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ORIGINAL RESEARCH

Unilateral Genital Tract Obstruction with Ipsilateral Renal Anomaly Syndrome: Classification, Clinical Manifestations, and Precise Diagnose

Ling Zhang[1,2], Ronghua Liu[1,2], Shuangmei Ye[1,2], Mingfu Wu[1,2], Rong Liu[1,2]

[1]Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China; [2]National Clinical Research Center for Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

Correspondence: Mingfu Wu; Rong Liu, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Anv, Wuhan, Hubei, 430030, People's Republic of China, Email wu_mingfu@tjh.tjmu.edu.cn; liurongdoctor@tjh.tjmu.edu.cn

Purpose: To recommend the classification of unilateral genital tract obstruction with ipsilateral renal anomaly (UGTOIRA) syndrome into five types based on the site of obstruction, and to analyze the clinical manifestations and precise diagnosis of the syndrome.

Methods: The data, including demographic characteristics, symptoms, and precise diagnoses from 59 patients over the last decade, were retrospectively analyzed. Data analysis was conducted using the statistical software package SPSS 26.0.

Results: All 59 patients diagnosed with UGTOIRA syndrome were classified into five types based on the site of obstruction: Type I (vaginal obstruction) (45, 76.3%), Type II (cervicovaginal obstruction) (7, 11.9%), Type III (cervical obstruction) (3, 5.1%), Type IV (unilateral partial cervical aplasia) (3, 5.1%), and Type V (Unilateral isthmus atresia) (1, 1.7%). Of these cases, there were 34 cases (57.6%) with communication and 25 cases (42.4%) without communication between the left and right genital tracts. The chief complaints included dysmenorrhea alone in 28 cases (47.5%), dysmenorrhea accompanied by blood dripping after menstruation in 12 cases (20.3%), blood dripping after menstruation alone in 14 cases (23.7%), purulent vaginal secretions in one case (1.7%), vaginal pain in one case (1.7%), irregular menstruation in one case (l.7%), and infertility in two cases (3.4%). The precise diagnostic criteria include the affected side, abnormalities in the kidney and ureter, the site of obstruction, the location of blood accumulation, the size of the ipsilateral genital tract, whether there is communication and its site, the type based on the site of obstruction, and the presence and type of complications.

Conclusion: This classification of UGTOIRA syndrome encompasses the anatomical features of all cases reported in our study. Only by fully understanding the anatomical characteristics of this syndrome and identifying its clinical manifestations can clinicians make precise diagnoses as early as possible and provide individualized management.

Keywords: uterine malformation, cervical malformation, vaginal malformation, classification, clinical manifestation, diagnosis

Introduction

In 1922, Purslow first reported a case of unilateral hematocolpos, hematometra, and hematosalpinx.[1] In 1971, Herlyn and Werner reported a case of open Gartner duct cyst, homolateral kidney aplasia, and double uterus, which was referred to as Herlyn-Werner syndrome.[2] In 1976, Wunderlich reported a case of bicornuate uterus, right vaginal atresia with uterine hemorrhage, and absence of the right kidney.[3] Since then, the syndrome characterized by the triad of uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis has been internationally referred to as HWW syndrome. To date, most cases of HWW syndrome reported in the literature have presented with a complete bicorporeal uterus, double cervix, obstructed hemivagina, and ipsilateral renal agenesis. With the increasing knowledge of this syndrome, there have also been reported a few cases of a septate uterus, a bicornuate uterus with unilateral cervical obstruction or atresia, a unilateral rudimentary horn with cavity without communication, and a duplicated and dysplastic kidney by a few studies.[4–8]

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We proposed a new term, "unilateral genital tract obstruction and ipsilateral renal agenesis (UGTOIRA) syndrome", to describe the syndrome consisting of unilateral genital tract obstruction with different anatomical types and ipsilateral renal agenesis, and recommend that UGTOIRA syndrome be classified into five types according to the site of obstruction.[9] The aim of this paper is to retrospectively analyze the different demographic characteristics, symptoms, and comprehensive diagnoses at clinical discharge in a case series of 59 patients with UGTOIRA syndrome. We also aim to determine the type of each case based on the obstruction site. Our goal is to summarize a scientific and precise typing method for UGTOIRA syndrome that encompasses the anatomical features reported in current literature and our study, providing a basis for developing the most suitable management plans for clinics.

Materials and Methods

Study Design

This study is a retrospective and descriptive analysis of the data collected from routine medical records, which includes demographic characteristics, symptoms, and comprehensive diagnosis at the time of clinical discharge.

Study Population

The cases were patients with UGTOIRA syndrome who were treated in the Department of Obstetrics and Gynecology of Tongji Hospital, affiliated with Tongji Medical College of Huazhong University of Science and Technology, from July 2012 to August 2022. The inclusion criteria included (1) enrolling patients who had undergone surgical treatment at our hospital, (2) performing preoperative genitourinary system segmental sequential ultrasound screening (SSUS), (3) accurately diagnosing abnormalities of the uterus, cervix, and vagina, as well as conditions affecting the bilateral fallopian tubes, ovaries, and pelvis during laparoscopic exploration or laparotomy, hysteroscopy, or gynecological examination with or without pathologic diagnosis. Additionally, (4) these patients had attended at least one follow-up visit to the hospital. The patients who did not simultaneously meet all four criteria were excluded from this study.

