CLINICAL REVIEW

Congenital Absence of the Vagina

The Mayer-Rokitansky-Kuster-Hauser Syndrome

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We describe 14 patients with congenital absence of the vagina associated with a variable abnormality of the uterus and review the literature. Associated developmental anomalies of the urinary tract and skeleton are common. As a result of the analysis of two affected families, we believe that the disorder may represent the variable manifestation of a single underlying genetic defect that can be expressed alone or in any combination of vertebral, renal, and genital abnormalities. Some affected persons may have lethal manifestations such as absence of both kidneys, and some cases may result from multifactoral causes rather than a single gene defect. Whatever the cause, the defect involves mesodermal development and the mesonephric kidney, the latter resulting in abnormalities in the paramesonephros (uterus and vagina) and in the metanephric kidney. Both nonoperative and surgical treatments are generally successful in repairing the vaginal abnormality.

THE RECOGNITION that the combination of congenital absence of the vagina and some form of abnormal or absent uterus constitutes a syndrome is principally the work of four persons. Mayer (1) described congenital absence of the vagina in 1829 as one abnormality in stillborn infants with multiple birth defects. Subsequently, Rokitansky (2) in 1838 and Küster (3) in 1910 delineated an entity in which the vagina is absent, a rudimentary, bipartite uterus is present, the ovaries are usually normal (Figure 1), and renal and skeletal anomalies are common. Hauser and colleagues (4-7) subsequently emphasized the frequency of the disorder and the spectrum of associated abnormalities. Pinsky (8) suggested that congenital absence of the vagina is a part of a symptom-complex rather than a true syndrome. However, it seems appropriate to refer to the disorder as the Mayer-Rokitansky-Küster-Hauser syndrome, although it has also been termed the Rokitansky-Küster-Hauser syndrome (9).

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The literature on the subject is extensive. At least 17 series involving some 500 cases have been reported since 1948, but most papers in English have focused on the management of the gynecologic abnormalities. Our report describes the findings in 14 cases, reviews the recent literature, and summarizes current concepts of the pathogenesis and treatment of the disorder.

Incidence

The frequency of congenital absence of the vagina is not entirely clear, incidences having been reported as varying from 1 in 4000 to 5000 female births (10, 11) to 1 in 20 000 female hospital admissions (12). If considered from the standpoint only of women presenting with primary amenorrhea, the disorder is fairly common (13). Indeed, in 538 patients from nine case series summarized by Ross and Vande Wiele (14) congenital absence of the vagina ranked second only to gonadal dysgenesis as a cause of primary amenorrhea. Furthermore, the disorder is more frequent than testicular feminization (14, 15) but less common than the associated anomalies such as congenital absence and ectopia of the kidney (16-20) and abnormalities of the vertebrae (21).

Clinical Features of the Syndrome

The principal clinical features of the Mayer-Rokitansky-Küster-Hauser syndrome are summarized in Table 1. Most patients are seen by physicians after the time of expected menarche because of primary amenorrhea and are found at physical examination to have absence or hypoplasia of the vagina. The uterus may vary from a virtually normal state, lacking only a conduit to the introitus, to the more characteristic finding of rudimentary bicornuate cords with or without a lumen. The typical anatomical findings are illustrated in Figure 1, a reproduction of the operative findings in the index case described by Rokitansky (2).

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Figure 1. Diagrammatic illustration of the genital tract of the Index Patient described by Rokitansky (2). The blind-ending introitus, replacement of the vagina and most of the uterus by fibrous tissue, and the bicornuate uterine remnants are characteristic findings. The left uterine remnant has been sectioned to show the incomplete development of a cavity. The ovaries, fallopian tubes, round ligament, and broad ligament are usually normal.

The karyotype is that of a normal 46,XX woman, and ovarian function is normal, both in regard to ovulation and endocrine function; for example, biphasic basal body temperature patterns are usual, and body development at the time of expected puberty is normal in that breast enlargement and the growth of axillary and pubic hair occur on schedule. Cyclic abdominal pain is prominent in those patients in whom a partial endometrial cavity is present. There is a frequent occurrence of renal, skeletal, and other congenital anomalies in affected patients.

The spectrum of the genital and nongenital findings in 14 patients studied here is shown in Table 2. The average age at diagnosis was 16 and varied from 10 years in one patient whose older sister was affected to 18 years. Five patients gave a history of cyclic abdominal pain. Two patients gave an initial history of family involvement (Figure 2). Patient 2 had an affected sister (Patient 3) who had been diagnosed elsewhere and who was subsequently examined by us. Patient 14, who also had severe thoracolumbar scoliosis, had a sister with scoliosis but normal cyclic menstrual periods and a maternal aunt with a double uterus. The mother of Patient 4 has severe scoliosis. In the remaining 10 patients the family history was negative. The birth order of the patients was not significant.

The average height was that of normal women, and breast development, axillary hair, and pubic hair were female in character. The introitus was normal, and in all but two the clitoris, labia majora, and labia minora were symmetrical and normal. In Patient 6 the labia majora was underdeveloped on one side, and in Patient 10 there was minimal fusion of the labia minora. The vagina was completely absent (dimple only) in four patients, and in the remainder it constituted a blind-ending pouch that varied from 1 cm to 6 cm in depth. Laparoscopy or laparotomy, or both, was done in five patients. In Patient 6 no uterine remnant was found, in three patients a bipartite uterine remnant was present, and in Patient 7 a uterus with hematometra was present. In all five the ovaries were considered normal, but in one patient a "cystic ovary" had been removed previously. In Patient 7 one tube and one ovary were removed because of extensive endometriosis.

Extragenital anomalies were common in this group. Eight patients had urinary tract abnormalities identified by intravenous pyelography. This was similar to the finding of renal abnormalities in 34% of 520 patients described in 17 series in the literature (Table 3) (5, 11, 13, 15, 22-38). The prevalence of skeletal abnormalities in our series (7 of 14) was greater ($P < 0.001$ by chi-square analysis) than that in the same published series (64 of 560 cases) summarized in Table 3. This difference is probably because skeletal surveys were obtained in most of our patients, whereas it is not clear whether such studies were done routinely in patients in other reports.

