Successful Management of Septate Uterus in Patients with Recurrent Pregnancy Loss: A Report of Two Cases

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Two women presenting with recurrent pregnancy loss were both diagnosed to have septate uterus. After hysteroscopic resection of the septum under laparoscopic guidance, successful term pregnancy was achieved in one patient, while second patient is currently on her 24th week of gestation. Septate uterus is the most common type of congenital uterine anomaly and has long been known to be associated with recurrent miscarriages, late-term abortion, and preterm labor. The pre-treatment abortion rate is 90%, which is both distressing for the patient and frustrating for the physician. Hysteroscopic septal resection under laparoscopic guidance is considered the standard for treatment, and is shown to improve reproductive outcome.

Key words: uterine anomaly, septate uterus, recurrent pregnancy loss

Introduction

The structurally anomalous uterus has long been recognized as a cause of obstetric complications. It may be associated with recurrent pregnancy loss, preterm labor, abnormal fetal presentation and infertility.[1] Septate uterus is considered the most common of the uterine anomalies, occurring in approximately 1 percent of the fertile population and is associated with the poorest reproductive outcomes. It is associated with diminished cavity size, impaired ability to distend, inadequate vascularity and abnormal endometrial development. These abnormalities contribute to increased rates of recurrent pregnancy loss[2].

With the advent of the hysteroscopic surgery for removal of uterine septum, there was significant improvement of live birth rate from 40% to 80% among patients[3]. This gave hope to our patients, who both had recurrent pregnancy loss due to a septate uterus.

This case report reviews the definition, identify causes and proper evaluation of recurrent pregnancy loss. With special focus on uterine septum as the etiology of the pregnancy loss, further discussing the pathophysiology, diagnosis, management and complications.

The Cases

Case # 1

L.T., a 36 year old, G3P1(0120) married, Filipino, Catholic, who came to our institution because of recurrent pregnancy loss.

The patient is non-hypertensive, non-diabetic, and non-asthmatic with a history of poliomyelitis infection at 7 years of age.

The patient is a housewife, a non-smoker and non-alcoholic beverage drinker. She had menarche at 17 years of age with subsequent menses occurring at regular intervals, 4 days in duration, using 5 pads per day, associated with dysmenorrhea during the first two days. She is married to a 36 year old non-smoking partner, with no history of sexually transmitted disease.

She had her first pregnancy 10 years prior to admission. At 8 weeks age of gestation she had spontaneous abortion for which she underwent completion curettage. Eight years prior to admission she had her second pregnancy, she had spontaneous abortion at 12 weeks age of gestation and completion curettage was performed. Five years prior to admission, she had a preterm delivery at 22 weeks age of gestation. The baby died soon after due to prematurity. In the interim, there was intentional use of oral contraceptive pill for about 3 years to prevent pregnancy for fear of having the same problem. Because of advancing age, the couple finally agreed to have work-up for the recurrent pregnancy loss. The laboratory results were normal(Table 1). Hysterosalpingogram showed a bicornuate configuration of the uterus with visualization of both fallopian tubes and eventual peritoneal spillage bilaterally(Figure 1).The 2-dimensional transvaginal ultrasound showed a normal sized retroverted uterus widened at its transverse diameter with a thin endometrium that splits in a Y-shaped configuration (Figures 2 & 3). The 3-dimensional ultrasound showed the septum from the mid segment towards the fundus, 2.5cm long with an intercornual distance of 0.35cm. The outer fundal contour was flat (Figure 4). The impression was a partial septate uterus (ASRM Class V).

Table 1. Laboratory results of patient # 1.

Examination	Result	Normal Range
FBS	101	70-110 mg/dl
TSH	1.2	0.3-3.8 mIU/ml
Partial Thromboplastin Time	29.9	28.9-39.1 sec
Prothrombin Time	9.6	12.6 sec