Definition of the Classification

The clinically diagnosed uterine, cervical, and vaginal malformations were categorized according to the ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies.[10]

We recommend classifying UGTOIRA syndrome into five types based on the site of obstruction as follows: (1) Type I (vaginal obstruction), characterized by oblique vaginal septum (OVS/V2) combined with a septate cervix (C1) or double cervix (C2); (2) Type II (cervicovaginal obstruction), characterized by OVS combined with a unilateral small cervix without atresia (C3a) or unilateral obliterated cervical orifice (C3b); (3) Type III (cervical obstruction), characterized by unilateral obliterated cervical orifice (C3b) with a normal vagina (V0); (4) Type IV(unilateral partial cervical aplasia), characterized by unilateral partial cervical aplasia with blind end (C3c)with a normal vagina (V0); and (5) Type V (Unilateral isthmus atresia), characterized by unilateral isthmus atresia with hematocele and without communicating to contralateral uterus (U4a), completely undeveloped ipsilateral cervix, which looks like a normal cervix (C0), and completely undeveloped ipsilateral vagina, which looks like a normal vagina (V0). Type I is divided into three subtypes based on the distance between the lowest point of the oblique septum and the vaginal orifice: Type I-a (low-OVS), Type I-b (middle-OVS), and Type I-c (high-OVS). The diagnostic criteria for low, middle, and high-OVS specify that the distance between the lowest point of the oblique septum and vaginal orifice should be ≤3 cm, 3–6 cm, or >6 cm, respectively. Type II is divided into two subtypes based on whether the external orifice of the cervix is blocked: Type II-a (C3aV2) and Type II-b (C3bV2). The first four types (including the subtypes) are divided into two groups based on whether there is communication or not. The sites of communication between the left and right genital tracts include (1) the lower part of the uterine cavity, (2) the internal orifice of the cervix, (3) a fistula in the cervical septum, (4) a foramen in the vaginal oblique septum, or (5) more than two communication sites.

Table 1 presents a detailed anatomical description of the five types of UGTOIRA syndrome, based on variations in vaginal, cervical, and uterine malformations as well as communicating sites. Figures 1–5 illustrate the utero-cervical-vaginal anatomy in each type.

Table 1 The Anatomical Combination of the Utero-Cervical-Vaginal Anatomy and the Site of Communication in Different Types of UGTOIRA Syndrome

Type	Vagina	Cervix	Uterine	Communication Site
Type I (vaginal obstruction)	Low oblique vaginal septum	Double cervix	Complete bicorporal uterus	Without communication (Figure 1A)
				With a foramen in the oblique vaginal septum (Figure 1B), or with a fistula connecting the oblique vaginal septum and the contralateral cervix (Figure 1C)
		Septate cervix	Complete bicorporal uterus	Without communication (Figure 1D)
				With a foramen in the oblique vaginal septum (Figure 1E), or with a fistula in the cervix septum (Figure 1F)
			Bicorporal septate uterus	Without communication (Figure 1G)
				With a foramen in the oblique vaginal septum (Figure 1H), or with a fistula in the cervix septum (Figure 1I), or with communication between both internal orifices of the cervix (Figure 1J)
			Complete septate uterus	Without communication (Figure 1K)
				With a foramen in the oblique vaginal septum (Figure 1L), or with a fistula in the cervix septum (Figure 1M), or with communication between both internal orifices of the cervix (Figure 1N)
Type II (cervicovaginal obstruction)	High or middle oblique vaginal septum	Unilateral small cervix	Partial bicorporal uterus	With the communication between the left and right lower portions of the uterine cavity (Figure 2A)
			Bicorporal septate uterus	Without communication (Figure 2B)
				With a fistula in the cervix septum (Figure 2C), or with communication between both internal orifices of the cervix (Figure 2D)
			Partial septate uterus	With the communication between the left and right lower portions of the uterine cavity (Figure 2E)
			Complete septate uterus	Without communication (Figure 2F)
				With a fistula in the cervix septum (Figure 2G), or with communication between both internal orifices of the cervix (Figure 2H)
		Unilateral obliterated cervical orifice	Complete bicorporal uterus	Without communication (Figure 2I)
			Bicorporal septate uterus	Without communication (Figure 2J)
				With a fistula in the cervical septum (Figure 2K), or with communication between both internal orifices of the cervix (Figure 2L)

(*Continued*)

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Table 1 (Continued).

Type	Vagina	Cervix	Uterine	Communication Site
Type III (cervical obstruction)	A normal vagina	Unilateral obliterated cervical orifice	Bicorporal septate uterus	Without communication (Figure 3A)
				With a fistula in the cervical septum (Figure 3B), or with communication between both internal orifices of the cervix (Figure 3C)
			Complete septate uterus	Without communication (Figure 3D)
				With a fistula in the cervical septum (Figure 3E), or with communication between both internal orifices of the cervix (Figure 3F)
Type IV (unilateral partial cervical aplasia)	A normal vagina	Partial non-development of unilateral cervix with a blind end	Complete bicorporal uterus	Without communication (Figure 4A)
				With a fistula in the site of partial cervical fusion (Figure 4B)
Type V (Unilateral isthmus atresia)	A normal vagina	Completely undeveloped ipsilateral cervix which looks like a normal cervix	Unilateral isthmus atresia	Without communication (Figure 5)

