3D ultrasound findings in women attending a South Australian recurrent miscarriage clinic

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Abstract

Background: Women who suffer recurrent miscarriage are a heterogeneous group. Known causes include genetic and endocrine abnormalities, anti-phospholipid syndrome and autoimmune disease. Congenital uterine abnormalities (CUAs) such as bicornuate, unicornuate, septate and arcuate uterine abnormalities are known to negatively impact on pregnancy rates, and to increase the miscarriage rates of genetically normal pregnancies. In some countries, such as Britain, 3D ultrasound of the pelvis is offered routinely to women with recurrent miscarriages.

Aim: To determine the prevalence of CUAs and other pelvic pathology, in women attending a South Australian recurrent miscarriage clinic.

Materials and methods: 3D transvaginal ultrasounds performed during the luteal phase of the menstrual cycle were offered to all patients attending the recurrent miscarriage clinic, who had not previously had a hysteroscopy, laparoscopy, HyCoSy or MRI study of their pelvis. A Philips IUI 8 MHz transvaginal probe for freehand sweep, and dedicated 3D transvaginal probe was used. 3D scans provide a coronal view of the uterus, ideal for detecting abnormalities which may be missed during routine conventional 2D scanning.

Results: A total of 210 women were recruited, 200 results were available, and 29% were found to have a CUA. 15% had polycystic ovaries detected, 15% were found to have fibroids, 12% adenomyosis and 1.5% Asherman's syndrome.

Conclusions: 3D ultrasound evaluation of patients attending a recurrent miscarriage clinic detects CUAs, and has a high detection rate of other pelvic abnormalities that may contribute to recurrent miscarriages.

Keywords: 3D ultrasounds, bicornuate uterus, congenital uterine abnormalities, recurrent miscarriages, septate uterus.

Introduction

3D ultrasound investigations may be used in conjunction with 2D ultrasounds for a full evaluation of the pelvis, so that structural abnormalities as well as ovarian, tubal, myometrial, endometrial and cervical areas can be evaluated in a single study period. 3D ultrasound is a non-invasive method of investigation that allows the uterine dimensions to be measured, which helps in the diagnosis of congenital uterine abnormalities (CUAs).[1]

Congenital uterine abnormalities have been thought to be a cause of pregnancy loss and adverse pregnancy outcomes, and the reported prevalence of these abnormalities in women suffering recurrent pregnancy loss varies from 6% to 38%.[2] CUAs are thought to result from abnormal formation, fusion or resorption of the Müllerian ducts during fetal life.[1] Although miscarriages are frequently caused by a genetic problem such as an abnormal karyotype in the embryo or fetus, the parental causes most likely to impact on a pregnancy are chromosomal translocations, autoimmune diseases, endocrine or metabolic disorders, uterine anomalies and age-related issues.[3] The prevalence of major CUAs is thought to be at least threefold higher in women with a history of recurrent miscarriages in both embryonic (gestational age of 10 weeks or less from the last menstrual period) and fetal (gestational age of greater than 10 weeks), compared with the low-risk population, and thus CUAs may indeed be responsible for pregnancy loss in a significant proportion of women with recurrent miscarriages

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doi: 10.1002/ajum.12032

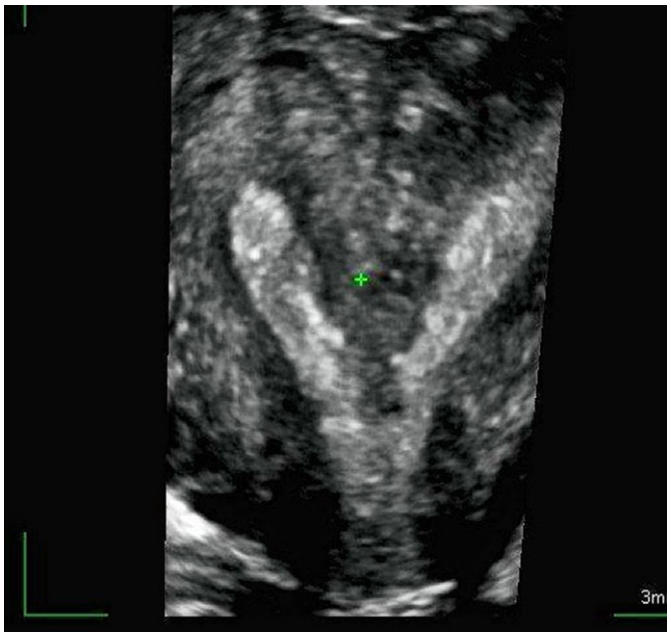

Figure 1: A septate uterus on 3D ultrasound.