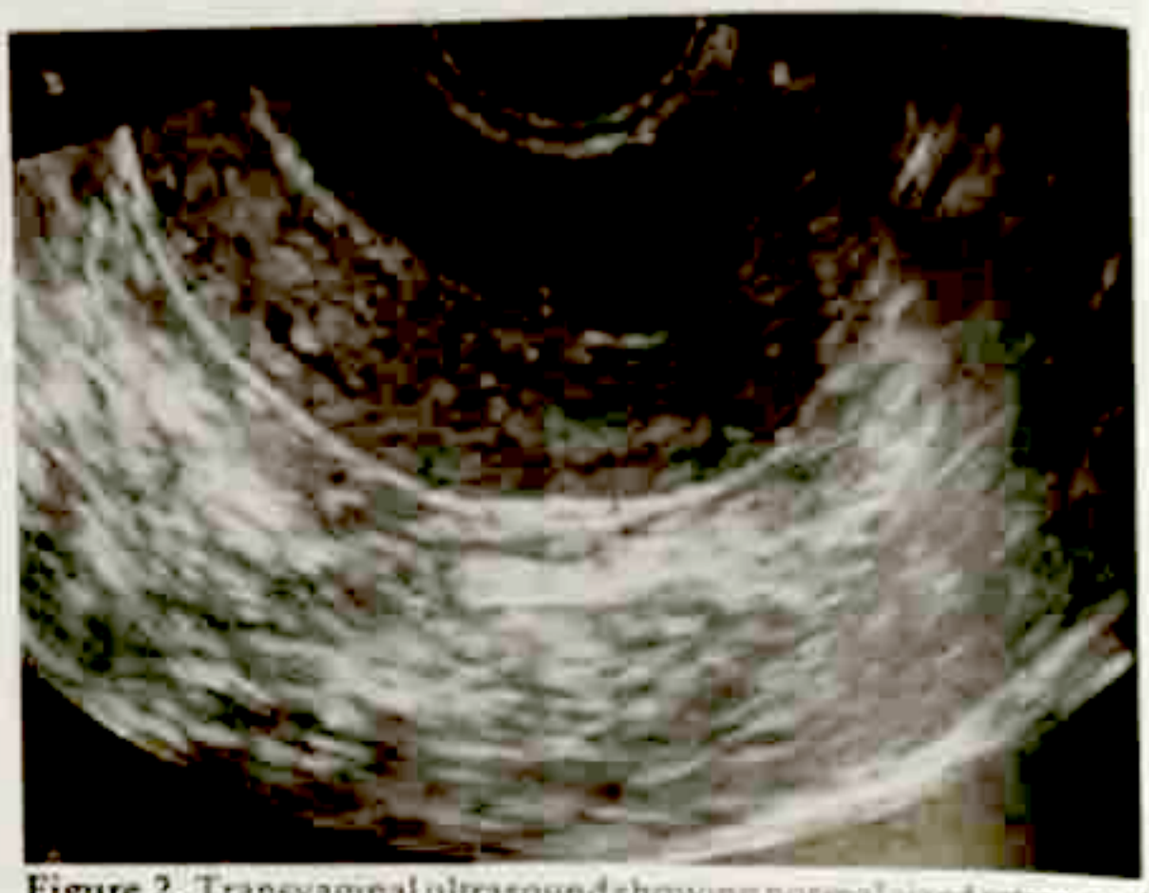

Figure 2. Transvaginal ultrasound showing normal sized retroverted uterus with thin endometrium that splits in a Y-shaped configuration.

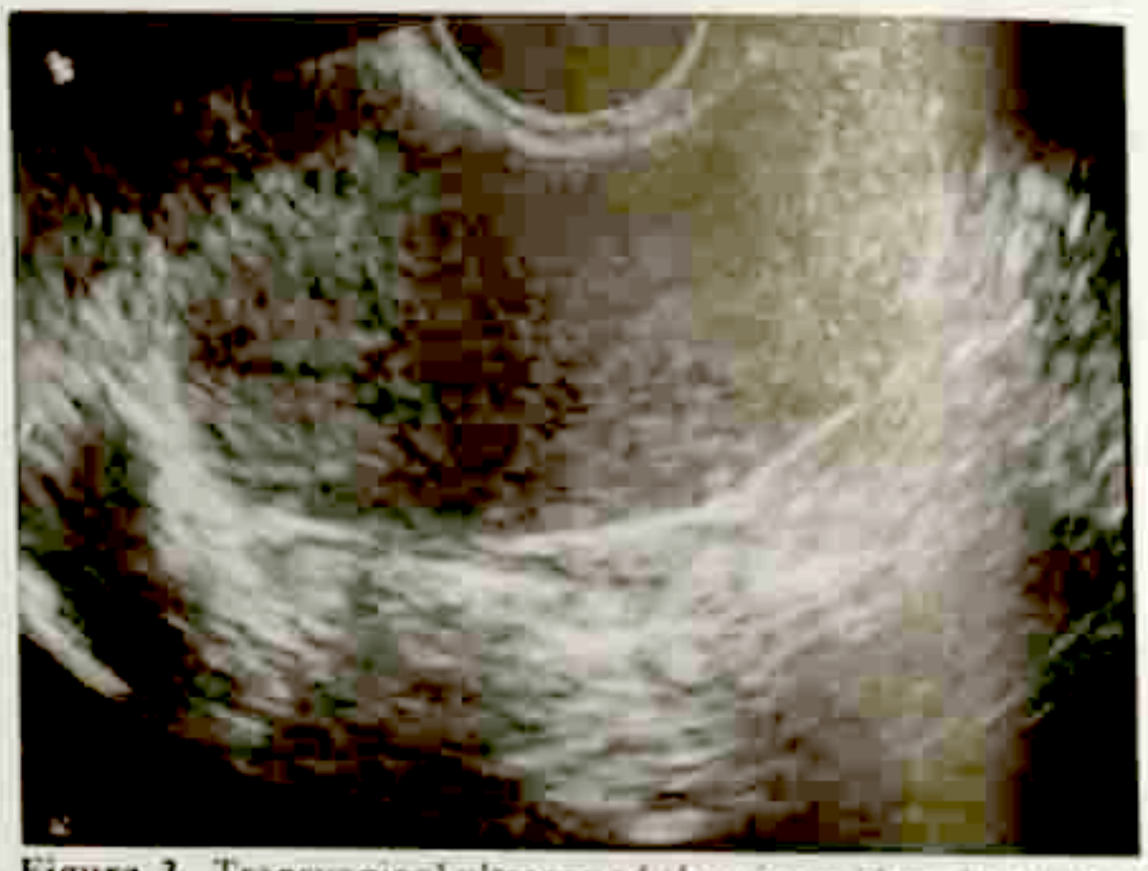

Figure 3. Transvaginal ultrasound showing widened transverse diameter.

Figure 1. Hysterosalpingogram showing bicornuate uterus with patent fallopian tube.

