Uterine Isthmic Atresia: Hope for a Rare Mullerian Anomaly*

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The true incidence and prevalence of congenital Mullerian duct anomalies are difficult to determine. Some patients may present as adolescents with apparent primary amenorrhea, cyclical abdominal pain and sexual difficulties. It is important to ascertain a correct diagnosis for timely and appropriate interventions necessary to prevent sequelae that often affect the future fertility of these patients. This is a case of a fifteen year old with severe cyclical pelvic pain and hematuria with amenorrhea. Work up included a transrectal ultrasound and a magnetic resonance imaging of the pelvis revealing presence of a uterine corpus and cervix but absence of uterine isthmus. A conservative surgical approach was planned. The patient underwent end-to-end anastomosis of the cervix and uterine corpus. At present, the patient is regularly menstruating with no pelvic pain.

Key words: amenorrhea, atresia, end-to-end anastomosis, Mullerian anomaly, uterine isthmus

Introduction

Congenital Mullerian duct anomalies have always been challenging, from its diagnosis to management, mainly due to its rarity and no concrete guideline for its management. Patients with the obstructive kind usually present as adolescents with apparent primary amenorrhea, cyclical abdominal pain and sexual difficulties. Primary amenorrhea is defined by Speroff as the absence of menstruation by 14 years of age in the absence of secondary sexual characteristics or absence of menses by 16 years of age with normal sexual characteristics.[1] Cryptomenorrhea, on the other hand, is a condition wherein menstruation occurs, but is not visible usually due to an obstruction in the outflow tract eventually causing cyclical suprapubic pain. The latter, which is present in this patient, is usually mistaken for the former because of the deceptive absence of menstrual flow.

There are four proposed classifications of congenital malformations of the female genital tract: the widely accepted and often used American Fertility Society (AFS) classification of 1988, the Clinical and Embryological Classification System published in 2004, the VCUAM (Vagina, Cervix, Uterus, Adnexae and associated Malformations) proposed in 2005, and the ESHRE / ESGE Consensus classification or the CONUTA (Congenital Uterine Anomalies) classification of 2013.[2] Despite all these classifications, there are still some malformations that do not fit into a specific category, making the diagnosis and management of these unspecified anomalies more perplexing.

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The Case

S.A. is a 15-year-old girl who consulted due to cyclic hypogastric pain. She has an unremarkable past medical history. With just hypertension in her father and bronchial asthma in her maternal grandmother, her family history seems non-contributory. The patient's mother recalled an uneventful prenatal course during her pregnancy with the child. The patient is currently a senior high school student, who denies smoking and ever having sexual relations. Her cyclic hypogastric pain started at fourteen years of age with associated hematuria necessitating monthly absences from school due to severe pain. Except for monthly whitish mucoid discharge per vagina, no menstrual flow was ever noted. On physical examination, she weighed 48 kilograms and stood 152 centimeters tall, giving her a body mass index of 21. Sexual development was appropriate for age with a Tanner staging of 3 for breasts and Tanner 4 for pubic hair. On visual inspection, she had normal external genitalia. The hymenal membrane was intact with an annular opening. On internal examination, the vaginal canal was supple and 7 centimeters in length. On speculum examination, the cervix was smooth and measured 2cm x 2cm. On bimanual examination. There seemed to be a palpable indentation between the small retroverted uterus and the cervix. On rectovaginal exam, there was good sphincteric tone, intact rectal vault, and with multiple nodularities at the cul-de-sac of which measured 1cm x 0.5cm x 0.5cm at its largest. There were no adnexal masses palpated nor adnexal tenderness associated.