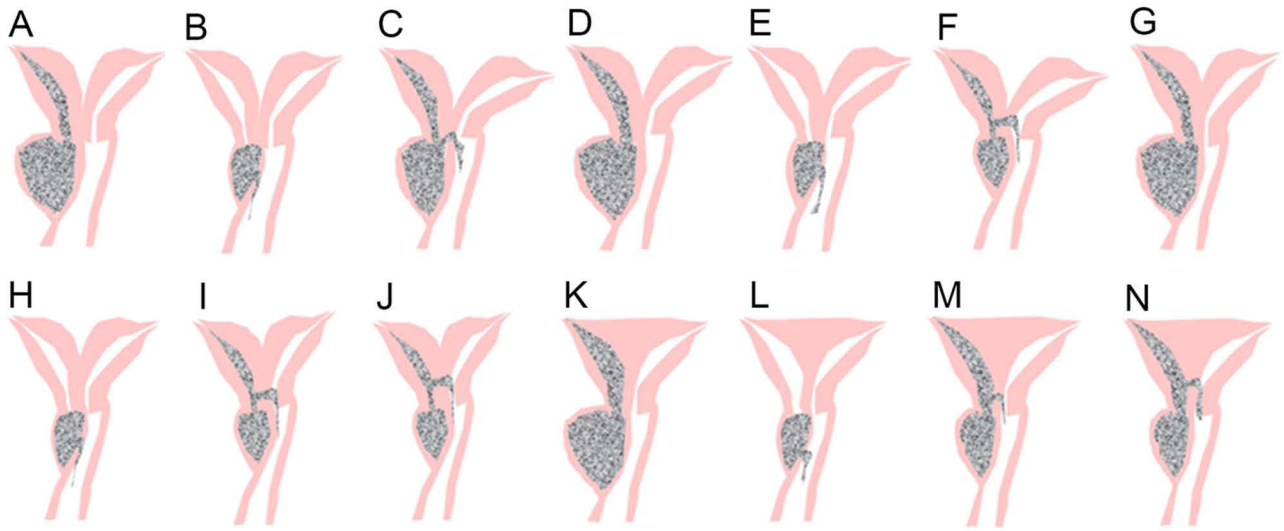

Figure 1 Anatomical illustrations of the utero-cervical-vaginal anatomy in type I UGTOIRA syndrome (vaginal obstruction).Complete bicorporeal uterus, double cervix without cervical obstruction, and low oblique vaginal septum, without communication (**A**), with a foramen in the oblique vaginal septum (**B**), with a fistula connecting the oblique vaginal septum and the contralateral cervix (**C**); complete bicorporeal uterus, septate cervix without cervical obstruction, and low oblique vaginal septum, without communication (**D**), with a foramen in the oblique vaginal septum (**E**), with a fistula in the cervix septum (**F**); partial bicorporeal septate uterus, septate cervix without cervical obstruction, and low oblique vaginal septum, without communication (**G**), with a foramen in the oblique vaginal septum (**H**), with a fistula in the cervix septum (**I**), with communication between both internal orifices of the cervix (**J**); complete septate uterus, septate cervix without cervical obstruction, and low oblique vaginal septum, without communication (**K**), with a foramen in the oblique vaginal septum (**L**), with a fistula in the cervix septum (**M**), with communication between both internal orifices of the cervix (**N**).