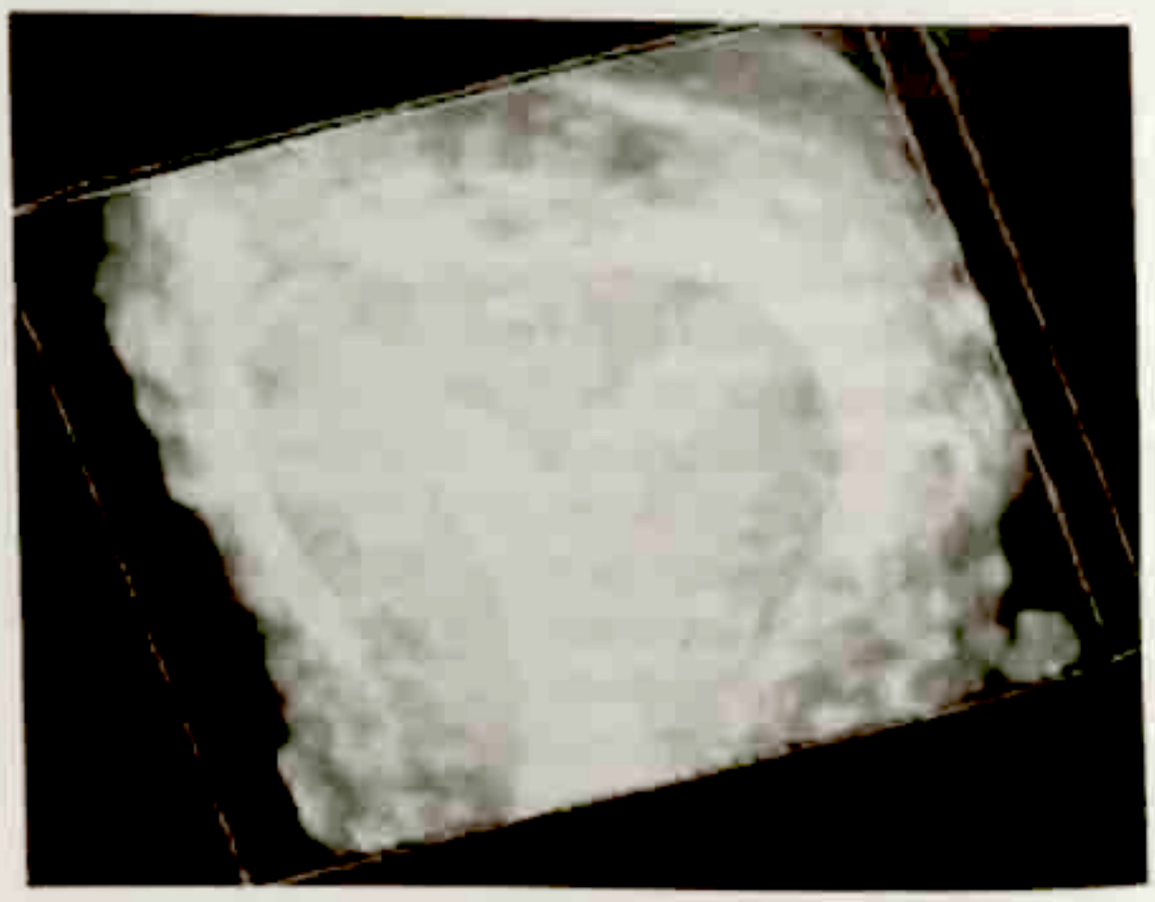

Figure 4. Three-dimensional ultrasound showing the uterine septum from the mid segment towards the fundus, with a flat outer fundal contour.

She underwent hysteroscopic resection of the uterine septum with laparoscopic guidance under general anesthesia. The intraoperative finding revealed the septum traversing the length of the endometrial cavity from the mid segment to the fundus, dividing the cavity unequally (Figure 5). The outer fundal contour was flat, grossly normal ovaries and fallopian tubes seen on laparoscopy (Figure 6). Resection of the uterine septum was performed until the two hemiuterine cavities were transformed into a single normal endometrial cavity(Figure 7). The postoperative course was uneventful.

Figure 5. Hysteroscopic finding of uterine septum (⊿) traversing the length of the endometrial cavity from the mid segment to the fundus dividing the cavity unequally.

Figure 6. Laparoscopic finding of flat outer fundal contour, grossly normal ovaries and fallopian tubes.

Figure 7. Single normal endometrial cavity after resection of the septum.

She conceived three months after surgery. The rest of the prenatal course was uneventful and delivered a live term baby girl by cesarean section due to cephalopelvic disproportion. The patient had an unremarkable postpartum course. The baby likewise did very well. Both were discharged in the second postoperative day with home medications and instructions for follow up.

Case #2

L.L., a 35 year old, G2P0(0020) married, Filipino, Catholic, who came to our institution because of recurrent pregnancy loss.

The patient is non-hypertensive, non-diabetic, and non-asthmatic. She is a college graduate who works as a secretary, a non-smoker and non-alcoholic beverage drinker. She had menarche at 14 years of age with subsequent menses occurring at regular intervals, 4 days in duration, using 4 pads per day, with no associated dysmenorrhea. She is married to a 36 year old non-smoking partner, with no history of sexually transmitted disease.

She had her first pregnancy four years prior to admission, at 8 weeks age of gestation she had spontaneous abortion for which she underwent completion curettage. Three years prior to admission, she had her second pregnancy. She had spontaneous abortion at 12 weeks age of gestation and completion curettage was performed. She had a work-up for recurrent pregnancy loss one year prior to admission. The screening for antiphospholipid antibody, diabetes and thyroid disease turned negative(Table 2). The hysterosalpingogram showed a bicornuate uterus with patent fallopian tubes(Figure 8), the 2-dimensional transvaginal ultrasound showed a septate uterus with

myoma nodule 1 cm x 0.8 cm, left cornu(Figure 9). The 3-dimensional ultrasound showed a smooth outer fundal contour with a Y-shaped configuration of the endometrial cavity with the intervening septum extending to the midcavity. The submucous component of the myoma is seen in the mid segment at the edge of the septum more towards the left cavity(Figure 10). The impression was a partial septate uterus (ASRM Class V) with submucous myoma.

Table 2. Laboratory results of patient # 2

Examination	Result	Normal Range
FBS	101	70-110 mg/dl
TSH	0.9	0.3-3.8 mIU/ml
Partial Thromboplastin Time	32.7	28.9-39.1 sec
Prothrombin Time	9.9	12.6 sec
Antiphospholopid Panel	IgM antibody to cardiolipin- negative	
	IgG antibody to cardiolipin- negative	
DRVTT	Lupus anticoagulant not detected	

Figure 8. Hysterosalpingogram showing bicornuate uterus with patent fallopian tubes.