Severe cardiac abnormalities were present in two persons—tetralogy of Fallot in Patient 8 and coarctation of the aorta in Patient 7, who also had a cleft lip and esotropia. Patients 5 and 11 had the Klippel-Feil abnormality. Deafness in one ear was present in one patient, and Patient 10 had underdevelopment of the left thenar eminence. Because certain extragenital anomalies are a prominent feature of this syndrome, they will be considered in greater detail.

Extragenital Anomalies

RENAL ABNORMALITIES

The association between congenital absence of the vagina and developmental abnormalities of the urogenital system was recognized very early (2, 3), and approximately one third of patients have abnormal kidneys as delineated by intravenous pyelograms (Table 3). A detailed breakdown of the type of kidney abnormalities identified in these patients is given in Table 4. Seventy-four percent of the patients had either agenesis of one kidney or ectopia of one or both kidneys; another 5% had solitary fused kidneys of the horseshoe type. The remaining defects include abnormalities of the collecting system (13%), malfunctioning kidneys of uncertain cause (5%), or malrotation (5%). In addition, there have been a number of case reports of the association of congenital absence of the vagina with solitary ectopic kidneys located in the pelvis (15, 39-46).

The functional significance of the kidney abnormalities is uncertain, although as would be expected many instances of pyelonephritis have been noted in the structurally abnormal kidneys (20), including one patient in our series. Renal agenesis and ectopic kidneys are common in this disorder; this means that special care should be taken to evaluate the kidneys before any operative procedures in the pelvis.

Table 1. Principal Clinical Features of the Mayer-Rokitansky-Küster-Hauser Sydrome

1. Primary amenorrhea associated with congenital absence of the vagina
2. 46,XX karyotype
3. Uterus that varies from anatomically complete to rudimentary bicornuate cords to complete absence
4. Normal ovarian function and normal ovulation
5. Normal female breast development, body proportions, and body hair
6. Frequent association of renal, skeletal, and other congenital anomalies

Table 2. Clinical Features in 14 Patients With Congenital Absence of the Vagina

Patient	Age		History		Findings		Laparoscopy or Laparotomy for Diagnosis	Karyotype
	Diagnosis	Examination	Cyclic Abdominal Pain	Family History	Height	Pelvic Examination (Initial)		
	yrs				*cm*			
1	16	24	None	Negative	168	Blind-ending vagina*	None	46, XX
2	10	22	None	Affected sister (Patient 3)	170	Blind-ending vagina*	Age 21; laparoscopy; no uterus seen	46, XX (tandem satellites #14)
3	12	38	Yes	Affected sister (Patient 2)	167	Blind-ending vagina*	Age 20; bipartite uterus removed	
4	16	16	Yes	Mother with scoliosis	170	Vagina represented by dimple only	None	46, XX
5	16	27	None	Negative	154	Blind-ending 3-cm vagina	Age 19; "nubbin" of uterus removed	46, XX (prominent short arm #15)
6	13	23	None	Negative	157	Blind-ending 1-cm vagina; atrophied right labia majora and minora	No uterus remnant on laparotomy	46, XX
7	16	16	Yes	Negative	162	Vagina represented by dimple only	Small uterus attached to artificial vagina	46, XX
8	16	17	Yes	Negative	159	Blind-ending vagina*	None	46, XX (D chromosome had prominent short arm)
9	18	37	None	Negative	159	Blind-ending vagina*	None	46, XX
10	17	25	None	Negative	154	No vaginal opening and some labia minora fusion	None	46, XX
11	18	27	None	Negative	147	4-cm Blind-ending vagina	None	46, XX
12	17	18	Yes	Negative	157	Vagina represented by dimple only	None	46, XX
13	15	15	None	Negative	157	Blind-ending 1-cm vagina	None	46, XX
14	17	18	None	Sister with scoliosis; maternal aunt with bicornuate uterus	159	Blind-ending 4-cm vagina	None	46, XX

* Patient not seen by us until after start of therapy; initial length of vagina not documented.

SKELETAL ABNORMALITIES

Associated skeletal abnormalities were also recognized in the initial descriptions of the disease (2, 3). The overall incidence of skeletal abnormalities in 574 cases was 12% (Table 3), and the breakdown of these abnormalities is summarized in Table 5. Of the various types of skeletal involvement, two thirds involve the spine, and limb and rib abnormalities account for the majority of the remaining defects. Both the common occurrence and the spectrum of the spinal abnormalities have been described by Turunen and Unnérus (26), who identified 25 patients with skeletal involvement in a series of some 200 cases of congenital aplasia of the vagina. The specific abnormalities included wedge vertebrae, fusions, rudimentary vertebral bodies and

Table 2. (Continued)

Skeletal Abnormalities	Urinary Tract Abnormalities	Other	Treatment		Patient
			Medical (Age/Result)	Surgical (Age/Result)	
None	None	Sonography: 2- × 3-cm mass in region of uterus	Age 21; adequate intercourse with 4-cm vagina		1
Mild lumbar scoliosis	Ptosis of right kidney	None	Age 14; adequate intercourse with 6-cm vagina		2
None	Hydronephrosis			Age 20; two surgical reconstructions with adequate intercourse now	3
None	None	Sonography: no uterus detected	Age 16; course of treatment incomplete		4
Severe thoracolumbar scoliosis and failure of segmentation; Klippel-Feil deformity; short left 5th metacarpal	None	Deafness in left ear; bilateral salpingo-oophorectomy for "ovarian cysts"		Age 23; with good functional result	5
Severe thoracolumbar scoliosis and spina bifida occulta	Deformity: one upper pole calyx on left		Age 20; satisfactory intercourse		6
None	Small right kidney	Cleft lip, esotropia, multiple aortic coarctations; sonography: hematometra		Age 16; with repeat due to fistula; now satisfactory with connection to uterus	7
Sacralization L5 with transitional vertebrae	Congenital absence of right kidney	Age 7; Tetralogy of Fallot repaired	Age 17; course of treatment incomplete		8
None	None			Age 24; with 3-cm depth now	9
Lumbarization of S1 vertebrae, mild scoliosis; mild scoliosis at L2-L3	Ectopic left kidney with sacral location	Left thenar eminence loss	Age 21;10-cm depth now		10
Failure of segmentation of C3 and C4, thoracic scoliosis; Klippel-Feil deformity	None		Age 24; now 10-cm depth		11
None	None	Systolic murmur, cause uncertain	Age 18; satisfactory result		12
None	Congenital absence of left kidney	None	Age 15; course of treatment incomplete		13
Severe thoracolumbar scoliosis	Congenital absence of left kidney	None	Age 18; course of treatment incomplete		14

other asymmetry, and supernumerary vertebrae (26). These spinal abnormalities are similar in type and in distribution to those reported in the population at large (21).

