcuate uteri. Forty women (Group 3) with live newborns and some miscarriages were diagnosed with 2 hypoplastic, 8 bicornuate, 4 septate, 7 subseptate, 12 unicornuate, 1 didelphys, 6 arcuate uteri. Fifty-five women (Group 4) with recurrent miscarriages (infertile) were diagnosed with 4 hypoplastic, 14 bicornuate, 9 septate, 6 subseptate, 16 unicornuate, 1 didelphys and 5 arcuate uteri. Groups 1 and 2 had 8 sets of twins in bicornuate uteri. In addition, there were two sets of twins in Groups 3 and 4 (one in each Group) in bicornuate uteri. Both sets of twins in Groups 3 and 4 did not survive and died at 13 and 16 weeks gestation respectively. They were in retroverted uteri and both were in the smaller left horn of the bicornuate uterus. Six sets of twins in Groups 1 and 2, in bicornuate uteri, survived and were successfully delivered at 36 weeks. All the patients with twins were sent to ultrasound examination due to large for date pregnancies. These patients with twins were not sent to do any further examinations with other modalities and were followed only with transabdominal sonograms. The diagnosis of bicornuate uteri with twins was made by transabdominal sonography at 12 weeks gestation. Unicornuate and bicornuate uteri were increasingly noted in Groups 3 and 4. Group 1 showed 19.2%, Group 2 showed 19.8%, Group 3 showed 25.6% and Group 4 (infertile) showed 35.2% of uterine malformations. Group 4 showed the highest percentage of uterine malformations. Didelphys uteri were noted in the women with miscarriages and were not found in fertile women. This study also found 42 retroverted uteri; 30 were found in the infertile Groups 3 and 4 and 12 were found in the fertile Groups 1 and 2. In these groups, there were 21.7% unicornuate, 7.0% hypoplastic, 21.7% bicornuate, 1.2% didelphys, 12.1% septate, 14.7% subseptate and 21.1% arcuate uteri. All 22 cases diagnosed by MRI proved correct for the malformations initially noted in the HSG. Forty patients were diagnosed using 3-D sonography, 36 uterine malformations were confirmed and 4 cases were missed by 3-D sonography. Twenty four unicor-
nuate uteri in Groups 3 and 4, diagnosed with TVS, had short cervices measuring less than 2.5 cm in length. Sixteen patients were sent to have hysteroscopy and 5 were sent to have laparoscopy for the treatment of endometriosis and to confirm the presence of arcuate uteri after they were found by MRI. All 14 endometrial polyps were missed by TVS, but were picked up by hysteroscopy. There were number of genitourinary tract anomalies in these patients among them absence of one kidney, ectopic kidneys, duplicated renal pelvis, horse shoe kidneys, absence of one ovary, and malposition of kidneys and ovaries. Among the 55 patients in Group 4, three had one miscarriage and five had 2 miscarriages.

The 800 women studied by ultrasound presented for a variety of reasons such as, determination of early pregnancy, infertility causes, previous miscarriages, and to rule out fibroids, dermoids, uterine malformations, polycystic ovary (PCOD), pelvic inflammatory disease (PID), etc. [Table 1].

**DISCUSSION**

The true incidence of uterine malformation in the general population is hard to determine as most data are derived from studies of patients with reproductive problems so that accurate diagnosis and complete assessment of the uterine malformation has not always been performed. The frequency of uterine malformation in most literature is 0.1% to 3.5%. There are no studies in the literatures in regards to the frequency of uterine malformation among women belonging to restricted gene pool communities. Part of the problem lies in defining “restricted gene pools” and in quantifying this phenomenon. The entire populace of the study population (La Crete) consists of only 26 distinct families with a long tradition (over 500 years) of marrying only within these families. Of the 156 subjects included in this study, 78 (50%) belonged to only 4 of those families. Higher frequencies of uterine malformation are associated with higher rate of reproductive failure. No rates of uterine malformation for different ethnic groups are available in the literature.

The worst outcomes recorded in this study for mis-
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carriages were 41 patients (26.8%) with septated uteri (complete and partial forms). Twenty six septated uteri (both forms) were noted in Group 3 and 4. This is in agreement with the literature on septated forms of uterine malformations in relation to high incidence of miscarriages. Group 3 had 7.6% and Group 4 had 10.2% unicornuate uteri, producing the second highest incidence of miscarriages. Group 3 had 7.6% and Group 4 had 10.2% unicornuate uteri, producing the second highest incidence of miscarriages. The next highest number of miscarriages was in those patients with bicornuate uteri; Group 3 had 5.1% and Group 4 had 8.9%. This might indicate that this kind of malformation is the one most likely to affect the reproductive outcome and increases the chance of miscarriage.

There is an increase incidence of unicornuate and bicornuate uteri in the infertile population in Groups 3 and 4 in comparison with fertile patients in Groups 1 and 2. This supports the study done by Green and Harris in 1976 and Acien in 1993 on poor reproductive outcomes associated with a bicornuate uterus. One hundred and fifty six patients with suspected uterine malformation diagnosed by transabdominal sonography and TVS were sent to have hysterosalpingography to confirm the diagnosis. Twenty two of them had an MRI to further prove the diagnosis of subseptate and arcuate uteri, which is difficult to diagnose using other modalities.