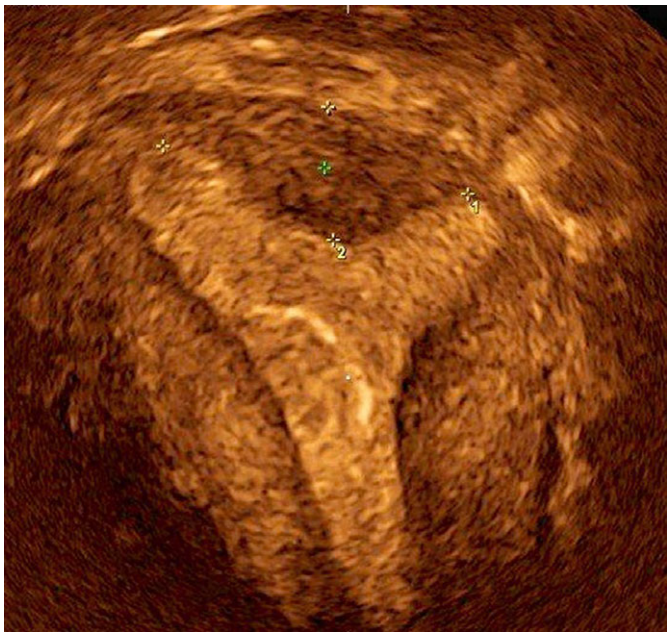

Figure 2: An arcuate uterus on 3D ultrasound.

(Figures 1 and 2).[4] 3D ultrasound was offered as part of the work up in the RM clinic to ascertain if it could contribute towards the assessment of these patients.

Materials and methods

This prospective cohort observational study formed part of a Clinical Trial named PAPO (Prediction of Adverse Pregnancy Outcomes) study (Clinical trial number ACTRN12609000254291). The study was approved by the Women's and Children's Hospital Human Research Ethics Committee in North Adelaide South Australia, REC1481/6/09. Informed and written consent was obtained from all participants. CUAs were classified in accordance with the modified American Fertility Society Classification (Table 1).[5]

Table 1: American Fertility Society (AFS) classification of Müllerian duct anomalies.

Class I	Hypoplasia and agenesis. (a) vaginal, (b) cervical, (c) fundal, (d) tubal, (e) combined
Class II	Unicornuate. (a) communicating, (b) non-communicating, (c) no cavity, (d) no horn
Class III	Didelphys
Class IV	Bicornuate. (a) partial, (b) complete
Class V	Septate. (a) partial, (b) complete
Class VI	Arcuate
Class VI	Diethylstilbestrol (DES) drug related

Women with a history of at least two consecutive miscarriages had 3D ultrasounds performed in the Women's Ultrasound department in a tertiary referral hospital in Adelaide. The scans were performed in the luteal phase of the menstrual cycle using a Philips IU22 C8-4V freehand sweep +/− Philips 3D 9-3V with dedicated 3D vaginal probes, or GE Voluson E8, RIC 5-9-D vaginal probe. 3D scans provide a coronal view of the uterus, ideal for detecting the abnormalities that may be been missed during routine conventional 2D scanning. Polycystic ovaries may be detected on 3D ultrasound, as large volume ovaries containing greater than 12 follicles each, measuring from 2 to 9 mm in width.[6] Adenomyosis is a non-neoplastic condition characterised on ultrasound by the presence of myometrial cysts or heterogeneous areas, diffuse vascularity, asymmetry of the myometrial walls, and a globular or bulky uterine configuration.[7] HyCoSy was offered to the patients if the uterine findings were unclear on the 3D scan alone. The sonographers are all employees at a Public Hospital offering Tertiary Obstetric Ultrasounds, and all were reported by a Senior COGU Specialist. The women also had the full routine miscarriage investigations offered by the clinic, which include thrombophilic, endocrine, autoimmune, metabolic and genetic investigations (Table 2). The reason for dividing the patients into two groups, ≤35 years and >35 years, is due to the independent effect of maternal age on the risk of spontaneous abortion.[8]