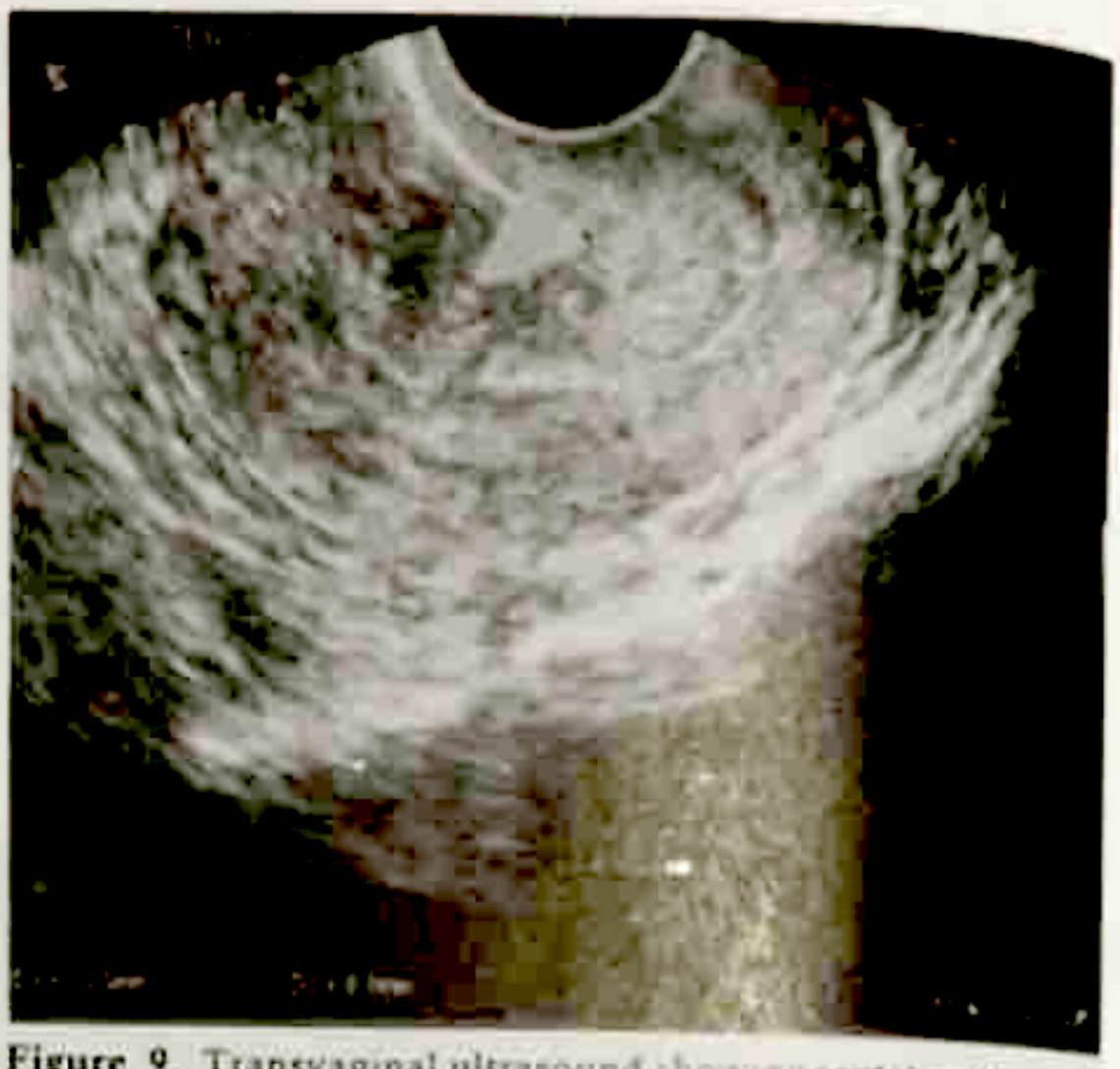

Figure 9. Transvaginal ultrasound showing septate uterus with myoma nodule (◢) at left cornu, measuring 1cm x 0.8cm.