The frequency of the Klippel-Feil abnormalities in the case series summarized in Tables 3 and 5 was low (3 in 46 patients with skeletal involvement). However, there are a number of individual reports in the literature on the association of congenital absence of the vagina with the Klippel-Feil syndrome (congenital fusion of the cervical spine, short neck, low posterior hairline, and painless limitation of cervical movement) (35, 47-50), and two patients in our series have this abnormality. There is also a known association between the Klippel-Feil abnormality and malformations of the kidney (35, 48, 50), but the

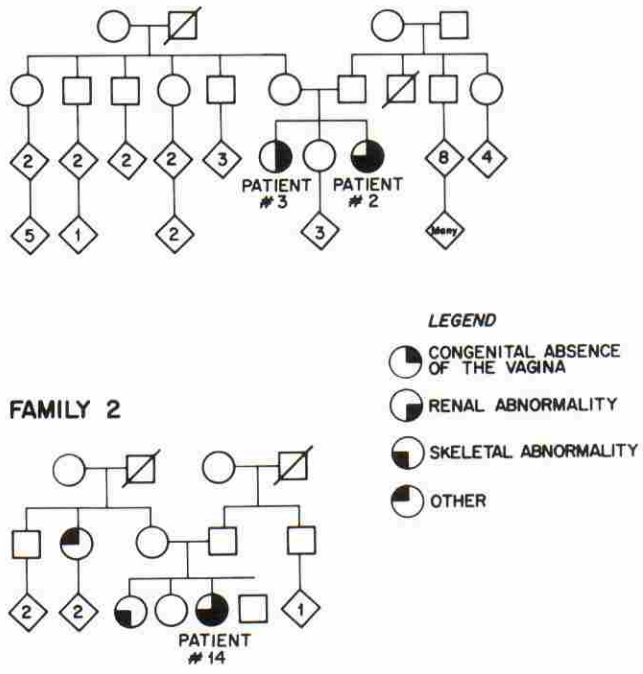

Figure 2. Pedigrees of two families in the present series with absence of the vagina.

frequency of absent vagina or renal abnormalities, or both, in large series of patients with Klippel-Feil is uncertain (51).

An association is believed to exist between defects of the urogenital system and congenital abnormalities of the spine (20). Some patients in our series had involvement of vagina and kidney without involvement of the spine, and others had involvement of spine and vagina with normal kidneys. Two persons with involvement of spine and vagina (Patients 14 and 4) had family members with spinal abnormalities but normal vagina and uterus. These associations suggest the possibility, supported by embryologic considerations (*see below*), that involvement of the spine, urogenital tract, and vagina may be a variable manifestation of a common defect.

OTHER ABNORMALITIES

Various abnormalities of the hand have been described, including syndactyly (25), absence of a digit (52), and hypoplasia of the thenar eminence (38). Although inguinal and femoral hernias have been described, some of which contain ovaries, fallopian tubes, and uterine remnants (53-56), hernias are less common in this disorder than in the testicular feminization syndrome (7). Associated congenital heart lesions have also been described (5, 13, 24, 29, 33, 38) and were found in two of our patients, but it is not clear that such involvement is specific or more frequent than in association with other congenital birth defects. In contrast to certain other syndromes involving the urinary tract, deafness has been reported only rarely (33, 47, 57), including one instance in our series (Table 2). Various other abnormalities have also been observed rarely, such as cleft palate (25), situs inversus (35), and malrotation of the bowel (5) (Table 3).

Endocrinology

Because of the occasional observation of corpora lutea in the ovaries at laparotomy (13, 58) and documentation of ovulatory peaks of plasma luteinizing hormone (LH) (59), it generally has been assumed that ovarian function is normal. Indeed, the fact that successful pregnancies have been reported after vaginal surgery in patients who had normal uteri (60-62) indicates that ovarian function

Table 3. Prevalence of Nongenital Abnormalities in Patients With Congenital Absence of the Vagina

Series	Reference (Year)	Urinary Tract Abnormalities	Skeletal Abnormalities	Congenital Heart Disease	Inguinal Hernia	Other Abnormalities
		← *no./total no.* →				
1	22 (1948); 11 (1949); 23 (1953); 24 (1968)	49/121	6/100		10/100	
2	25 (1957); 26 (1967)	21/73	25/200			
3	27 (1957)	5/19	2/19			
4	28 (1957)	8/17				
5	29 (1957)	9/71	3/71	1/71	1/71	
6	30 (1958); 31 (1958)	4/11	1/11			
7	5 (1961)	3/21	2/21	1/21	4/21	One incompletely turned mesocolon
8	32 (1966)	11/23	4/23			
9	33 (1966)	3/12	1/12	1/12	1/12	One deafness, unilateral
10	34 (1966)	12/19				
11	35 (1968)	5/12	4/12		1/12	One situs inversus
12	24 Discussion (1968)	10/17	4/17	1/17		
13	36 (1970)	7/14	4/14			
14	13 (1970)	3/15		1/18		
15	37 (1971)	3/7	1/10			
16	38 (1972)	2/32	4/32	1/32		One atrophy of thenar eminence
17	15 (1975)	17/36	3/18	1/39		
18	Present series	8/14	7/14	3/14	0/14	One atrophy of thenar eminence; One deafness
Total		180/534 (34%)	71/574 (12%)	10/224 (4%)	17/230 (7%)	