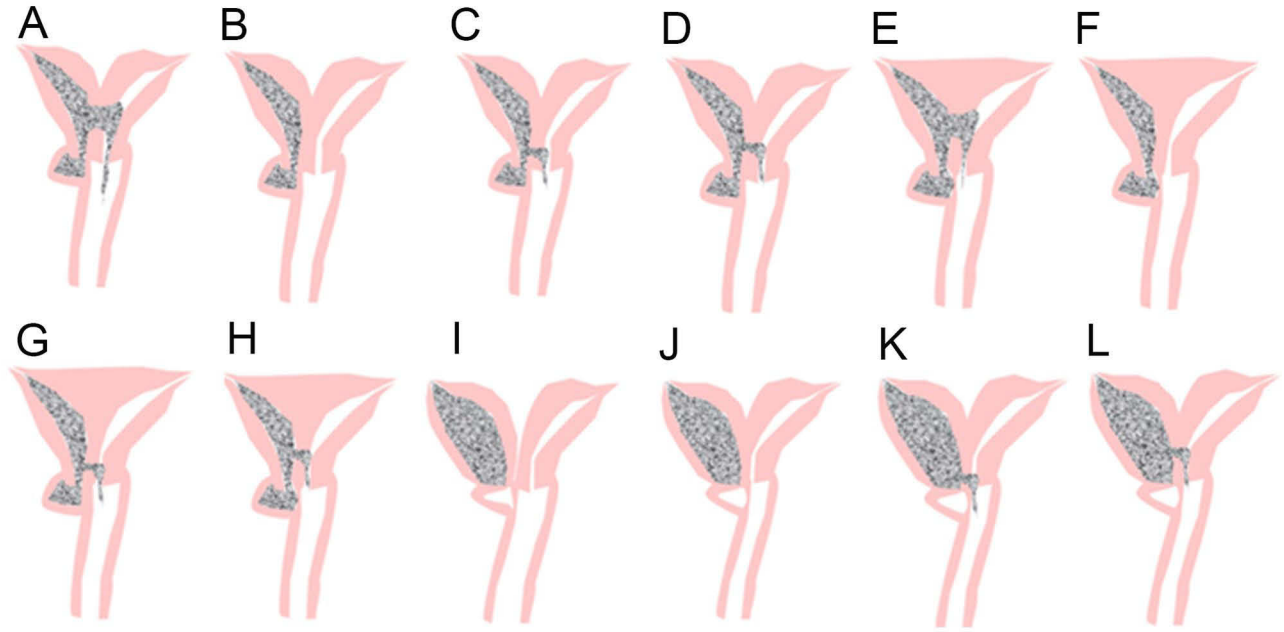

Figure 2 Anatomical illustrations of the utero-cervical-vaginal anatomy in Type II UGTOIRA syndrome (cervicovaginal obstruction).Partial bicorporeal uterus, septate cervix with unilateral cervical dysplasia, and high oblique vaginal septum, with the communication between the left and right lower portions of the uterine cavity (**A**); partial bicorporeal septate uterus, septate cervix with unilateral cervical dysplasia, and high oblique vaginal septum, without communication (**B**), with a fistula in the cervix septum (**C**), with communication between both internal orifices of the cervix (**D**); partial septate uterus, septate cervix with unilateral cervical dysplasia, and high oblique vaginal septum, with the communication between the left and right lower portions of the uterine cavity (**E**); complete septate uterus, septate cervix with unilateral cervical dysplasia, and high oblique vaginal septum, without communication (**F**), with a fistula in the cervix septum (**G**), with communication of both internal orifices of cervix (**H**); complete bicorporeal uterus, double cervix with unilateral obliterated cervical os, and high oblique vaginal septum, without communication (**I**); partial bicorporeal septate uterus, septate cervix with unilateral obliterated cervical os, and high OVS, without communication (**J**), with a fistula in the cervical septum (**K**), with communication of both internal orifices of cervix (**L**).

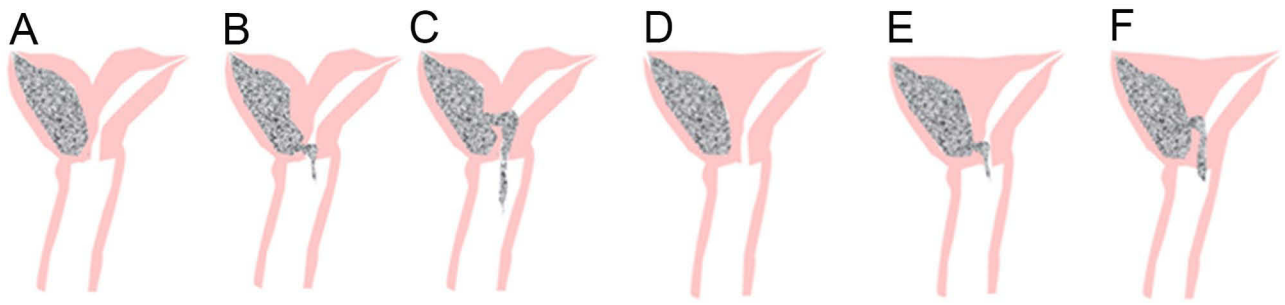

Figure 3 Anatomical illustrations of the utero-cervical-vaginal anatomy in Type III UGTOIRA syndrome (cervical obstruction).Partial bicorporeal septate uterus, septate cervix with unilateral obliterated cervical os, with one normal vagina, without communication (**A**), with a fistula in the cervical septum (**B**), with communication between both internal orifices of the cervix (**C**); complete septate uterus, septate cervix with ipsilateral obliterated cervical os, with one normal vagina, without communication (**D**), with a fistula in the cervical septum (**E**), with communication between both internal orifices of the cervix (**F**).

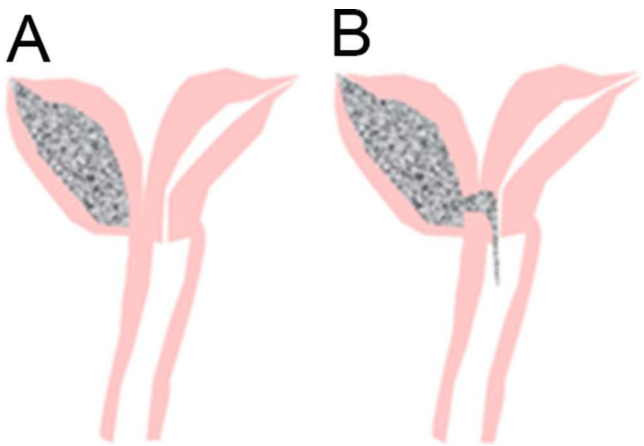

Figure 4 Anatomical illustrations of the utero-cervical-vaginal anatomy in Type IV UGTOIRA syndrome (unilateral partial cervical aplasia). Complete bicorporeal uterus, double cervix with unilateral partial cervical aplasia, with one normal vagina, without communication (**A**), with partial cervical fusion and a fistula in the cervical fusion (**B**).

Figure 5 Anatomical illustration of the utero-cervical-vaginal anatomy in Type V UGTOIRA syndrome (Unilateral isthmus atresia). Complete bicorporeal uterus with unilateral isthmus atresia, double cervix with completely undeveloped ipsilateral cervix which looks like a normal cervix, with one normal vagina, without communication.

Methods of Diagnosis

The comprehensive diagnosis at discharge is considered as the final diagnosis. The diagnostic criteria for UGTOIRA syndrome include unilateral genital tract obstruction with ipsilateral renal anomaly. The diagnostic basis includes

intraoperative findings, such as the presence or absence of a vaginal oblique septum, the distance between the lower edge and the external orifice of the vagina, malformation of the cervix and uterine body, location of obstruction, presence or absence of communication sites, location of blood accumulation, condition of fallopian tubes and ovaries, and complications such as endometriosis, adhesion, and inflammation. These findings are combined with postoperative pathological diagnosis and preoperative imaging diagnosis for unilateral obstructive genital tract malformation associated with ipsilateral renal agenesis. The primary diagnosis is UGTOIRA syndrome, and there are related complications as the secondary diagnosis.