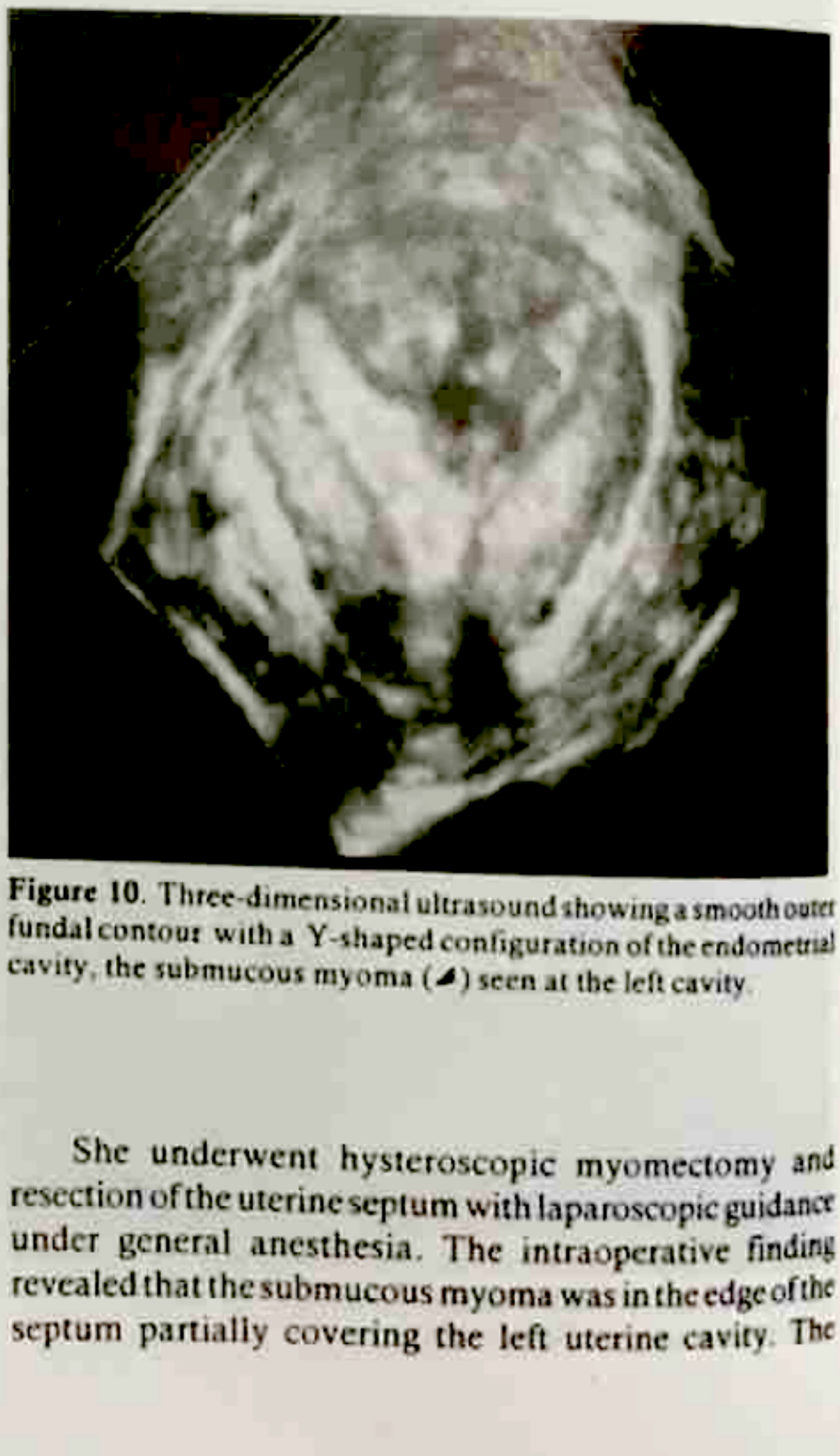

Figure 10. Three-dimensional ultrasound showing a smooth outer fundal contour with a Y-shaped configuration of the endometrial cavity, the submucous myoma (◢) seen at the left cavity.

She underwent hysteroscopic myomectomy and resection of the uterine septum with laparoscopic guidance under general anesthesia. The intraoperative finding revealed that the submucous myoma was in the edge of the septum partially covering the left uterine cavity. The

septum traversing the length of the endometrial cavity from the mid segment to the fundus, dividing the cavity unequally(Figure 11). The outer fundal contour was flat, grossly normal ovaries and fallopian tubes seen on laparoscopy(Figure 12). Resection of the uterine septum was performed until the two hemiuterine cavities were transformed into a single normal endometrial cavity (Figure 13). The postoperative course was uneventful.

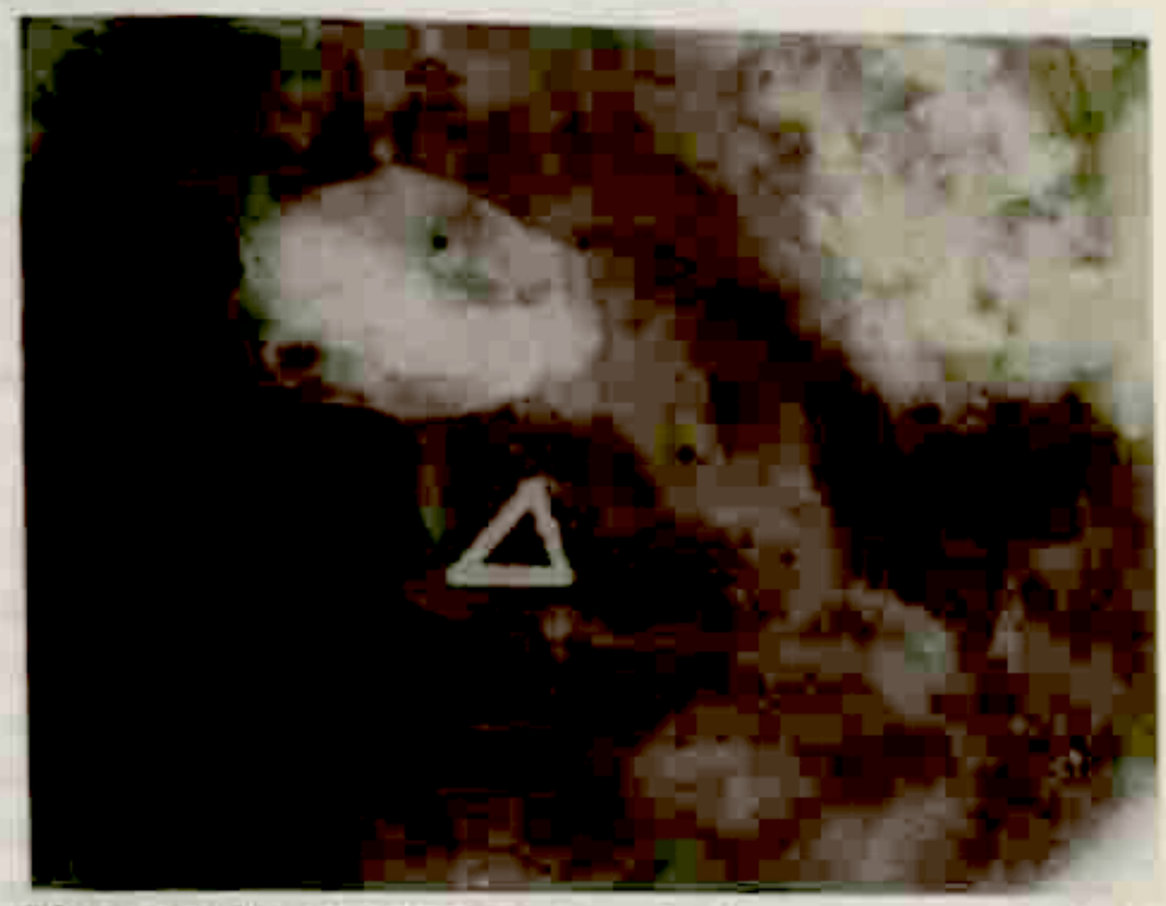

Figure 11. Hysteroscopic finding of submucous myoma (◢) in the edge of the septum partially covering the left uterine cavity, the septum (◿) traversing the length of the endometrial cavity from the mid segment to the fundus.

Figure 12. Laparoscopic finding of flat outer fundal contour, grossly normal ovaries and fallopian tubes.