Results

210 patients were offered a 3D ultrasound, 200 were available for assessment and 10 were lost to follow-up. The ages of these women ranged from 22 to 44 years of age, and they had had from 2 to 15 losses prior to presentation. There were 108

Table 2: Recurrent miscarriage workup.

Work up	Tests
AGE	AMH levels
Structure	3D Ultrasound
Genetics	Karyotype products of conception
Thrombophilia (TP)	APS. Protein C, Protein S, ATIII levels (Only test for genetic thrombophilias if the patient has had a prior thrombotic event)
Endocrine	Thyroid, prolactin
Autoimmune	ANA, ENA, thyroid antibodies
Metabolic	GTT and insulin studies, homocysteine
Infectious	Vaginal swabs

patients aged 35 years or less, mean 31 years, and 92 patients aged 36 years or more, mean age 39 years. Primary miscarriage was defined as 'two or more consecutive miscarriages with the same partner, without a live birth'. Secondary miscarriage was defined as 'two or more consecutive losses with the same partner, after at least one live birth'.[2] There were 92 primary patients and 108 secondary patients. The majority of the losses were embryonic losses prior to 10 weeks from the last menstrual period, 10 had both embryonic and fetal losses, and one had two fetal losses. Preterm labours (>20 weeks) were not included.

Overall, 29% of the women presenting to the clinic had a CUA. In women aged 35 years or less (≤35 years), 35.2% had structural abnormalities detected. 7.9% had a bicornuate uterus, 2.6% had a unicornuate uterus, 57.9% had a septum (Figure 3) and 31.6% were found to have an arcuate-shaped uterus. In the women aged >35 years, 21.7% had structural abnormalities. 10% comprised a bicornuate uterus and there were no unicornuate uteri detected, 65% had a septum and 25% had an arcuate shape detected.

In women ≤35 years, 35.2% had a CUA detected as described, and when these patients were evaluated according to age and previous pregnancy status, 68.4% of them (primary patients) had a CUA detected. In patients in this age group who had a past live birth (secondary patients), 31.6% had a CUA detected. There was a statistically significant difference in the incidence of CUAs between the primary and secondary patients, P = 0.04.

In women >35 years, 21.7% had a CUA detected, 35% of these were in the primary group, and 65% were in the secondary group. In primary patients aged ≤35 years, the estimated odds ratio for a CUA was 3.92 (95% CI 1.12–14.96) compared to women aged >35 years.

Other findings included polycystic ovaries, fibroids, adenomyosis and Asherman's syndrome, polycystic ovaries (greater than 12 follicles per ovary, measuring 2–9 mm) were noted in 30 (15%) of the patients, 23 (21.3%) in women ≤35 years and 7 (7.6%) in women aged >35. An ultrasound detection of polycystic ovarian morphology was correlated with endocrine findings, before a diagnosis of polycystic ovarian syndrome was made. Fibroids were detected in 30 (15%) of the patients, 8 (26.7%) in the age group ≤35 years and 22 (73.3%) in the women aged >35, as would be expected. One patient with fibroids also had an endometrioma. Adenomyosis was diagnosed in 23 (12%) patients presenting to the clinic, 13 (12%) in women ≤35 years and 10 (10.9%) in women >35. Asherman's syndrome was diagnosed in three patients in the clinic (Figure 4).