Statistical Analysis

The statistical software package SPSS 26.0 (IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA) was utilized for data analysis. The data relating to the classified variables are represented as n (%) and the data relating to the continuous variables are represented as M (25%, 75%). All continuous variables are rounded to the nearest integer, and percentages are rounded to one decimal place. The independent sample Mann–Whitney *U*-test was used to compare the distribution and median difference in index values between two groups. The incidence was compared using the chi-squared test. The Pearson chi-squared test (the first row) was selected when the total sample size n of the two groups was ≥ 40 and the expected count (theoretical number, T) of all cells was ≥ 5. If $P \approx 0.05$ was obtained, we would use Fisher's exact test (the fourth line). When $n \geq 40$ but $1 \leq T \leq 5$, we used continuous correction. Fisher's exact test was directly used for multi-row and multi-list comparisons. P-values were rounded to three decimal places. Differences were considered statistically significant when the p-value was < 0.05.

Results

Baseline Characteristics

A total of 59 cases were included in the study. The frequency of left and right genital tract obstruction was 29 cases (49.2%) and 30 cases (50.8%), respectively. All 59 patients (100%) were associated with ipsilateral renal agenesis, and three patients (5.1%) were also associated with a long and thin tube connecting the ipsilateral bladder to the vagina, which was considered an ectopic insertion of a ureteral remnant into the vagina. The other baseline characteristics are summarized in Table 2. There was no significant difference in the distribution of menarche age between the communication and non-communication groups (p=0.449). The median age of symptom onset, diagnosis, and operation for patients without communication was significantly lower than that of patients with communication. The p-values for all three were 0.000. The median interval time between menarche and the onset of symptoms, menarche and diagnosis, and menarche and operation in patients without communication were also significantly shorter than those in patients with communication, with all three p-values being 0.000. The median interval time between the onset of symptoms and diagnosis, diagnosis and operation, and the onset of symptoms and operation showed no significant difference between the communication and non-communication groups. The corresponding p-values were 0.800, 0.364, and 0.150, respectively.

Clinical Manifestations

The numbers and incidences of different complaints for various types and sub-types of UGTOIRA syndrome are shown in Figure 6, while those in the communication and non-communication groups are displayed in Figure 7. The chief complaints included dysmenorrhea (28, 47.5%), dysmenorrhea and post-menstrual bleeding (12, 20.3%), post-menstrual bleeding (14, 23.7%), purulent vaginal discharge (1, 1.7%), vaginal pain (1, 1.7%), irregular menstruation (1, 1.7%) and infertility (2, 3.4%). There were no significant statistical differences in the incidence of complaints among different types and subtypes (P=0.484). The incidence of dysmenorrhea in the non-communication group (20/25) was significantly higher than that in the communication group (8/34) (p = 0.000), and the incidence of post-menstrual blood dripping in the communication group (12/34) was significantly higher than that in the non-communication group (2/25) (p = 0.000).

Table 2 Baseline Characteristics (n=59)

Baseline Characteristics	Total (n=59)		Communication (n=34)		Non-communication (n=25)		P-value	
	Range (Min-max)	Median (25%, 75%)	Range (Min-max)	Median (25%, 75%)	Range (Min-max)	Median (25%, 75%)	Distribution	Median
Menarche age (years)	10–14	12 (11,13)	11–14	12 (12,13)	10–14	12 (11,13)	0.449	0.785
Age of onset of symptoms (years)	5–52	14 (12,23)	11–52	22 (14,25)	5–20	12 (11,14)	0.000	0.000
Age at diagnosis (years)	5–52	15 (12,23)	12–52	22 (16,26)	5–20	12 (11,14)	0.000	0.000
Operation age (years)	5–52	15 (12,23)	12–52	22 (16,26)	5–20	12 (11,14)	0.000	0.000
Interval between menarche and onset of symptoms (months)	0–480	24 (3135)	1–480	108 (24,171)	0–84	3 (2,11)	0.000	0.000
Interval between onset of symptoms and diagnosis (months)	0–72	0 (0,3)	0–72	0 (0,7)	0–60	0 (0,3)	0.904	0.800
Interval between menarche and diagnosis (months)	1–480	36 (5135)	2–480	120 (45,171)	1–84	4 (3,18)	0.000	0.000
Interval between diagnosis and operation (months)	0–12	0 (0,0)	0–12	0 (0,0)	0–12	0 (0,0)	0.203	0.364
Interval between onset of symptoms and operation (months)	0–72	0 (0,6)	0–72	0 (0,12)	0–60	0 (0,0)	0.089	0.150
Interval between menarche and operation (months)	1–480	36 (5135)	2–480	125 (45,176)	1–84	4 (3,18)	0.000	0.000