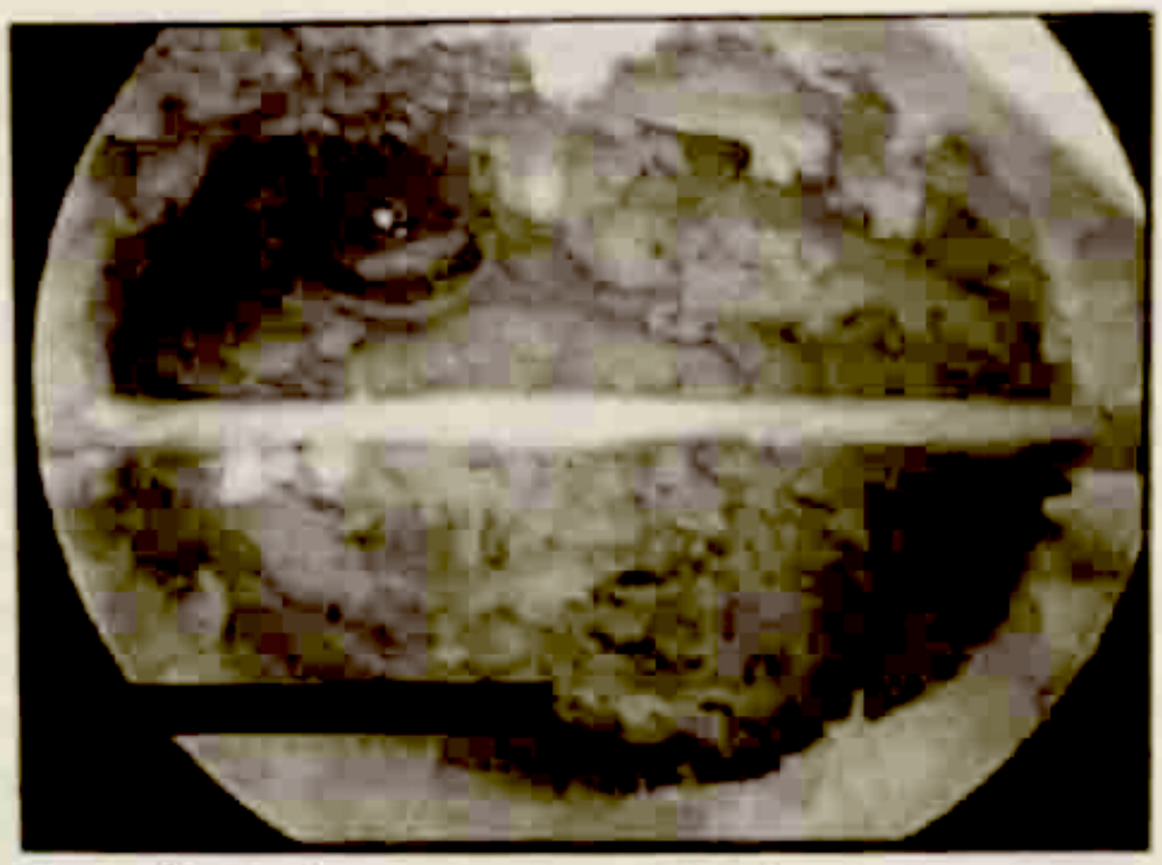

Figure 13. Single normal endometrial cavity after hysteroscopic myomectomy and resection of the septum.

She spontaneously conceived three months after surgery. Her last normal period was March 7, 2009. Her first trimester ultrasound, done at 7 weeks AOG showed good cardiac activity, normal yolk sac with absence of subchorionic hemorrhage. Currently, she's on her 24th week of gestation.

Discussion

Recurrent Pregnancy Loss

The two patients presented with successive pregnancy losses. Recurrent pregnancy loss is defined as three or more consecutive spontaneous abortions.[4] Around 1 percent of couples will experience recurrent pregnancy losses before the 28th gestational week. Accurate prevalence figures are not available. Present estimates say that 2 to 5 percent of women have this problem.[5] The American College of Obstetrics and Gynecology in 2001 suggested that women with two or more consecutive failures with the same partner should undergo an investigation since the risk of another pregnancy loss increases with each successive loss[6]. It is recommended that examinations in recurrent pregnancy loss should as a minimum be carried out (Table 3) and, in addition, factors with association and prognostic impact documented in studies of adequate size and quality could be investigated (Table 3).[5] The risk of recurrence increases with maternal age and the number of successive losses.[6] Advanced maternal age affects ovarian function giving rise to a decline in the number of good quality oocytes. This may result in chromosomally abnormal conceptions which rarely develop further.

Women less than 20 years of age have a 12.2% abortion rate, while men of the same age contribute to 12%. It is well-established that the risk of miscarriage resulting from trisomic conceptuses increases with maternal age.[3] Since both patients and their partners were between 35-39 years of age, the frequency of abortion is 18.7% and 15.8% in women and men, respectively. Despite this, age factor alone is not the sole cause of their pregnancy loss. Couples with at least one full term livebirth , has a 12% recurrence of losses. The absence of term livebirth with one to four prior losses, is associated with 24-32% recurrent pregnancy loss. If prior outcomes were all miscarriages, 2-3 losses may cause 47-54% of recurrence.[5] Therefore, both patients have a risk for subsequent losses which approximate to fifty percent. The first patient is a 36 year old, who suffered three pregnancy losses, the first two were spontaneous abortions at 8 and 12 weeks, respectively, and the third pregnancy was delivered preterm at 22 weeks, who died due to prematurity. The second patient, a 35 year old, had two pregnancy losses, both ended in spontaneous abortion in the first trimester.

Table 3. Recommended investigations of recurrent pregnancy loss patients.