Discussion

3D ultrasound is a non-invasive method of investigation that allows the uterine dimensions to be measured, which helps in the diagnosis of CUAs.[1] 3D ultrasound is used in conjunction with 2D ultrasound for a full evaluation of the pelvis, so that structural abnormalities as well as ovarian, tubal, myometrial, endometrial and cervical areas can be evaluated in a single study period. The true population prevalence of CUAs is difficult to assess as the diagnostic tests are rarely applied to a low risk population. A systematic review by Chan *et al.* showed a

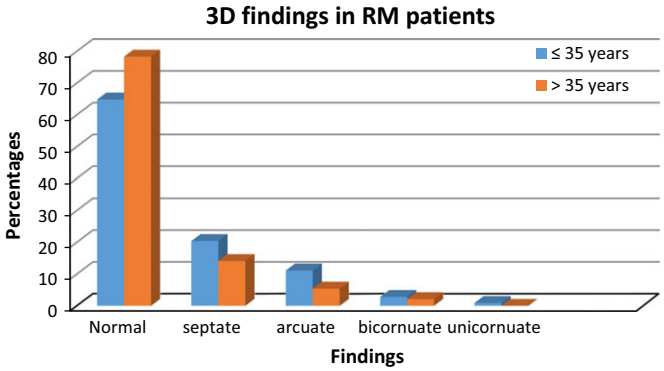

Figure 3: 3D congenital uterine abnormalities (CUAs) detected in patients aged ≤35 years or >35 years.

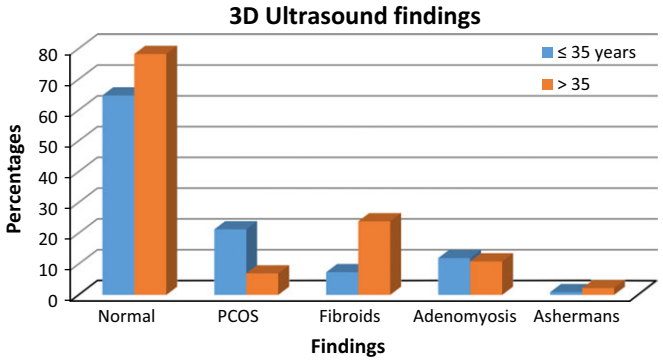

Figure 4: Other pathology detected at the time of the 3D ultrasound, in women aged ≤35 years compared with those aged >35 years.

prevalence of 5.5% in an unselected population, 8% in an infertile population and 13.3% in women with miscarriages, and 24.5% in women with infertility and miscarriages.[4] The limitation of this study is the relatively small size, however, it has demonstrated the usefulness of 3D ultrasound in the evaluation of these patients.

In total, 72% of the patients who had a 3D ultrasound were found to have uterine and/or pelvic abnormalities that could have contributed to their pregnancy losses. In this study, 29% of the patients presenting to the clinic who underwent a 3D ultrasound were found to have a CUA. A systematic review, evaluating the impact of congenital uterine abnormalities on reproductive outcomes, showed that women with canalisation defects, such as septate and subseptate uteri, had the poorest reproductive performance.[9] In addition to having a reduced conception rate, they are at an increased risk of first trimester miscarriage, preterm birth and fetal malpresentation at delivery.

Previous studies of women suffering recurrent early pregnancy losses have shown a variable prevalence of CUAs. Salim *et al.*[2] detected a prevalence of 23.8% of all abnormalities, and 6.9% major abnormalities in 509 women with recurrent miscarriages. Clifford *et al.*[10] found 1.8% major abnormalities in 500 cases. The prevalence in our study is broadly in agreement with the findings of Salim *et al.*[2] The lower finding by Clifford *et al.*[10] could have been the use of 2D ultrasound, which is known to be less sensitive for the detection of these abnormalities than 3D ultrasound.