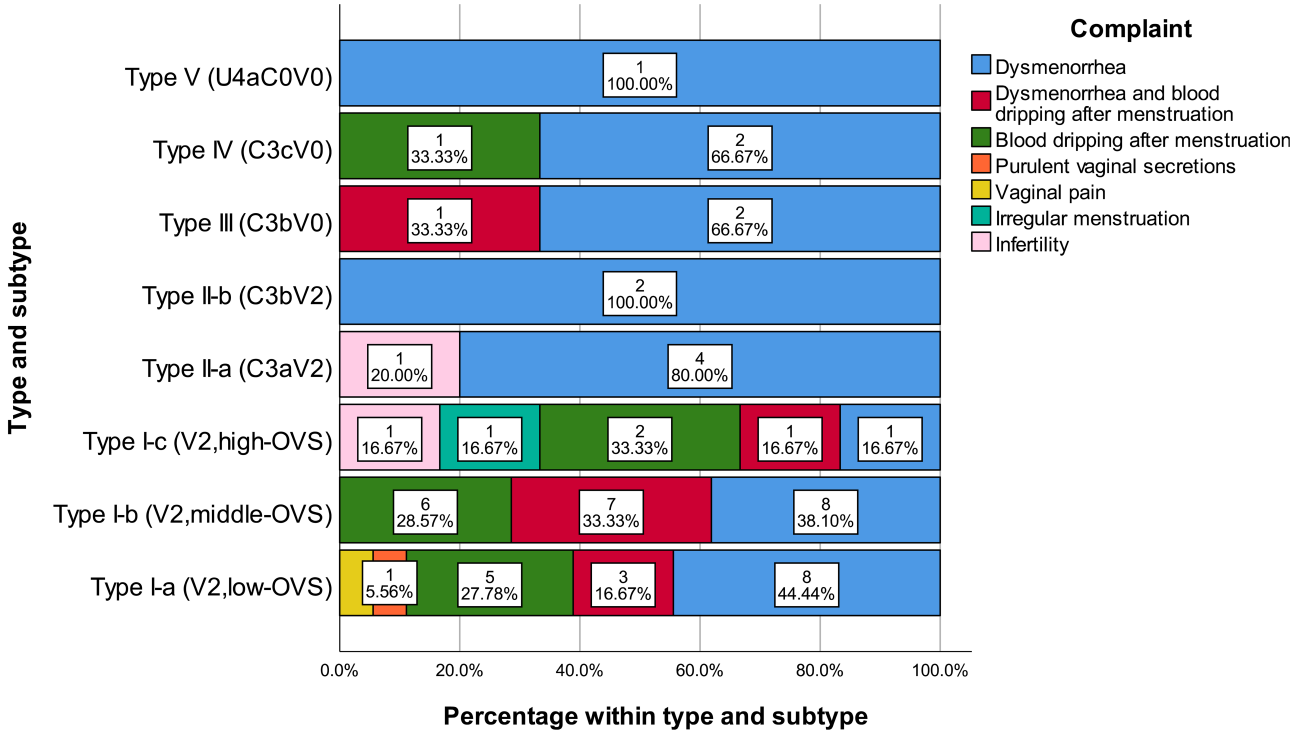

Figure 6 The number and incidence of different complaints in different types and subtypes of UGTOIRA syndrome (n=59).

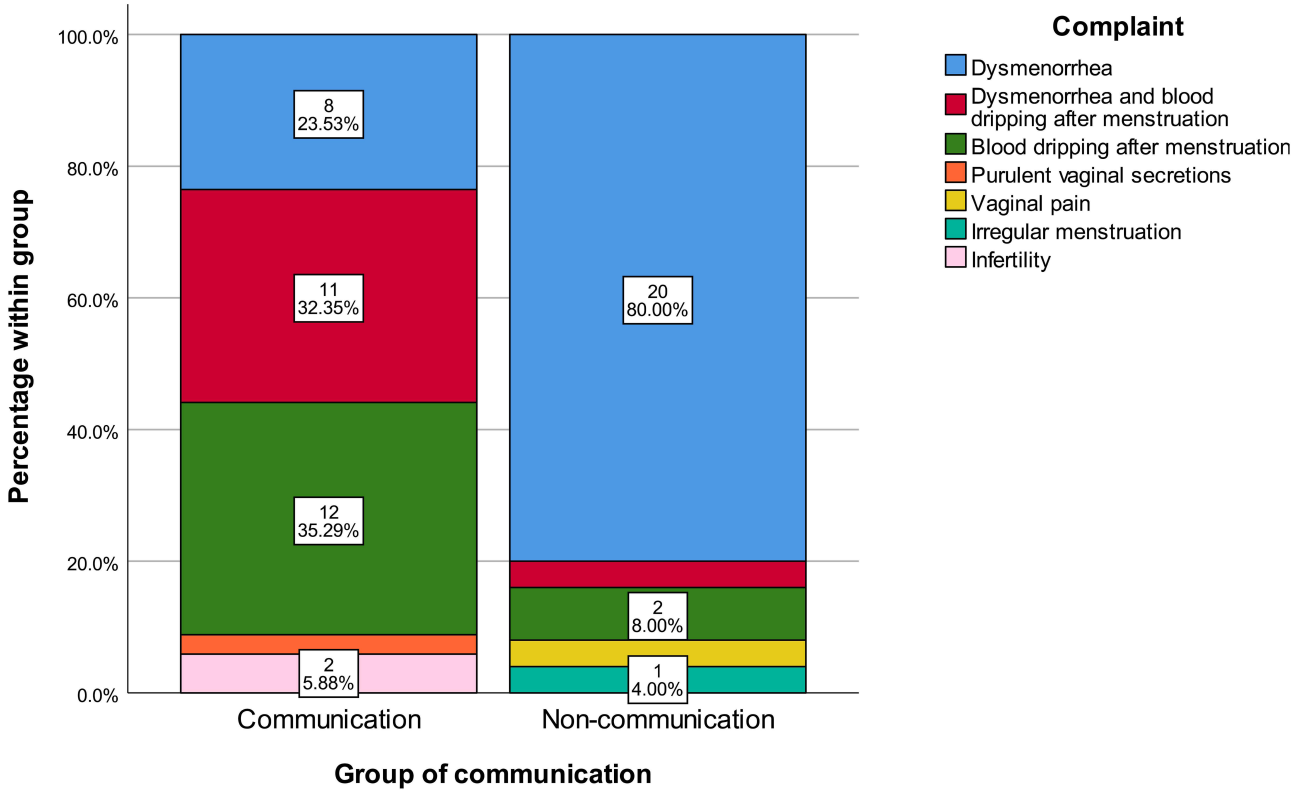

Figure 7 The number and incidence of different complaints in communication and non-communication groups (n=59).