Table 4. Classification of 164 Urologic Abnormalities in 162 Patients With Renal Involvement*

	no.	*%*
1. Ectopic kidney	71	43
With other kidney normal	49	30
With other kidney absent	20	12
With other kidney ectopic	2	1
2. Agenesis of kidney	70	43
With other kidney in normal position	50	31
With other kidney ectopic	20	12
3. Abnormalities of the renal pelvis and/or ureters	19	12
4. Solitary fused kidney	8	5
5. Malfunctioning or atrophic kidneys	8	5
6. Malrotation	7	4
7. Prior nephrectomy (unknown reason)	1	1

* Some patients had more than one abnormality.

is normal in some patients. Recent detailed endocrinologic studies support this view. Brown, Kellar, and Matthew (58) demonstrated cyclical ovarian function in three patients with congenital absence of the vagina, as assessed by urinary estrogen measurements. Fraser and colleagues (63) subsequently assessed ovarian function in two affected women by measuring total estrogens, pregnanediol, LH, and follicle-stimulating hormone (FSH) in urine every day for 61 and 88 days, respectively; the patterns of hormone excretion were within normal limits, with cycle lengths varying from 30 to 34 days. D'Alberton and associates (64) studied pituitary-ovarian relation in a 26-year-old patient by measuring plasma LH, FSH, progesterone, and estradiol for a 30-day period; cyclic variations of pituitary gonadotropins and gonadal steroids in plasma were similar to those in women with normal menstrual cycles, indicating normal ovulation and normal life span of the corpus luteum. Because ovarian function is generally normal, the significance, if any, of the reports that 16 of 21 patients in the series of Hauser and Schreiner (5) and two of 14 patients described by Papp and associates (36) had polycystic ovaries is not clear.

Cytogenetics and Familial Occurrence

In several series, the karyotype of affected patients has been that of normal 46,XX women (13, 33, 36, 65). However, associated chromosomal abnormalities have been reported, including XX/XO mosaicism (66), an abnormality of the short arm of one G-group chromosome (49), and 47,XXX/46,XX mosaicism (67). All of our patients had 46,XX karyotypes, but the karyotypes of three patients had atypical features that probably represent normal variations. Patient 2 had tandem satellites on chromosome 14, Patient 5 had a prominent short arm of chromosome 15, and Patient 8 had a prominent short arm of a D-group chromosome.

The vast majority of cases have been assumed to be sporadic in nature. Indeed, Bryan, Nigro, and Counseller (11) reported that only one of 100 patients had a history of other family members with absence of the vagina (11), and Turunen and Unnérus (26) found only one positive family history in more than 200 cases in Finland. However, there are now several well-documented instances of familial occurrence of vaginal agenesis in which the diagnosis appears to be unequivocal. Anger, Hemet, and Ensel (68) described a family in which three sisters had congenital absence of the vagina; abnormalities of the spine and kidneys were documented in only one of the three. Jones and Mermut (69) reported a second family in which congenital absence of the vagina unassociated with other described anomalies occurred in two siblings. A third family has been described by Winter and colleagues (57) in which vaginal agenesis occurred as part of a more complicated familial syndrome involving the kidneys and the middle ear.

Our series includes another instance of congenital absence of the vagina in siblings (Figure 2, Family 1). In a second family (Figure 2, Family 2), the index-case patient had congentital absence of the kidney, congenital absence of the vagina, and severe thoracolumbar scoliosis, whereas a sister had scoliosis but a normal vagina, uterus, and kidneys, and a maternal aunt had a double uterus. Thus, in the familial cases variable expressivity of the defect seems to be common. This family, together with that of Winter and coworkers (57), raises the interesting possibility that the variability of expression might include other abnormalities of the genital tract such as a double uterus (70, 71) and instances in which skeletal abnormalities only could be present. A third patient reported that her mother has severe scoliosis, but this family was not available for study.

The finding of occasional familial occurrence is consistent with several different interpretations. First, some cases may be due to a hereditary abnormality, whereas the remainder are the result of some other type of developmental defect. Second, all cases may result from a mutant gene, but, due to natural selection against the transmission of the gene, familial cases are unusual. Third, if congenital absence of the vagina can represent only one manifestation of a variably expressed genetic defect, ascertainment may not be adequate in most instances, so that the real frequency of familial involvement has been underestimated.

Can additional anatomical defects result from the same

Table 5. Classification of 70 Skeletal Abnormalities in 46 Patients With Skeletal Involvement*

	no.	*%*
1. Spinal abnormalities	48	68
Scoliosis (mild to severe)	12	17
Spina bifida	9	13
Sacralization of L5 or lumbarization S1	8	11
Failure of segmentation of vertebrae (other than L5 or S1)	5	7
Hemivertebrae	2	3
Klippel-Feil deformity	3	4
"Butterfly" vertebrae	1	1
Undefined spine abnormalities	8	11
2. Limb abnormalities	10	14
Malformed arm or leg	6	9
Syndactyly	3	4
Hip dislocation	1	1
3. Other abnormalities	12	17
Rib deformity or extra ribs	7	10
Sprengel's deformity of scapula	1	1
Cleft palate	1	1
Torticollis	1	1
Asynclitism of pelvis	1	1
Pectus excavatum	1	1

* Some patients had more than one abnormality.

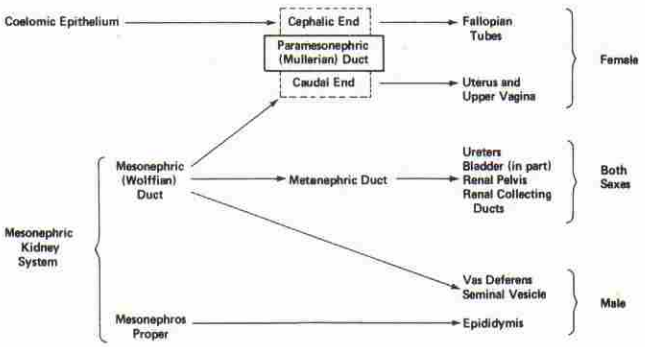

Figure 3. Schematic diagram of the role of the mesonephric kidney system and coelomic epithelium in the development of the normal urogenital tract.