Transrectal ultrasound (Figure 1) revealed a cervix measuring 3.4cm x 2.7cm x 1.9cm with a homogenous stroma and a distinct endocervical canal that ended blindly. There appeared to be a 0.6cm hyperechoic gap between the cervix and the corpus with note of few vessels in the area. There was no direct communication between the uterine canal and endocervical canal. The uterine cavity was dilated by a low level echo fluid collection with a volume of 5.4cc. The endometrium measured 0.2cm thick both anteriorly and posteriorly. The right ovary measured 4.2cm x 3.8cm x 3.6cm with a unilocular anechoic cyst that measured 3.8cm x 3.5cm x 2.7cm with a rim of normal ovarian stroma containing several antral follicles. Adjacent to the right ovary was a 2.7cm x 2.3cm x 2.6cm unilocular, thin walled cyst containing low level echo fluid within. There were adhesions noted at the right adnexal area. The left ovary was not visualized. The sonologic impression was congenital absence of the uterine isthmus, thin endometrium with hematometra, right ovarian cysts consider physiologic cyst and endometriotic cyst, pelvic adhesions and sonographically absent left ovary. With ultrasonologic guidance, a Pipelle (curette) endometrial biopsy instrument was inserted in the cervix to probe the extent of the endocervical cavity and its patency. The instrument traversed 3.9cm of the endocervical canal but could not be pushed through beyond the cervix. (Figure 2)

A pelvic MRI was requested to confirm the diagnosis revealing a uterus with the axis of the body oriented to the left and perpendicular to the axis of the cervix. Fluid collection was seen within the endometrial cavity with note of an abrupt end of the endometrial canal at the lower uterine segment. The cervix was not enlarged and its endocervical canal axis was oriented obliquely to the right. These findings were compatible with uterine isthmus atresia. (Figure 3)

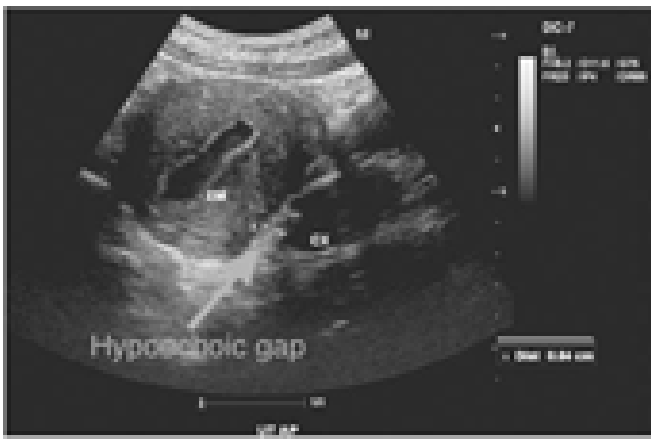

Figure 1. Ultrasound in anteroposterior view showing a 0.6cm hypoechoic gap between the cervix and the uterus. There is no direct communication between the uterine canal and the endocervical canal.

Legend:

CX: cervix

EM: Endometrium

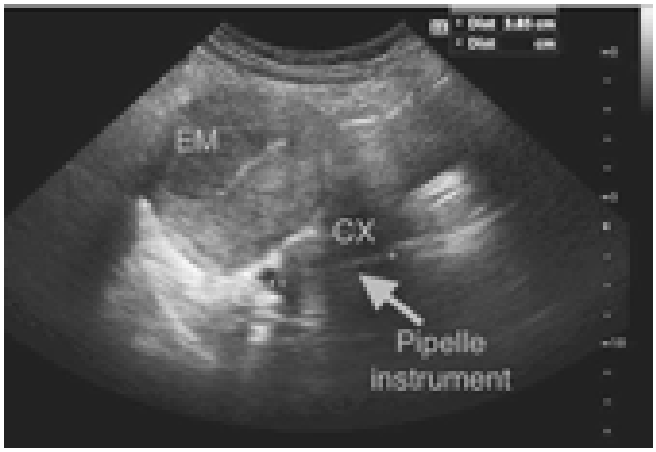

Figure 2. Ultrasound in anteroposterior view showing the hyperechoic instrument, 3.9cm in length, which could not pass through beyond the cervix.