Diagnosis

All 59 cases (100%) underwent genitourinary system segmental sequential ultrasound screening (SSUS) in our hospital. Five cases (8.5%) underwent MRI, including four cases that had undergone MRI prior to referral, and two cases (3.4%) underwent CT, including one case that had undergone CT prior to referral. Laparoscopy was used in 25 cases (42.4%), hysteroscopy in 46 cases (78.0%), laparotomy in eight cases (13.6%), colposcopy in one case, and cystoscopy in one case (1.7%).

All patients diagnosed with UGTOIRA syndrome were classified into five types according to the site of obstruction as follows: Type I (V2, C1/C2) (45, 76.3%), Type II (V2, C3a/C3b) (7, 11.9%), Type III (V0C3b) (3, 5.1%), Type IV (V0C3c) (3, 5.1%), and Type V (V0C0U4a) (1, 1.7%). Combined cervical malformations included septate cervix (C1, 28, 47.5%), double cervix (C2, 17, 28.8%), unilateral small cervix (C3a, 5, 8.5%), unilateral obliterated cervical orifice (C3b, 5, 8.5%), and partial non-development of the unilateral cervix with a blind end (C3c, 3, 5.1%). Combined uterine malformations included complete bicorporeal uterus (U3b, 42, 71.2%), bicorporeal septate uterus (U3c, 7, 11.9%), complete septate uterus (U2b, 8, 13.6%), partial septate uterus (U2a, 1, 1.7%), and unilateral isthmus atresia (U4a, 1, 1.7%). The numbers and incidences of different types and subtypes of UGTOIRA syndrome are presented in Table 3. There were 34 cases (57.6%) with communication and 25 cases (42.4%) without communication between the left and right genital tracts. The numbers and incidences of different sites of communication between the left and right genital tracts in different types and subtypes of UGTOIRA syndrome are shown in Figure 8. There were four cases, two of which were type I-a, one was type I-b, and the remaining one was type II-b, demonstrating combined congenital atresia of the umbrella end of the ipsilateral fallopian tube.

The sites of blood accumulation included the posterior OVS, cervical canal, uterine cavity, fallopian tube, and pelvic cavity. Complications included endometriosis in the uterus, ovary, and pelvic cavity; inflammation of the genital tract and pelvis; and pelvic adhesions. The numbers and incidences of different hematocele sites and various complications in different types and subtypes of UGTOIRA syndrome are summarized in Figures 9 and 10, respectively. The incidences of hematocele in different sites showed a statistically significant difference between the communication group and the non-communication group (p=0.015). The incidences of different hematocele sites in various types and subtypes exhibited a statistically significant difference (P=0.000). There was no statistically significant difference in the incidences of endometriosis, genital tract and pelvic inflammation, and pelvic adhesion between the communication group and the non-communication group, with p-values of 0.854, 1.000, and 1.000 respectively. The incidences of endometriosis and pelvic adhesion in different types and subtypes exhibited statistically significant differences, with p-values of 0.004 and 0.023, respectively. There was no statistically significant difference (p=0.119) in the incidences of genital tract and pelvic inflammation among different types and subtypes.

Table 3 The Numbers and Incidences of Different Types and Subtypes of UGTOIRA Syndrome (n=59)

Type	No. (% of All)	Communication No. (% of Type)	Subtype	No. (% of Type)	Communication No. (% of Subtype)	Uterine Abnormalities (No.)
Type I (V2, C1/C2)	45 (76.3)	29 (64.4)	I-a (low-OVS)	18 (40.0)	9 (50.0)	U3b (9), U3c (4), U2b (5)
			I-b (middle-OVS)	21 (46.7)	16 (76.2)	U3b (16), U3c (2), U2b (3)
			I-c (high-OVS)	6 (13.3)	4 (66.7)	U3b (5), U2a (1)
Type II (V2, C3a/C3b)	7 (11.9)	2 (28.6)	II-a (C3aV2)	5 (71.4)	2 (40.0)	U3b (5)
			II-b (C3bV2)	2 (28.6)	0 (0)	U3b (2)
Type III (V0C3b)	3 (5.1)	2 (66.7)	No subtype			U3b (2), U3c (1)
Type IV (V0C3c)	3 (5.1)	1 (33.3)	No subtype			U3b (3)
Type V (V0C0U4a)	1 (1.7)	0 (0.0)	No subtype			U4a (1)
Total no. (% of all)	59 (100)	34 (57.6)	U3b (42, 72.4), U3c (7,12.1), U2b (8,13.6), U2a (1, 1.7), U4a (1,1.7)			