mutant gene? Interestingly, in bilateral renal aplasia the most frequent associated anomalies are absence of the uterus and vagina with normal fallopian tubes or absence of the vas, epididymis, and seminal vesicles (72); bilateral and unilateral renal aplasia can occur in the same family (57, 72); and a third of infants with congenital absence of one kidney also have abnormalities of the genital tract (16). Thus, it is conceivable that some individuals with the Mayer-Rokitansky-Küster-Hauser abnormality may not survive because of a lethal manifestation of the gene such as absence of both kidneys. It is also possible that the analogous syndrome in men is congenital absence of the vas deferens (73-77), a disorder that is also associated with a high frequency of congenital absence of the kidneys (78). Although no family has yet been reported in which both men and women are affected, these two syndromes might have a unitary origin. Family histories of patients with congenital absence of the vagina should be probed for instances of isolated skeletal and renal abnormalities, for spontaneous abortions that might result from congenital absence of both kidneys, and for involvement of male relatives. It is possible that the discordance of vaginal agenesis in identical twins is the result of variable manifestations of an underlying genetic defect rather than to a nongenetic cause for the abnormality (79).

Embryogenesis

The fundamental issue is whether the developmental abnormalities of the genital tract, the urinary system, and the skeleton can be explained by some common embryonic defect. The female internal genitalia, like the male internal accessory organs of reproduction and the ureters, bladder, and renal pelvis of both sexes, are derived ultimately from the embryonic mesonephric kidney system (80, 81). This developmental sequence is summarized schematically in Figure 3. At approximately 7 mm to 8 mm (5 weeks), the mesonephric system in the human embryo consists of a mesonephric kidney (mesonephros proper) and a mesonephric or Wolffian duct that connects the mesonephric kidney with the urogenital sinus. The Wolffian duct is the anlage of the ureteric bud that will eventually provide the excretory ducts for the final (metanephric) kidney in both sexes, of Gartner's duct in women, and of the vas deferens and seminal vesicles in men. At approximately 10 mm of development in the embryos of both sexes, the development of the paramesonephric or Müllerian duct begins. The origin of the Müllerian duct, which is the anlage of the uterus and vagina (in part), has been studied in considerable detail by Gruenwald (82-85). The duct has two components—a cephalic or anterior portion that is derived from the coelomic epithelium and a caudal end that is probably derived from the Wolffian duct (82, 85). Its formation begins at 10 mm in both sexes, when an evagination appears in the coelomic epithelium just lateral to the mesonephros proper (86). This evagination develops into a tubular structure, and the caudal end becomes so intimately connected with the Wolffian duct that no basement membrane separates their epithelia. Whether the Müllerian duct "splits off" from the Wolffian duct in its later caudal development into an independent duct system that empties into the urogenital sinus or whether the Wolffian duct simply acts as a "guide" for subsequent Müllerian duct development is uncertain. However, Müllerian duct development cannot take place in the absence of the Wolffian duct.

Although the cephalic end of the Müllerian duct is the anlage of the fallopian tubes and the caudal portions of the Müllerian duct fuse (in humans) to form the uterus, the exact embryogenesis of the vagina is not so clear. A major uncertainty has existed as to the magnitude of the contributions of the urogenital sinus and the Müllerian duct to vaginal development (87-89). It is established that the fusion of the caudal end of the Müllerian duct with the urogenital sinus (at about 30-mm development) is followed by a major epithelial proliferation and elongation that results in the formation of an initially solid vaginal plate. The vaginal plate in turn canalizes beginning at the 150-mm stage to form the vagina proper (87). Bulmer (89) has concluded that the cellular origin of the vaginal plate is principally from the urogenital sinus, but interaction of both Müllerian duct and urogenital sinus is probably essential for normal vaginal development. The Wolffian duct is thought to play no role in the embryogenesis of the vagina (89, 90). The forces that regulate the development of a normal vagina and uterus in the female embryo are unclear, but it is generally believed that hormonal secretions of the ovary are not involved in this process (91).

The most common finding in the Mayer-Rokitansky-Küster-Hauser syndrome consists of normal ovaries and fallopian tubes with only solid nubbins for uterine horns and no vagina whatsoever. This is the exact lesion that would be predicted if the initial phase of Müllerian duct development, namely the formation of its cephalic end from the coelomic epithelium, were normal but the subsequent development along the Wolffian duct were impaired so that the uterine and vaginal segments of the Müllerian duct are absent or incomplete. Since the Wolffian duct is also the anlage of the metanephric duct, both the urinary tract abnormalities (principally renal absence and ectopia) and the defects in the uterus and vagina could result from a single abnormality in the Wolffian duct. Furthermore, one would also predict that defects in the Wolffian ducts in male embryos could result in the typical syndrome of congenital absence of the vas deferens with or without renal disease (73-78).

The skeletal abnormalities can also be fitted into this overall schema. The skeleton, like the mesonephros, is derived from mesoderm. At approximately the same stage of development that has been pinpointed for the embryonic defect in the urogenital tract (10 mm to 11 mm), vertebrae develop from adjacent mesodermal cell concentrations at about the same somite levels as those of the mesonephros (80). It seems reasonable to suggest that some defect in the organization of the mesoderm in these somites could cause the skeletal abnormalities as well as defective mesonephric development and the subsequent abnormalities in the kidneys and genitalia. The molecular nature of a defect in mesoderm that could result in such a spectrum of abnormalities is, of course, unknown.

It is also possible that many instances of this birth defect result from nongenetic causes that have not yet been identified. For example, the administration of oxidized linoleic acid to pregnant rats causes several malformations of the urogenital tract in the offspring, including absence of the vagina (92).

Diagnosis

The fundamental criteria for the diagnosis of the syndrome are outlined in Table 1 and include primary amenorrhea and a 46,XX karyotype, absence or hypoplasia of the vagina, and evidence of ovulation. Because of the clinical similarity to some types of hereditary male pseudohermaphroditism, it is mandatory to establish that the karyotype is that of a normal woman. Analysis of the karyotype will also identify most instances of gonadal dysgenesis in which the phenotype overlaps that of the Mayer-Rokitansky-Küster-Hauser syndrome, particulary those that are ascertained before puberty (93). In addition to establishing normal ovulatory biphasic body temperature patterns, or cyclic progesterone production, or both, and normal female karyotype, the urinary tract should also be evaluated, as the presence of a single pelvic kidney may influence the means chosen for repair of the vagina (11, 41).