Legend:

CX: cervix

EM: Endometrium

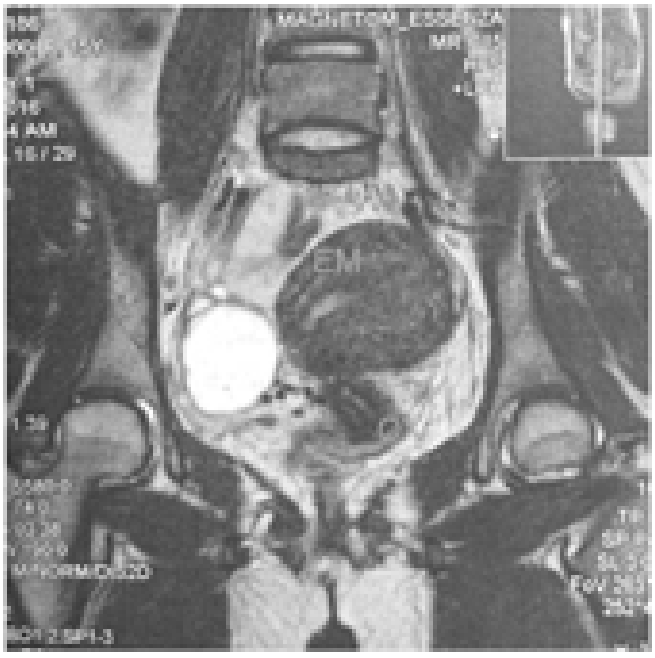

Figure 3. MRI showing the uterine body and the cervix. Note the abrupt cut - off of the endometrial canal at the lower uterine segment.

Legend:

CX: cervix

EM: Endometrium

The initial working impression was primary amenorrhea secondary to outlet obstruction from uterine isthmic atresia; pelvic endometriosis with right endometriotic cyst; gross hematuria, consider bladder endometriosis, rule-out uterovesical fistula. The patient was referred to the urogynecology section for diagnostic cystourethroscopy, which was performed on the fifth day of the cyclic pelvic pain. On urethroscopy, the urethral mucosa was pink and smooth, and the urethrovesical junction was intact. On cystoscopy, the trigone was smooth, but hypervascular; bilateral ureteral orifices were patent with good efflux of urine. There is note of external compression on the posterior bladder wall. Another hypervascular area measuring about 2cm x 1cm was noted at the posterior bladder wall. Histologic sampling of the hypervascular area was not performed as it might incite bleeding. (Figure 4) Based on the clinical picture and cystoscopy findings, the impression of the urogynecology section was gross hematuria probably secondary to intravesical endometrial glands; hence the patient was given hormonal suppression.

Figure 4. Cystoscopy showing an external compression and a hypervascular area measuring 2cm x 1cm over the posterior bladder wall.

A definitive operative plan was discussed thoroughly with the patient and her guardians including pre operative ureteral stenting, in anticipation of extensive adhesions, end-to-end

anastomosis of the corpus and the cervix as well as the possibility of a hysterectomy in the unlilkely event that anastomosis will be very difficult to perform. The final preoperative diagnosis was congenital isthmic atresia, pelvic endometriosis with right endometriotic cyst, gross hematuria from bladder endometriosis. The patient eventually underwent cystourethroscopy, still revealing a smooth urethral mucosa and intact urethrovesical junction. The bilateral ureteral orifices were patent with good efflux of urine. Bladder biopsy was performed on the hyperemic areas at the posterior bladder wall revealing acute on chronic cystitis. Bilateral ureteral stenting was also performed. On exploratory laparotomy, the urinary bladder was densely adherent to the anterior aspect of the uterus. The uterus was anteverted, enlarged to 10 weeks size and twisted 180 degrees on its horizontal and vertical axis. No uterine isthmus was visualized; in its location were fibrous tissue and adhesions to the posterior aspect of the urinary bladder. (Figure 5) The left ovary was densely adherent to the posterior uterus and converted to a unilocular cystic mass measuring 3cm x 3cm x 3cm with smooth and intact capsule. The inner capsule measured 0.1 centimeter and was smooth, with no solid area or excresences seen; cut section revealed sebum, hair and teeth within, consistent with the histopathologic result of mature cystic teratoma. (Figure 6) The left fallopian tube was densely adherent to the left posterolateral uterine wall and left pelvic sidewall. The right adnexa was likewise adherent to the posterolateral uterine wall and pelvic sidewall but was grossly normal. A metal hysterometer was inserted in the cervix from the vagina to guide the dissection of the fibrous tissue on the proximal portion of the cervix to reveal the superior portion of the endocervical canal. (Figure 7) The uterus was incised from the caudal portion of the uterus revealing a 2 cm thick lower isthmic portion, after which, a 1 cm opening was created. A French 8 foley catheter was inserted through the cervix and isthmus, with the balloon inflated inside the uterus. End-to-end anastomosis was then performed using Vicryl 0 atraumatic suture by anchoring interrupted sutures at the 3, 6, 9 and 12 o' clock positions and a second layer of interrupted sutures at the 2, 5, 8 and 11 o'clock positions after trimming some part of the myometrium. (Figure 8 and 9) The foley catheter was left in place to 2 weeks and the patient was placed on oral Cefuroxime 500mg twice a day.