Investigation	Documentation
HSG or hysteroscopy or sonohysterography	A
Karyotyping of the couple	A
Thyroid hormones	A
Androgens, LH, FSH in patients with irregular menstruation	B
APTT-/dRVVT/lupus anticoagulant	A
IgG and IgM anticardiolipin antibodies	A
Factor V Leiden mutation	A
Mannan-binding lectin	B
Maternal HLA-G and HLA-DR types	B

Note: A=value documented in many studies; B=value suggested in few but large studies; HSG=hysterosalpingogram; APTT=activated partial thrombin time; dRVVT=dilute Russel's viper venom time

In the evaluation of patients with recurrent pregnancy loss, the possible cause should be determined in order to institute the proper treatment. The identifiable causes include genetic factors, prothrombotic state, endocrinological disorders, immunological factors and structural uterine defects.[4] In approximately 3-5 percent of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly. The most common abnormality is a balanced translocation, including reciprocal and Robertsonian translocations.[7] Several factors increase the possibility of carrier status of a chromosomal abnormality: low maternal age, a history of three or more miscarriages, a history of two or more miscarriages in a brother or sister, and a history of two or more miscarriages in the parents of either partner.[8] These factors were not observed in our patients, except for the history of three pregnancy losses in the first patient, hence the parental cytogenetic abnormality is not the cause for the pregnancy loss. Recurrent miscarriage may be due to an abnormal embryo, which account for approximately 50 percent of sporadic first trimester miscarriage. As the number of miscarriages increases, the prevalence of chromosomal abnormality decreases and the chance of recurring maternal cause increases.[9] Acquired maternal thrombophilia is a well-recognized cause of recurrent miscarriage. All women with a history of three or more early pregnancy losses, that is, before 10 weeks, or 1 or more premature births at ≥34 weeks with severe preeclampsia or placental insufficiency, should be offered a testing for antiphospholipid antibodies.[4] Systemic maternal endocrine disorders such as diabetes mellitus and thyroid disease have been associated with miscarriage. Women with diabetes who have a high glycosylated hemoglobin levels in the first trimester are at risk of miscarriage and fetal malformation.[7] Consideration of the timing of miscarriage is important, as different causes tend to manifest at different age of gestation. In women who have had three or more miscarriages, of which at least one occurred in the mid-trimester, the underlying etiology may be quite different to those with only first trimester losses.[4] In a study conducted by Drakeley , et al., results of investigation showed that factors associated with mid-trimester loss are antiphospholipid syndrome, cervical incompetence, infection, hypothyroidism and uterine anomaly.[10] Second trimester losses, such as what happened to the third pregnancy of the first patient, are commonly caused by specific types of uterine anomalies, which is what was discovered in the patient. In first trimester losses, important causes include maternal diseases, poorly controlled diabetes mellitus, uncontrolled thyroid disease and antiphospholipid antibody syndrome[4], all of these entities were ruled out in the second patient after laboratory examination showed negative findings, hence the most likely cause of her pregnancy loss is a uterine anomaly.

Anatomic Factor

Congenital Uterine Anomaly

Congenital malformations may be associated with recurrent pregnancy loss, preterm labor, abnormal fetal

presentation, and infertility.[11] Congenital uterine anomalies resulting from mullerian fusion defects are the most common types of malformations of the reproductive system.[12] The American Society for Reproductive Endocrinology developed a classification system that allows organization according to major anatomical types. Table 4 classifies mullerian anomalies. Class V mullerian anomaly is represented by septate uterus.[13] The two patients belonged to the class V mullerian anomaly. Among the different types of structural uterine anomalies, the septate uterus is the most common and associated with the poorest reproductive outcome, with fetal survival rates of 6-28% and a high rate of spontaneous miscarriage(>60%).[1] Overall, uterine anomalies are associated with difficulty maintaining a pregnancy, and not an impaired ability to conceive.[2] This low efficiency in maintaining pregnancy were seen in both patients.

Table 4. Classification of mullerian anomaly.

Class	Description
I	Mullerian agenesis or hypoplasia a. Vaginal b. Cervical c. Fundal d. Tubal e. Combined
II	Unicornuate uterus a. With rudimentary horn b. Without rudimentary horn
III	Uterus didelphys
IV	Bicornuate uterus a. Complete b. Partial c. Arcuate
V	Septate uterus a. Complete b. Incomplete septum
VI	DES uterus

Uterine Fibroid

Uterine fibroid may also affect implantation and increase the risk of miscarriage. Data from several IVF series suggest that reproductive outcome is significantly compromised by submucosal fibroids, modestly compromised by intramural fibroids, and possibly compromised by subserosal fibroids. It is not known if the endometrium covering a submucous fibroid responds suboptimally to steroid hormones. However, it appears from a number of retrospective and cohort studies that there is good evidence that removal of submucous fibroids reduces miscarriage rate.[3]

Embryology and Pathophysiology

Normal development of the female reproductive tract requires a complex series of events: mullerian duct elongation, fusion, canalization, and septal resorption; failure on any part of this process can result in a congenital anomaly. The uterine septum is due to the incomplete resorption of tissue, it may project minimally from the uterine fundus or may extend to the cervical os, almost dividing the uterine cavity into two.[1] The degree of septation is variable; a complete septum extends from the uterine fundus through the cervix, and a partial septum demonstrate resorption of a portion of the caudal aspect of the septum. Despite the endometrial cavity abnormality, the external uterine contour appears normal.[2] The two patients had partial septate uterus: the septum did not traverse the entire length of the endometrial cavity but only from the fundus down to the midcavity. The mechanism by which the septate uterus causes pregnancy loss is not clearly understood. Pregnancy loss associated with the septate uterus classically occur between 8 and 16 weeks of gestation.[1] The first patient had her first two pregnancy losses at 8 and 12 weeks, respectively. For the second patient, she had successive pregnancy losses of similar age of gestation. It has been suggested that spontaneous miscarriage may be the result of a poor blood supply to the septum leading to poor implantation dynamics.[11] Candiani, et al. observed altered patterns of vascularity in specimens of septal mucosa, reinforcing the idea that septal implantation may result in poor embryo growth.[14] The first patient had a preterm delivery at 22 weeks. Premature delivery may be caused by increased intrauterine pressure, and estrogen and progesterone receptor deficiency associated abnormal endometrial development may cause abnormal uterine contractions that lead to fetal wastage.[1]