In our series, laparotomy was not done on all patients. Laparoscopy (Patient 2 and Reference 94) and pelvic pneumography (95, 96) have been used to delineate the exact anatomical features of the uterus in some patients. The nature of the uterine remnant in others can be defined by ultrasonographic techniques (97). Sonograms that show three types of intra-abdominal abnormalities in this disorder (complete absence of a uterine remnant, presence of solid uterine remnants, and presence of a uterus with cavity and hematometra) are presented in Figure 4.

Treatment

Vaginal agenesis can be treated by surgical or nonsurgical means. Steinmetz (98) has reviewed the early history of surgical construction of the vagina, including the use of skin grafts, loops of bowel, and simple reconstructions with the use of molds. Most modern surgical series in this country have used a variation (99) of the procedure of McIndoe and Banister (100), who modified prior methods using split-thickness skin grafts and used instead a single, large thigh graft around a solid rubber mold for the creation of an artificial vagina. In 1959 McIndoe (101) reviewed his own experience with 105 patients and reported that most patients had an ultimately satisfactory outcome. A similar success was noted by Thompson, Wharton, and TeLinde (28) in 32 patients treated by the McIndoe operation who were followed-up for more than a year. Cali and Pratt (24) summarized the results in 123 patients treated with the procedure; seven had major complications such as fistulae or hemorrhage, and 10 required secondary operations. In those followed-up for 10 years or more, greater than half were found to have some contraction of the vaginal outlet, but more than 90% reported good-to-excellent sexual function. Thus, any evaluation of treatment must distinguish between anatomical and functional criteria.

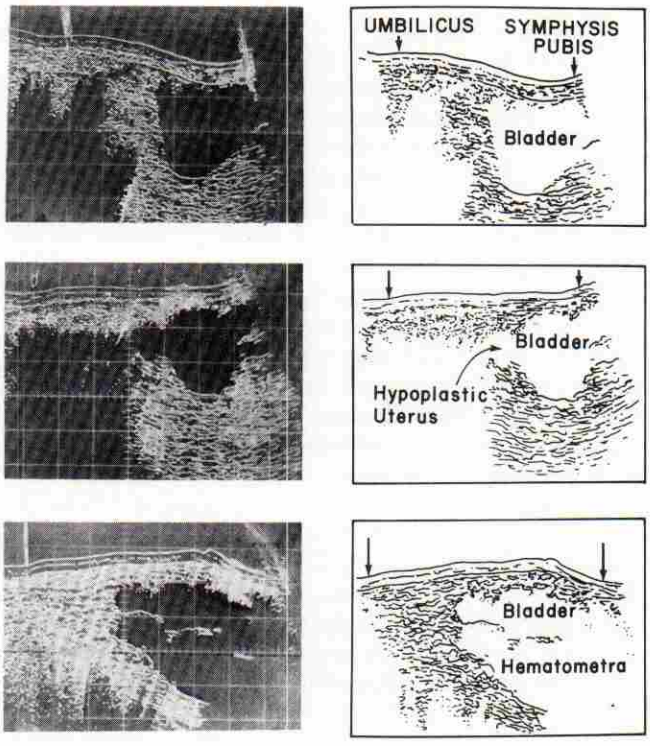

Figure 4. Results of sonographic examinations in three patients with congenital absence of the vagina demonstrating the variability of the uterine remnant. Representative midline longitudinal cross sections are shown. **Top.** Patient 4, in whom no uterine remnant was demonstrable; **Middle.** Patient 1, in whom solid uterine remnant was present; **Bottom.** Patient 7, in whom the uterine remnant contained a hematometra.

In a complete departure from the surgical approach, Frank (102) in 1938 described a simple nonoperative method for the development of vaginal depth by repeated application of pressure against the vaginal dimple with a simple dilator. Steinmetz (98) and Marshall (103) have emphasized the efficacy, safety, and simplicity of this nonoperative procedure. Wabreck and associates (37) found that there were essentially no complications and that functionally satisfactory results were obtained in more than 90% of 20 cases of vaginal agenesis treated by the Frank nonoperative method. Because of the overall complication rate of 5% to 10% in all surgical series, the nonoperative treatment should probably be tried routinely. Continued coitus or instrumental dilatation is probably essential for

maintaining the neovagina formed either by the nonoperative or surgical methods. D'Alberton and Santi (104) have suggested that repeated intercourse alone may lead to a functionally adequate vagina if a small dimple is present initially, but the possibility that urethral coitus might occur in such instances should be kept in mind (105).

Operative treatment is definitely indicated in those patients in whom a well-formed uterus is present and the possibility of fertility exists. These persons are usually identified shortly after expected menarche because of the presence of hematometra or retrograde menstruation, or both. In several instances construction of an artificial vagina in such patients has been followed by conception and delivery (60-62). Patient 7 in our series was treated in this manner with the expectation that she might wish to become pregnant in the future.

Interestingly, the artificial vagina acquires almost all of the characteristics of normal vaginal epithelium, including a stratified squamous epithelium of the mucous membrane type with glycogen production and cornification that varies normally throughout the cycle of estrogen production (106-111). This seems to be true also for the epithelium formed by ingrowth after the Frank procedure (109).

Associated Medical Problems

Secondary renal disease is frequent in subjects with developmental abnormalities of the genitourinary tract (19, 20), and, as would be expected, pyelonephritis is a common occurrence in subjects with congenital absence of the uterus. However, to date no specific effect of congenital absence of the uterus on life span and no primary abnormalities in renal function have been documented. The most serious of the renal abnormalities (compatible with life) is the solitary pelvic kidney, and intravenous pyelography is indicated before doing any pelvic surgery.

Various malignancies have been described in the genital tract. These include ovarian carcinoma (25, 111-113), one instance of adenocarcinoma of the cervix in a patient with congenital absence of the vagina and a normal uterus (114), and two cases of carcinoma of the artificial vagina after surgical reconstruction (115, 116). Because the disorder is relatively common, it is possible that there is no increased incidence of malignancy.