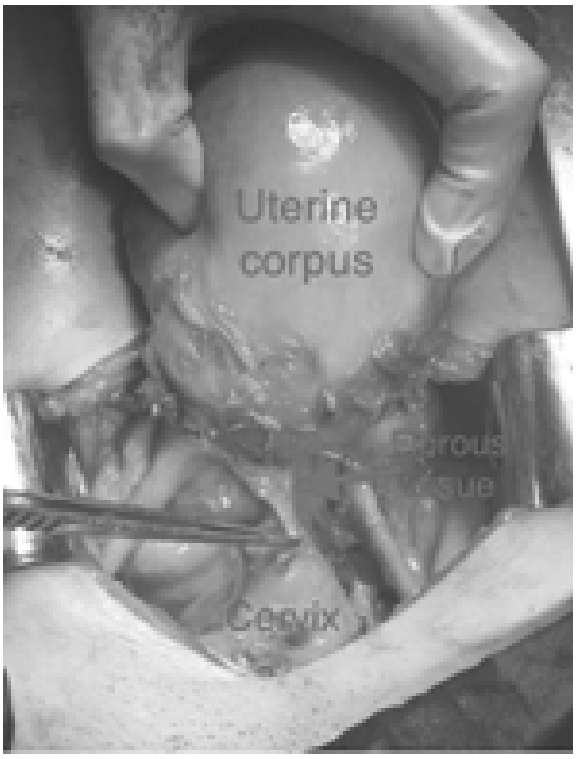

Figure 5. Absence of uterine isthmus, in its place is a fibrous band of tissue.

Figure 6. Dermoid cyst on the left.

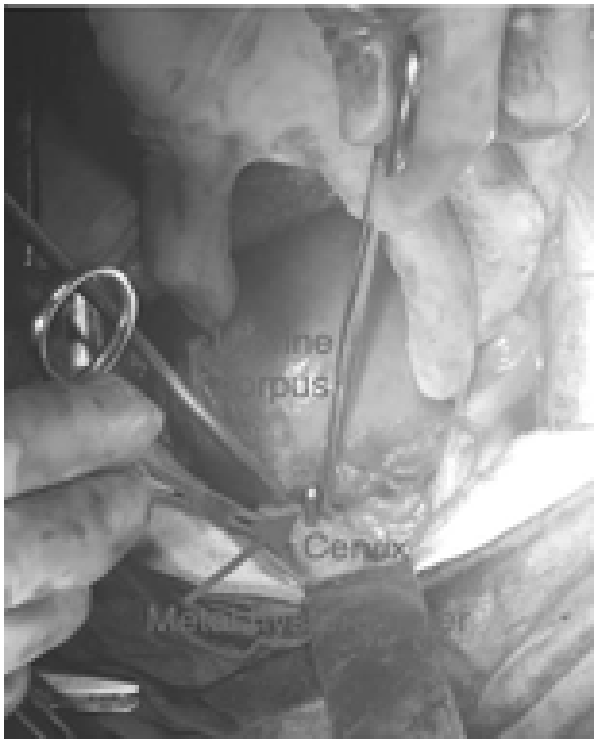

Figure 7. A metal hysterometer was inserted in the cervix from the vagina and was eventually seen at the exploratory laparotomy site.