Diagnosis

Traditionally, laparoscopy, hysterosalpingography(HSG) and/or hysteroscopy have been used to diagnose these uterine malformations in women with recurrent pregnancy loss.The hysterosalpingography results for the patients revealed bicornuate uterus and

patent fallopian tubes. Hysterosalpingography can detect a two-chambered uterus and allow assessment of the size and extent of a septum.[12] It has the advantage of allowing concomitant assessment of tubal patency, the main drawback is that it can not reliably differentiate between septate and bicornuate uterus.[1] Septate uterus is always confused with a bicornuate uterus since both exhibit two endometrial cavities and one cervix. In a study done by Proctor, et al., they concluded that when presenting with recurrent first trimester loss and a divided uterine cavity by hysterosalpingogram, virtually all women have uterine septum.[16] The 2006 Royal College of Obstetricians and Gynecologists Guideline on the Investigation and Treatment of Couples with Recurrent Miscarriage suggested that all women with recurrent miscarriage should have a pelvic ultrasound to assesss uterine anatomy and morphology.[1] The subsequent 2-dimensional and 3-dimensional ultrasound were diagnostic for subseptate uterus in both patients. Transvaginal ultrasound permits a better assessment, with a sensitivity of 100% and specificity of 80% in the diagnosis of septate uterus.[17] The appearance of the septate uterus on transvaginal ultrasound include a convex, flat, and minimally indented(≤ 1 cm) fundal contour with an echogenic mass dividing the cavity, the proximal part of which possesses an echographic texture indicative of myometrium merging into hypoechoic fibrous tissue distally.[1] A regular two-dimensional ultrasound is a good screening tool for uterine malformations, but it is not as efficient as the three-dimensional ultrasound in detailing the type of anomaly. Jurkovic, et al. reported that three-dimensional ultrasound has a sensitivity and specificity of 100% for the diagnosis of major mullerian anomalies. Since it gives both diagnosis and classification of uterine abnormality, it may preclude the need for diagnostic hysteroscopy and laparoscopy.[18] Nonetheless, hysteroscopy and laparoscopy, aside from helping differentiate bicornuate uterus from septate uterus has the therapeutic surgical advantage compared to the later.

Treatment

Although uterine septum does not always cause poor pregnancy outcome, its discovery in women with recurrent pregnancy loss provides an indication for surgical correction. In the first patient who already suffered three consecutive pregnancy losses, the finding of a partial septate uterus was enough indication for the operation since one is almost sure that it is the root cause of her recurrent pregnancy wastage. The second patient had two pregnancy losses, surgical correction was still warranted because all the other causes for the miscarriage were already ruled out. The patients underwent combined hysteroscopy-laparoscopy as therapeutic procedures, and the correction of the uterine anomaly addressed their problem of recurrent miscarriage.

Surgical correction of the septate uterus traditionally was performed by transabdominal metroplasty. Open uterine surgery is coupled with postoperative reduction of the intrauterine volume and the formation of intrauterine and intraperitoneal adhesions with tubal occlusion. Abdominal metroplasty requires a longer postoperative interval before conception (3-6 months), and surgical damage to the full thickness of the uterine fundus is associated with a significant risk of scar rupture during pregnancy and dictates that the mode of delivery in a subsequent pregnancy must be by cesarean section.[1] With the introduction of the less invasive hysteroscopic surgery, the septum may now be easily and safely removed via the resectoscope.[4] While there is no randomized controlled study to confirm the value of this procedure in the septate uterus, recent data suggest a benefit in those with three or more, and possibly two, miscarriages. The best evidence to date comes from non-randomized studies showing excellent outcomes with treatment by hysteroscopy[1]. Post-treatment abortion rates are about 10% in contrast to the 90% pre-treatment rate.[8] Hysteroscopic septal incision can be performed using the microscissors, electrosurgery, or laser and outstanding results can be achieved by all techniques. Concomitant laparoscopy is used in most hysteroscopic metroplasty to detect an impending uterine perforation or to instantly identify one when it happens.[1] As seen from the cases, the septae were incised from the apex up to its fundal attachment using the loop electrode. Throughout the procedure, transillumination was done, observing laparoscopically the glow of the hysteroscope light source through the uterus. Transection was deemed complete when the two hemiuterine cavities were unified into a single, normal endometrial cavity; both tubal ostia were viewed simultaneously; and no appreciable septum was left. There is a lack of consensus regarding postoperative management. The insertion of intrauterine device and hormonal therapy with estrogen after hysteroscopic metroplasty is unnecessary. Since hysteroscopic surgery is an invasive procedure, some investigators recommend the use of short perioperative course of prophylactic antibiotics.[1]

Several case reports showed that even when no complications occur at surgery, subsequent pregnancies are still at risk of uterine rupture. In addition, incomplete uterine septa may be associated with an increased risk of retained placentas[1]. Thus obstetricians who care for these patients should be aware of these potential hazards.

Recommendations

Pregnancy loss is a distressing event, screening after the second loss as suggested by the American College of Obstetrics and Gynecology is more acceptable because nobody would want a third pregnancy loss.

As a minimum, examinations to be carried out with documented value in many studies, include hysterosalpingogram or hysteroscopy, karyotyping of the couple, thyroid hormones, APTT, lupus anticoagulant, IgG and IgM anticardiolipin antibodies, factor V leiden mutation. Further investigations with value suggested in few but large studies include androgens, LH, FSH in patients with irregular menstruations, mannan-binding lectin and maternal HLA-G and HLA-DR types.[5]

There is no consensus as to the importance of all risk factors and there is very little agreement regarding the level of positivity of the tests. Despite these, Christiansen, et al. recommend that investigation should not for economic or other reasons. Stop as soon as the first risk factor has been identified.[5]

Clinicians encountering patients with recurrent pregnancy loss, should discuss whether attempts should be made to treat all risk factors at the same time or only one of them before or during the next pregnancy attempt. Most of the time, patients will want all factors corrected or treated before attempting a subsequent pregnancy.

Conclusion

In principle, recurrent pregnancy loss should be screened for all potential risk factors. Single sufficient factors may not always be the case for all recurrent pregnancy loss. Risk approximation from previous gestational events and increasing age contribute to a thorough evaluation for other possible etiologies. An earlier investigation has spared the second patient from a third recurrence compared to the first patient. The two patients diagnosed with uterine septum causing the recurrent pregnancy loss, were successfully managed with a simple hysteroscopic resection of the septum, concomitant removal of the submucous fibroid embedded in the septum in the second patient was possible. With proper evaluation and availability of the hysteroscopic approach to an early treatment of septate uterus, a positive outcome is often achieved: no longer a subsequent miscarriage but a successful term pregnancy.

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