Some studies have suggested that the pathophysiology of early pregnancy loss in those patients with septate uteri may be explained by the presence within the uterus, of a relatively avascular septum, and thus the inability of this septum to provide an adequate blood supply to the implanted and developing embryo.[11] Histological evaluation of some septae that showed significantly reduced vascular supply in relation to the rest of the uterus, supported this view.[12] However, other studies have suggested that there is an increased blood supply that interferes with the implantation of the conceptus.[13,14] Other causes may be increased uterine contractions or reduced uterine capacity. Salim *et al.*[2] tried to quantify the degree of uterine distortion by calculating the ratio between the fundal distortion and the length of the cavity on hysterosalpinography. They found no association between the severity of the uterine abnormality and the number of previous miscarriages. In contrast, the results of this study showed that the degree of distortion of the uterine cavity in septate uteri was higher in women with recurrent miscarriages, compared to low-risk women, mainly due to a reduced length of the unaffected cavity.

Some studies have reported an increase in adverse pregnancy outcomes in women with an arcuate uterus, mainly second trimester/fetal losses.[4] The pathophysiology of miscarriage in these women is unknown. However, other studies did not find this association. The prevalence of an arcuate uterus in women suffering recurrent miscarriages was 8.5% in our study, 6% in the 35 and under age group, and 2.5% in those aged over 35. Interestingly, these women were offered a hysteroscopy as part of their assessment, and a small septum was detected in 4 of 12 cases that had not been detected even on 3D ultrasound. This septum may have accounted for the losses.

Polycystic ovarian syndrome is a heterogeneous endocrine disorder characterised by anovulation, hyperandrogenism, infertility and metabolic dysfunction.[6] Polycystic ovaries may be detected on 3D ultrasound, as large volume ovaries containing greater than 12 follicles each, measuring from 2 to 9 mm in width. However, the detection of 'polycystic ovaries' does not establish a diagnosis of the polycystic ovarian syndrome, unless other features are present, such as hyperandrogenism and chronic anovulation. Recently, Dewailly *et al.*[15] suggested that PCOS should be defined as >25 follicles per ovary or ovarian volume greater than or equal to 10 mL, depending on the available technology. However, for this study, performed prior to this definition, the '12 follicles' definition was used.

We detected 'polycystic ovaries' in 14 patients, but only eight were finally confirmed as having the polycystic ovarian syndrome.

A recent study suggested that the prevalence of fibroids in women experiencing recurrent pregnancy losses is about 8.2%. This study showed that fibroids are associated with mid-trimester losses among women with recurrent miscarriages. Resection of fibroids associated with distortion of the uterine cavity can eliminate the mid-trimester losses and result in a doubling of the live birth rate.[16] A prevalence of 15% was detected in the whole group. Many of the fibroids were small and did not distort the uterine cavity. These patients were offered a referral to a gynaecologist for a surgical discussion regarding the feasibility of removal of the fibroids.

Adenomyosis is a non-neoplastic condition, affecting many women, characterised by a benign invasion of the myometrium by ectopic endometrium, that is accompanied by hyperplasia of the adjacent smooth muscle.[7] Such invasion may be detected during a 3D ultrasound; however, there are insufficient studies available to be able to assign causation. Endometriomas and endometriosis may be detected by 3D ultrasound, however there is conflicting evidence regarding surgical removal of endometriomas, as such removal could damage the ovarian reserve.[17]

Asherman's syndrome is described as the presence of intrauterine adhesions composed of fibrotic tissue, and is a pathological condition that is thought to arise following trauma to the basal layer of the endometrium, usually following a curettage, infection or inflammation. Only three cases of Asherman's syndrome were detected, with significant synechiae. This was lower than expected considering that many of the patients presenting to a recurrent miscarriage clinic have had multiple dilatations and curettage procedures, a known risk factor in the development of this syndrome.[18] Knopman *et al.* showed that

3D ultrasound was able to demonstrate the presence of Asherman's syndrome, and identify the severity of the disease, regarding the percentage of the uterine cavity that was obstructed.[19]

Conclusion

This study demonstrates the usefulness of 3D ultrasound scans in evaluating women suffering recurrent pregnancy losses. Larger studies are needed to confirm this. The information gathered may be used to refer the patients to gynaecologists for the hysteroscopic or laparoscopic evaluation of the uterus and pelvis, and possible removal of septae, synechiae or fibroids. The ultrasound study should be performed during the luteal phase following a miscarriage, in conjunction with the serological workup, so that valuable time is not wasted in this vulnerable group of patients.

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