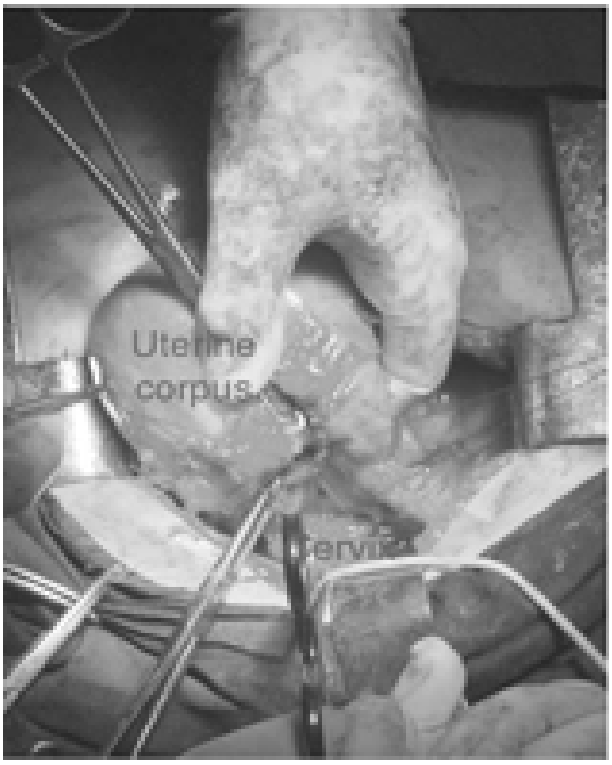

Figure 9. Uterine corpus and cervix after end-to-end anastomosis.

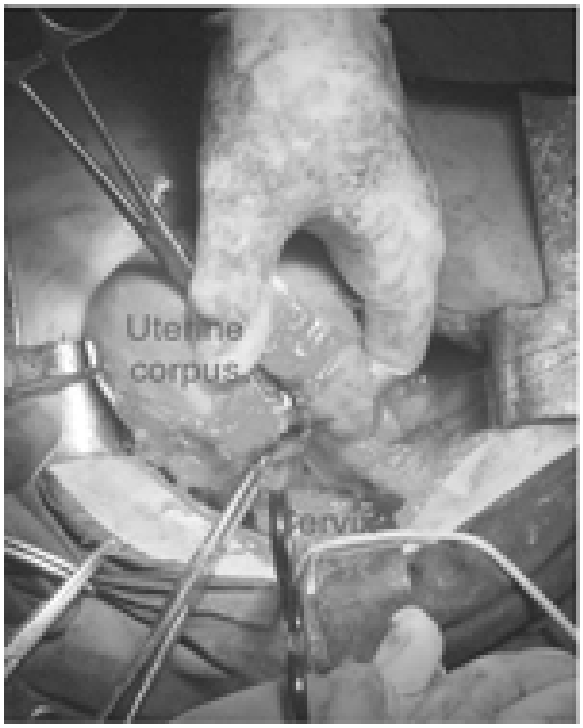

Figure 8. End-to-end anastomosis performed using Vicryl 0 atraumatic suture.

On the fifth postoperative day, a transrectal ultrasound was performed revealing multiple hyperechoic lines with no defect noted along the area of the uterine isthmus indicating that the anastomosis was intact. (Figure 10) Three months postoperatively, the patient was having regular monthly menses a repeat ultrasound done at the fourth day of the cycle showed normal uterus, thin endometrium with minimal hematometra, normal ovaries with follicle on the right, left periovarian adhesions. As of this writing, the patient is having regular monthly period with no complaints of dysmenorrhea and no recurrence of hematuria.