Perhaps the most common genital complication is that related to retrograde menstruation in those patients with a well-developed uterus; in some instances surgical removal is necessary, and in other instances an artificial vagina may be connected successfully to the uterus.

Kaplan (117, 118) has described the psychologic problems associated with congenital absence of the vagina and has emphasized that disturbances of body image and self-esteem are common, often associated with reactive depression. With adequate treatment and supportive care, however, most patients are able to have adequate sexual relations and to function effectively as well-adjusted women (109, 117-119).

Conclusions

Congenital absence of the vagina is a common cause of primary amenorrhea. Our series of such patients is notable in two regards. First, although the prevalence of associated developmental abnormalities of the urinary tract (8 of 14 patients, is similar to that described previously, the finding of skeletal abnormalities (primarily of the spine) in 7 of the 14 patients is greater than the 12% average incidence observed in previous reports ($P < 0.001$ by chi-square analysis). We attribute this difference to a more uniform evaluation of the patients in our study. Second, the family histories were informative in two instances. In one family, two siblings had congenital absence of the vagina and minor kidney involvement, and one of the two also had skeletal abnormalities. In the second family, one individual had congenital absence of the uterus, congenital absence of the kidney, and severe thoracolumbar scoliosis, whereas a sister had scoliosis but normal kidneys and vagina. These findings suggest that the disorder may represent the variable manifestation of a single underlying genetic defect that can present itself as any combination of vertebral, renal, and genital abnormalities. If this is the case, some affected persons may have lethal manifestations of the defect such as absence of both kidneys, and in men the phenotype may be expressed as congenital absence of the vas deferens. Other cases may result from multifactoral causes rather than a single gene defect.

Whatever the underlying cause, however, the defect probably results from an abnormality in mesodermal development early in embryogenesis (probably around the 10-mm stage) that causes defects in the development of the vertebrae and the mesonephric kidney. The abnormality of the mesonephros would cause abnormalities both in the paramesonephros (uterus and vagina) and in the metanephric kidney system.

Two forms of treatment are available, a nonoperative technique and surgical correction, both of which are associated with a high success rate.

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Appendix

PATIENT SUMMARIES

Patient 1: This 24-year-old white woman noted the onset of breast and pubic hair development at about age 12 or 13 and became concerned about the absence of menstruation at age 16. There was no cyclic abdominal pain. Family history was unremarkable. Physical examination was normal except for a blind-ending vagina. Two 2-cm masses were felt in the area of the uterine remnants. Nonoperative dilatation was begun at age 21 and resulted in a satisfactory functional vagina that is now 4-cm deep. Karyotype was 46,XX, and skeletal survey and intravenous pyelogram had normal findings. A 2-cm by 3-cm solid structure in the region of the uterus was demonstrated by sonography (Figure 4, *middle*).

Patient 2: A 22-year-old white woman was evaluated initially at age 10 because of a history of primary amenorrhea due to congenital absence of the vagina in her older sister (Figure 2). Breast and pubic hair development began at age 12. There was no cyclic abdominal pain. Curvature of the spine was noted at age 12. Physical examination was normal except for a blind-ending vagina. Dilatation was begun at age 14 and resulted in a satisfactory vagina now 6-cm deep. No uterus was visualized at laparoscopy. Karyotype was 46,XX with tandem satellites of chromosome 14. A mild lumbar scoliosis and ptosis of the right kidney were identified by X-ray examination. Cyclic ovarian function was demonstrated by repeated measurements of gonadotropins, estrogens, and progesterone.

Patient 3: The 38-year-old sister of Patient 2 noted cyclic abdominal pain with primary amenorrhea at age 12 associated with normal breast and pubic hair development. A blind-ending, shallow vagina was identified at that time. Vaginal reconstruction was performed at age 20, and a small bipartite uterus with a rudimentary endometrial cavity in one horn was removed. The reconstruction had to be repeated within a year, but she now has satisfactory intercourse. Mild left hydronephrosis was identified by intravenous pyelography.

Patient 4: This 16-year-old black girl noticed the onset of breast and pubic hair development at age 11 and became concerned about amenorrhea at age 16. Mild cyclic abdominal pain had been present for several months. Severe scoliosis was present in her mother. Physical examination was normal except that the vagina was represented only by a dimple. No uterus was palpable, and no evidence for a uterus was found by sonography (Figure 4, *top*). Karyotype was 46,XX. Intravenous pyelogram and skeletal films had normal findings. Normal cyclic ovarian function was demonstrated by analysis of serial plasma progesterone levels. Nonoperative treatment by the Frank technique has been started recently.

Patient 5: This 27-year-old white woman noted the onset of breast and pubic hair development at age 11 and became concerned about amenorrhea at age 16. There was no cyclical abdominal pain. However, laparotomy was done at age 17 for a single episode of severe abdominal pain, and no uterus could be identified. At age 19 a bilateral salpingo-oophorectomy was done at another hospital for "ovarian cysts" (record not available). As a child she was noted to have severe hearing deficit in the left ear not associated with infection. During adolescence asymptomatic scoliosis of the thoracic and lumbar regions was noted. The initial vaginal depth was 3 cm. At age 23 a functionally successful vaginal reconstruction was performed with a skin graft. Family history was negative. Since removal of the ovaries she has received estrogen replacement. Marked obesity, obvious thoracolumbar scoliosis, and a somewhat short neck with a painless decrease in range of motion of the head laterally were noted at physical examination at the time of referral here. Karyotype was 46,XX with enlargement of the short arms of chromosome 15. Block vertebrae with failure of segmentation were present throughout the cervical spine from C2 to C7, more marked between C2 and C3 and between C5 and C6. There was also failure of segmentation in the upper thoracic spine, especially T2-T3, which was difficult to evaluate due to associated scoliosis with convexity to the right. An associated mild scoliosis of the lower cervical vertebrae with convexity to the left was also present. The left fifth metacarpal was short. Intravenous pyelogram findings were normal.