Forty patients were sent to have 3-D sonography. Sixteen patients were sent to have hysteroscopy and 5 went to have laparoscopy to treat endometriosis. Four cases of uterine malformations were missed using 3-D sonography due to the presence of fibroids causing the uterine wall to appear convex. The 3-D sonography imaging showed 90% sensitivity and specificity, but was less sensitive in the presence of uterine lesions such as fibroids and polyps. MRI on the other hand showed 100% sensitivity and specificity. It had more accuracy, precision and reliability and so should be the modality of choice after the initial diagnosis with TVS. Six patients had problem with this imaging modality due to its claustrophobic effect. MRI is an expensive procedure and the waiting time can be up to 6 months in Canada. TVS with colour flow can differentiate vascular from non-vascular uterine septation.

Unicornate uteri have the highest rate of cervical shortening and this could affect the reproductive performance. In addition, it is a helpful tool for the sonographer to correlate the shortening of the cervix to the unicornuate uterus, as Groups 3 and 4 had 85.7% cervical shortening. The least frequent malformation noted

Figure 4: HSG Uterine septum - The arrow shows the septation between the uterine horns reaches the cervix. HSG is less sensitive in diagnosis of this kind of malformation when comparing to MRI and laparoscopy

Figure 5: HSG Arcuate uterus. The arrow shows the concave aspect in the myometrium

Figure 6: Transvaginal sonogram (TVS) - The arrow shows 2 uterine horns joined with one cervix and one vaginal vault

Figure 7: Magnetic resonance imaging (MRI) - The arrow shows one cervix, one vaginal vault and 2 uterine horns
was the didelphys uterus: two in 800 patients. This finding indicates that this type of rare malformation is very high in this population, knowing that the incidence of didelphys uterus is normally 1/3000.\(^{17}\)

The incidence of uterine malformation for fertile patients was recorded at 39.2% and in the infertile patients at 60.8%. This indicates that it is common to have uterine malformation, but it increases in the infertile women by 21.6% in this study. TVS and hysteroscopy were both sensitive, but hysteroscopy was more specific in detecting focal endometrial polyps. Laparoscopy is an invasive procedure and was used for the treatment of the five patients with endometriosis that was discovered by MRI. Forty-two retroverted uteri were diagnosed using TVS in the infertile Groups 3 and 4. This might indicate a relationship between retroverted uteri and infertility, but this is not relevant in this study, as the only link is where women have a fixed retroverted uterus on pelvic examination. This might indicate either past serious infection with scarring causing fallopian tube blockage, or scarring due to endometriosis.

The methods of choice to detect uterine malformation should be discussed between the physician and the radiologist to reach the best available method with least invasiveness to the patient. This study showed that the use of 3-D, TVS and transabdominal sonography should be used first followed by the more expensive modality of MRI. HSG is an invasive method, but can provide a faster diagnosis without the claustrophobic effect to some patients of an MRI scanner.

Two women with unicornuate uteri had children; this might indicate that women with this type of malformation can be pregnant and have successful delivery. Eleven hypoplastic uteri were recorded in this study, five in the fertile group and six in the infertile group. More studies are needed in order to know the effect of this malformation on fertility. Double the number of bicornuate uteri was confirmed in the infertile compared to the fertile group. This might indicate a relationship between these types of malformation and increased infertility.

Sixteen septate and subseptate uteri were found in Groups 1 and 2 compared to 26 found in Groups 3 and 4. Again this might indicate the relationship between these types of malformations and infertility. This support many studies regarding the relation of septated forms of uterine malformation to early miscarriages. The size of the septation may influence the reproductive outcome. There were 22 arcuate uteri in the fertile group compared to 11 in the infertile group; this might indicate that this type of malformation does not affect the uterine reproductive performance. This type is difficult to find by TVS or transabdominal sonography and better diagnosed using MRI, 3-D sonography, or laparoscopy. DES (diethylstilbestrol) is a synthetic form of oestrogen that was prescribed between 1938 and 1971 to help women with certain complications of pregnancy. It was linked to uterine malformation and increased incidence of clear cell adenocarcinoma of the vagina and cervix of the unborn female fetus in women...
who were taking this drug. Therefore DES is not related to congenital uterine malformation classifications, but sonographers should know the effects of this drug.

**LIMITATIONS AND FURTHER STUDIES**

The limitation in this study was that we did not use 3-D sonography for all patients. It is more accurate than other modalities and less sensitive in the presence of fibroids. Moreover, we did not send all the 800 women to special procedures such as MRI, HSG, hysteroscopy and laparoscopy as we relied upon the normal results of the sonograms. In this way, we may have missed many uterine malformations and that could increase the incidence to even more than the recorded 19.5%. Future studies should divide the groups into fertile, infertile and sterile women. Future studies should also focus on the distributions and the percentages of each anomaly and correlate them with the general population. Correlation with different communities practising endogamous marriages might be beneficial.

**CONCLUSION**

Analysis of 800 fertile and infertile patients in the La Crete female population has provided new insights into the incidence of uterine malformations in this population which practises endogamous marriage. La Crete has an incidence of 19.5%, 5.5 times higher than the general population. Arcuate and retroverted uteri may be irrelevant to the reproductive performance of women. The septated versions of uterine malformation and bicornuate uterus increase in the infertile groups depending on the size of each uterine horn. Different diagnostic methods should be used to classify each type of uterine malformation. For precise classification of these malformations, a combination of TVS, 3-D sonography (non-invasive technology) and HSG (invasive) seems to be necessary and less expensive than MRI technology. Uterine malformations are relatively frequent in fertile women, but more frequent in infertile groups and in communities with endogamous marriages. These malformations can impair pregnancy outcomes. Uterine malformations are more common in women with recurrent miscarriages. The reproductive performances of unicornuate and didelphys uteri were poor. Mullerian defects can permit normal delivery, depending on the type of uterine malformation.

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