Discussion

In females, the paramesonephric or Mullerian ducts arise from the mesoderm lateral to the mesonephric ducts by the seventh week as focal invaginations of the coelomic epithelium on the upper pole of each mesonephros. The paired

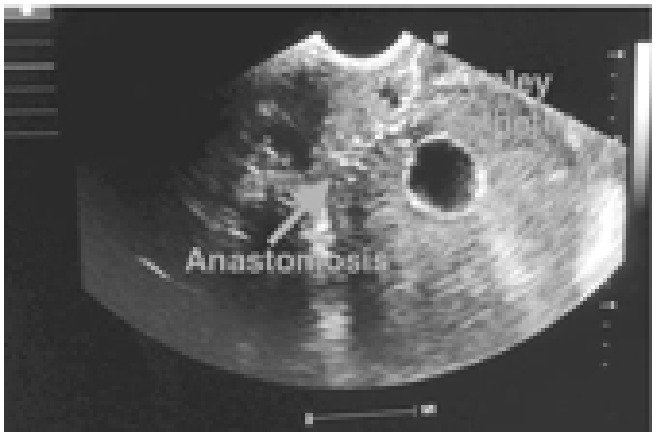

Figure 10. Post operative ultrasound showing the catheter left in place and intact anastomosis.

mesonephric and paramesonephric ducts represent the indifferent stage of the fetal internal genital canal systems. The uterus, fallopian tubes, cervix and upper vagina arise from the Mullerian ducts. By the eighth week, the paired Mullerian ducts lie medial to the mesonephric ducts. The Mullerian ducts then fuse to form a confluence in a process referred to as the Mullerian organogenesis, which represents the initial stage in the development of the upper two-thirds of the vagina, the cervix, the uterus and both fallopian tubes. Cephalad, the fused segments of the ducts become the future uterus. The unfused cranial ends of the Mullerian ducts assume a funnel shaped configuration and remain open to the future peritoneal cavity as the fimbrial portions of the fallopian tubes. The caudal end of the fused ducts will form the upper two-thirds of the vagina. Lateral fusion of the Mullerian ducts occurs between the seventh and ninth weeks, at this stage a midline septum is still present in the uterine cavity. This usually regresses at around 20 weeks. Vertical fusion occurs in the eighth week when the caudal end ot the fused Mullerian meets up with the ascending endoderm of the sinovaginal bulb to form a continuous lumen after canalization.[3] Normal development of the mullerian ducts depends on all these events: organogenesis, fusion and septal resorption. Failure of organogenesis will result in agenesis or hypoplasia or unicornuate uterus. Failure of fusion results in a bicornuate or didelphys uterus. Septal resorption defect results in septate or arcuate uterus.[4] Since the fallopian tubes, uterus, cervix, and upper third of the vagina have the same embryological origin, it is difficult to ascertain as to when the insult in our patient occurred.

Computation for the true incidence of mullerian duct anomalies from different patient populations, due to misdiagnosis, under-reporting, non-standardized classification systems and differences in diagnostic data acquisition have resulted in widely disparate estimates in reported prevalence that widely ranged from 0.16% to 10%.[5]

Since sonographically, a normal uterus disconnected from a normal cervix was appreciated, it was deduced that the patient has uterine isthmic atresia. With what is known of the embryogenesis of the uterus, it is difficult to speculate how this could have occurred. It is also difficult to classify this using the AFS classification (Table 1) although it most likely belongs to Class I. The case also does not seem to fit any category from the Clinical and Embryological Classification System (Table 2), the VCUAM classification (Table 3), nor the CONUTA Classification System (Table 4). It can therefore be placed under unclassified anomalies.

Due to the paucity of similar cases, information on the ideal approach to its management is wanting. The objectives are clear however; relieve her of the cyclical pelvic pain as a short-term treatment goal; and to preserve reproductive ability in the long term.

Due to the rarity of this case, only one other a similar case presenting with amenorrhea and pelvic

Table 1. AFS classification of congenital malformations of the gemale genital tract.

Class I	Hypoplasia and agenesis	(a) Vaginal, (b) cervical, (c) fundal, (d) tubal
Class II	Unicornuate	(a) Communicating, (b) noncommunicating, (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 VII	DES drug-related	

Grimbizis. Classification of female genital anomalies. Fertil Steril 2010.