Patient 6: This 23-year-old white woman noticed breast and pubic hair development around age 13 and became concerned about amenorrhea about a year later. There was no cyclic abdominal pain. At age 13 she began wearing a back brace for severe thoracolumbar scoliosis. She wore the brace for about 2½ years and has been subsequently asymptomatic. At age 20 she underwent what was described as hymenotomy and exploration of the pelvic floor at another hospital. The vagina was found to be 1-cm deep and blind-ending, with no upper vagina or uterus discovered on dissection. Marked thoracolumbar scoliosis, a slightly atrophied right labia majora and minora, and a blind-ending vagina were noted at physical examination at the time of referral. Karyotype was 46,XX. Deformity of one upper pole calyx of the kidney was identified by intravenous pyelography, and severe scoliosis and spina bifida occulta were seen at X ray. Normal ovarian cycles were demonstrated by measurement of serial plasma progesterones. Dilatation was begun with pressure leading to a satisfactory functional vagina.

Patient 7: A 16-year-old white girl noticed the onset of breast and pubic hair development about age 14. At age 16 severe cyclic abdominal pain began, and no menses occurred. Past medical history was significant in that she had repair of cleft lip at 3 months, correction of left esotropia at 6 years, and repairs of coarctations of the thoracic aorta at 7 years and of the abdominal aorta at 15 years. The abdominal coarctation was at the level of the right renal artery and was associated with hypertension that was not relieved by repair of the vessel. Family history was negative. Blood pressure was 180/90 mm Hg, and arterial narrowing was noted on funduscopic examination. Pelvic examination was unremarkable except for a dilated urethra, a vaginal dimple only, and a midline tender mass the size of a 12-week gestation at rectal examination. The presence of a fluid-filled mass in the area of the uterus was confirmed by sonography (Figure 4, *bottom*). Karyotype was 46,XX. Ovulation was documented by the finding of a random plasma progesterone of 16 ng/ml. A small right kidney was noted on the intravenous pyelogram. Vaginoplasty was performed, the hematometra was evacuated, one tube and one ovary were removed because of endometriosis, and the artificial vagina was attached to the uterine cavity. However, a rectovaginal fistula developed, and the operation was repeated using an abdominal approach and skin graft. Except for a small vesicovaginal fistula that is healing, the result is satisfactory because cyclic menstruation is occurring.

Patient 8: A 17-year-old white girl noticed breast and pubic hair development between ages 12 and 14. She also noticed mild cyclic abdominal pain commencing around age 13. She became concerned about amenorrhea at age 16 and was referred here. At age 7 a tetralogy of Fallot had been repaired. Family history was negative. There was a grade II/VI systolic ejection murmur over the left sternal border, and a blind-ending vagina was found at physical examination. Karyotype was 46,XX with prominent short arms of a D-group chromosome. Absence of the right kidney and sacralization of L5 with a transitional vertebrae were seen at X-ray examination. Treatment by the nonoperative pressure method has been started.

Patient 9: This 37-year-old white woman became concerned about amenorrhea at age 18. There was no cyclic abdominal pain. At age 24 she had vaginoplasty without grafting. Family history was negative. Examination here was normal except for obesity and a 3-cm blind-ending vagina and no palpable uterus. Karyotype was 46,XX. Skeletal X rays and intravenous pyelograms were normal. She reports that intercourse is satisfactory.

Patient 10: This 25-year-old white woman noticed breast and pubic hair development at age 13. At age 17 she became concerned about amenorrhea. There was no cyclic abdominal pain. Family history was negative. Examination was unremarkable except for no vaginal opening and slight fusion of the labia minora. There was hypoplasia of the thenar eminence of the left hand. Treatment with dilatation was begun at age 18 and resulted in a vaginal depth of 10 cm. After starting regular intercourse, dilatation was discontinued without shrinkage. Karyotype was 46,XX. An ectopic left kidney with a sacral location was identified by intravenous pyelography. No bony abnormality was present in the hands, but localized mild rotoscoliosis of the L2-L3 level and partial lumbarization of S1 as a transitional lumbosacral vertebra were identified by a skeletal survey.

Patient 11: This 27-year-old white woman noticed breast and pubic hair development between ages 10 and 12 and became concerned about amenorrhea at age 18. There was no cyclic abdominal pain. Family history was negative. Physical examination was normal except for a short neck with decreased lateral range of motion and a 4-cm blind-ending vagina. Nonoperative pressure dilatation starting at age 24 resulted in a

vagina that was 10-cm deep, and satisfactory intercourse was reported. Karyotype was 46,XX. Intravenous pyelogram was within normal limits. Failure of segmentation of C3-C4 and scoliosis of the upper thoracic spine with convexity to the left and compensatory scoliosis below with convexity to the right were noted on skeletal survey.

Patient 12: This 22-year-old white woman noticed breast and pubic hair development at age 12 and became concerned about amenorrhea at age 17. There was cyclic abdominal pain. She had been told in the past that she had a "congenital heart defect." She had polio as a child leading to some atrophy of the right leg. Family history was negative. A systolic murmur radiating to the neck, a vagina represented only by a dimple, and no palpable uterus were found at physical examination. The right leg was one inch shorter than the left. Dilatation was begun at age 18 and led to a satisfactory functional result. Karyotype was 46,XX. Intravenous pyelogram and skeletal survey had normal findings.

Patient 13: This 15-year-old white girl noticed breast and pubic hair development at age 12 and became concerned about amenorrhea at age 15. There was no cyclic abdominal pain. Family history was negative. Physical examination was normal except for a blind-ending vagina 1 cm in depth. No uterus was palpable. Karyotype was 46,XX. Skeletal survey was unremarkable, but congenital absence of the left kidney was found by intravenous pyelography. The nonoperative treatment with pressure has been started.

Patient 14: This 18-year-old white girl noted breast and pubic hair development at age 12 and became concerned about amenorrhea at age 17. There was no cyclic abdominal pain. Congenital absence of the left kidney was documented at age 12 at evaluation for urinary tract infection. At about the same time she began wearing a back brace for a severe congenital thoracolumbar scoliosis. An older sister had a similar spine deformity but normal menses and normal intravenous pyelogram (Figure 2). A maternal aunt had a bicornuate uterus in which she was able to conceive twice in one horn but which was removed after difficult deliveries. Marked thoracolumbar scoliosis was present. The vagina was blind-ending and 4 cm in depth with no palpable uterus. Karyotype was 46,XX. Treatment was begun with dilatation.

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