Table 2. Clinical and embryological classification of patients based on the embryological origin of the different elements of the genitourinary tract.

1. Agenesis or hypoplasia of a urogenital ridge; unicornuate uterus with uterine, tubal, ovarian, and renal agenesis on the contralateral side.
2. Mesonephric anomalies with an absence of the Wolffian duct opening to the urogenital sinus and ureteral bud sprouting (and, therefore, renal agenesis). The "inductor" function of the Wolffian duct on the Mullerian duct also fails, and there is usually uterovaginal duplicity plus blind hemivagina ipsilateral with renal agenesis, clinically presented as
   (a) Large unilateral hematocolpos
   (b) Gardner's pseudocyst on the anterolateral wall of the vagina
   (c) Partial reabsorption of the intervaginal septum, seen as a "buttonhole" on the anterolateral wall of the normal vagina, which allows access to the genital organs on the renal agenesis side
   (d) Vaginal or complete cervicovaginal unilateral agenesis, ipsilateral with renal agenesis, and with [1] no communication or [2] communication between both hemiuteri (communicating uteri).
3. Isolated Müllerian anomalies affecting
   (a) Müllerian ducts: the common uterine malformations as unicornuate (generally with uterine rudimentary horn), bicornuate, septate, and didelphys uterus
   (b) Müllerian tubercle: cervicovaginal atresia and segmentary anomalies, such as transverse vaginal septum
   (c) Both Müllerian tubercle and ducts: (uni- or bilateral) Mayer-Rokitansky-Kuster-Hauser syndrome
4. Anomalies of the urogenital sinus: cloacal anomalies and others
5. Malformation combinations: Wolffian, Müllerian, and cloacal anomalies

Grimbizis. Classification of female genital anomalies. Fertil Steril 2010.

Table 3. VCUAM classification system.

Vagina (V)	0	Normal
	1	(a) Partial hymenal atresia, (b) complete hymenal atresia
	2	(a) Incomplete septate vagina <50%, (b) complete septate vagina
	3	Stenosis of the introitus
	4	Hypoplasia
	5	(a) Unilateral atresia, (b) complete atresia
	S	[1] Sinus urogenitalis (deep confluence), [2] sinus urogenitalis (middle confluence), [3] sinus urogenitalis (high confluence)
	C	Cloacae
	+	Other
	#	Unknown
Cervix (C)	0	Normal
	1	Duplex cervix
	2	(a) Unilateral atresia/aplasia, (b) unilateral atresia/aplasia
	+	Other
	#	Unknown
Uterus (U)	0	Normal
	1	(a) Arcuate, (b) septate <50% uterine cavity, (c) septate >50% uterine cavity
	2	Bicornuate
	3	Hypoplastic
	4	(a) Unilaterally rudimentary or aplastic, (b) bilaterally rudimentary or aplastic
	+	Other
	#	Unknown
Adnexa (A)	0	Normal
	1	(a) Unilateral tubal malformation, ovaries normal, (b) bilateral tubal malformation, ovaries normal
	2	(a) Unilateral hypoplasia/gonadal streak, (b) bilateral hypoplasia/gonadal streak
	3	(a) Unilateral aplasia, (b) bilateral aplasia
	+	Other
	#	Unknown
Associated malformations (M)	0	None
	R	Renal
	S	Skeleton
	C	Cardiac
	N	Neurologic
	+	Other
	#	Unknown

Grimbizis. Classification of female genital anomalies. Fertil Steril 2010.

Table 4. CONUTA classification system

	Main class Uterine anomaly	Main sub-class	Co-existent sub-class Cervical/vaginal anomaly
Class 0	Normal uterus		*Cervix*
Class I	Dysmorphic uterus	a. T-shaped b. Infantilis	C0: Normal C1: Septate
Class II	Septate uterus	a. Partial b. Complete	C2: Double 'normal' C3: Unilateral aplasia/dysplasia
Class III	Dysfused uterus (including dysfused 'septate')	a. Partial b. Complete	C4: Aplasia/dysplasia *Vagina* V0: Normal vagina
Class IV	Unilaterally formed uterus	a. Rudimentary horn with cavity (communicating or not) b. Rudimentary horn without cavity/aplasia (no horn)	V1: Longitudinal non-obstructing vaginal septum V2: Longitudinal obstructing vaginal septum V3: Transverse vaginal septum/imperforate hymen V4: Vaginal aplasia
Class V	Aplastic/dysplastic	a. Rudimentary horn with cavity (bi- or unilateral) b. Rudimentary horn without cavity (bi- or unilateral)/aplasia	
Class VI	Unclassified malformations		

Grimbizis, et al. The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. Human Reproduction, Vol.28, No.8 pp. 2032-2044, 2013.

pain was reported by Yang, et al. in 2015. Hysteroscopy was done but the cervical canal ended abruptly, after which laparoscopy was performed showing a thin stenotic junction was found between the lower segment of the uterus and the cervix. Eventual end-to-end anastomosis by hysterotomy was performed after resection of the stenosis. Eventual fertility of the patient has not been reported.[6]

Due to enhanced retrograde menstrual flow because of the outflow tract obstruction, endometriosis is an understandable sequela in these cases. Medical therapies for endometriosis include non-steroidal anti-inflammatory drugs, combined hormonal contraceptives, progestegens and gonadotrophin-releasing hormone agonist among others.[7] Due to financial constraints, the patient was started on continuous combined hormonal contraceptives during the interim where a definitive operative plan was being conceptualized.

Apart from restoring the patency through an anastomosis, concerns regarding future fertility in these cases include maintaining ideal cervical length and uterine size. Rock, et al. suggested that as long as sufficient cervical stroma of at least 2 centimeters in diameter is present; attempts to create a neocervical canal through the fibrous cord could be made. Although there are cases of successful spontaneous and assisted pregnancies after anastomosis have been reported, the overall chance of spontaneous pregnancy is reduced due to the possible stenosis of the anastomosis or the resultant endometriosis. Even after patients become pregnant, close observation should be maintained during the period of gestation because there is a high risk for scar pregnancy, miscarriage, premature delivery and uterine rupture.[8] Based on a study involving 182 cases of women with uterine anomalies who got pregnant, Heinonen, et al. described the reproductive performance of these women in general to have a fetal survival rate of 66%, a perinatal mortality of 8% and premature labor occuring in 23%.[9] It is still undetermined if vaginal delivery can be recommended, but most obstetricians would tend to choose doing a cesarean section. Most believe that an abdominal delivery would be gentler on the integrity of the anostomosis. Considering the incision done in the performance of a low segment cesarean section would likely mean cutting close to or even through the anastomosis, a classical cesarean section may be deemed to be a better option.

An attempt to preserve reproductive ability is of the utmost importance in the surgical treatment of these cases. However, when technically unfeasible, relief of the cyclical pain due to the cryptomenorrhea must be addressed at the very least. For a majority of these patients, they end up having a hysterectomy primarily or as a second operation after a failed conservative reconstructive surgery. Biologically conceiving for these women would therefore mean in-vitro fertilization and embryo transfer involving a surrogate. Acien, et al. narrated a case of spontaneous gestation at term after previous reimplantation of uterine corpus in a neovagina. Creation of a neovagina and subsequent implantation of the uterine corpus was performed in a fourteen year old complaining of primary amenorrhea and cyclic pelvic pain, fourteen years after, the patient spontaneously conceived and delivered a live newborn via cesarean section.[10] Although the report was for cervicovaginal agenesis, this gives us hope that our patient could conceive naturally.

The operation performed provided our patient relief from her cyclic pelvic pain. At present, she is regularly menstruating with no complaints of hypogastric pain.

Conclusion

A rare case of uterine isthmic atresia in a 15-year-old girl complaining of severe cyclical pelvic pain resulting from obstructed menstrual flow was presented. After thorough assessment for the presence of viable cervical tissue and appropriate endometrial function, the patient underwent end-to-end anastomosis of the uterine corpus and cervix and is currently menstruating regularly with no other symptoms.

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