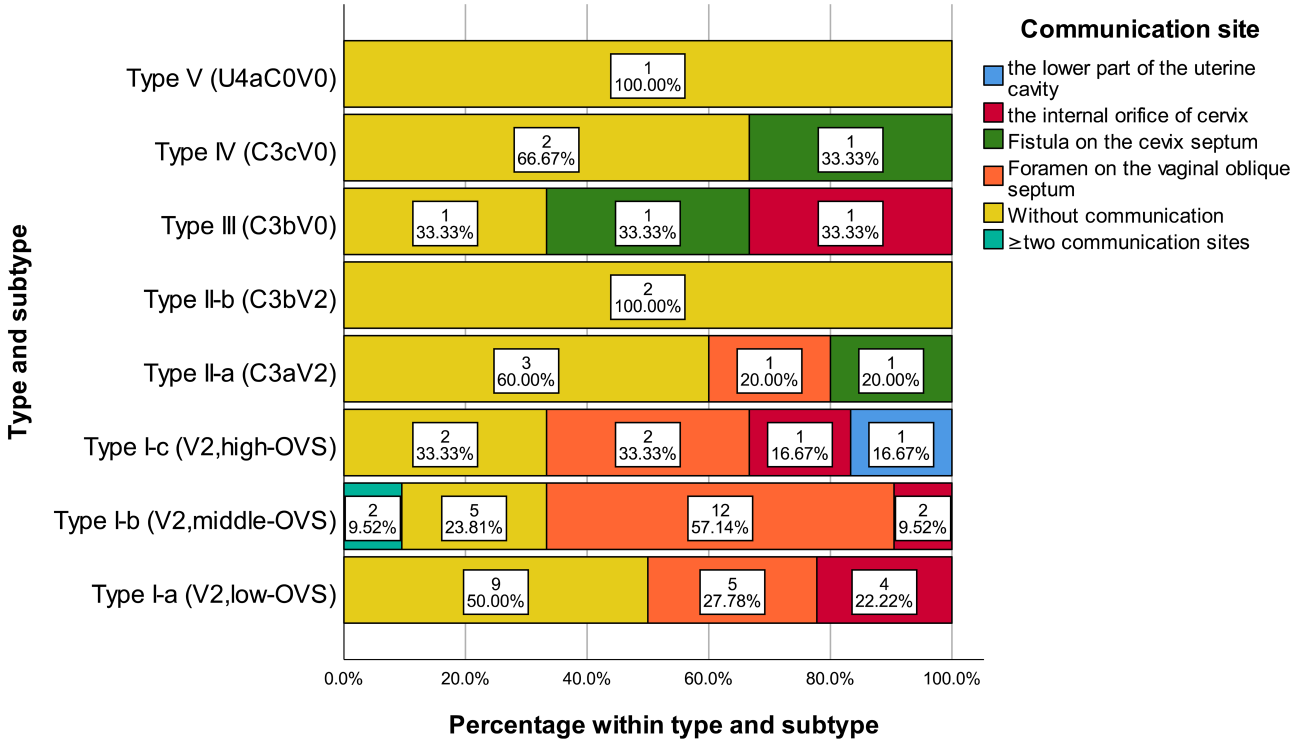

Figure 8 The number and incidence of different communication sites in different types and subtypes of UGTOIRA syndrome (n=59).

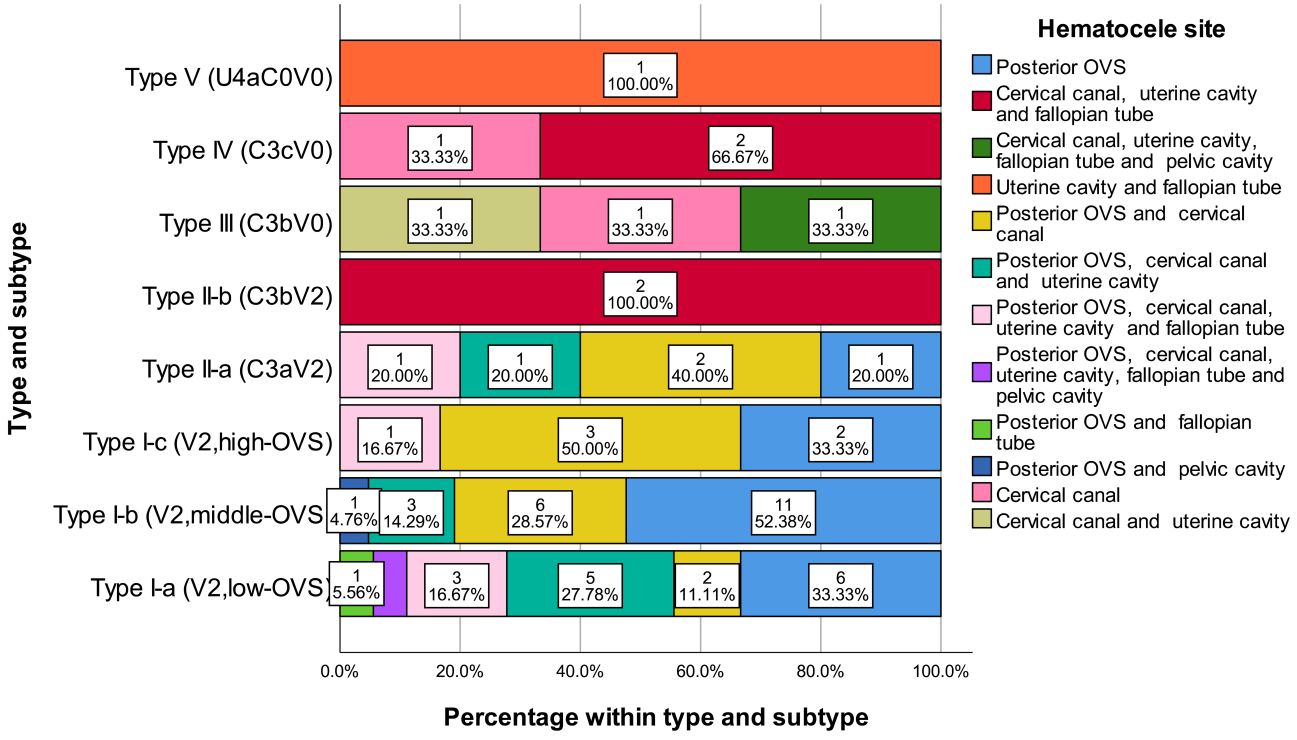

Figure 9 The number and incidence of different hematocele sites in different types and subtypes of UGTOIRA syndrome (n=59).

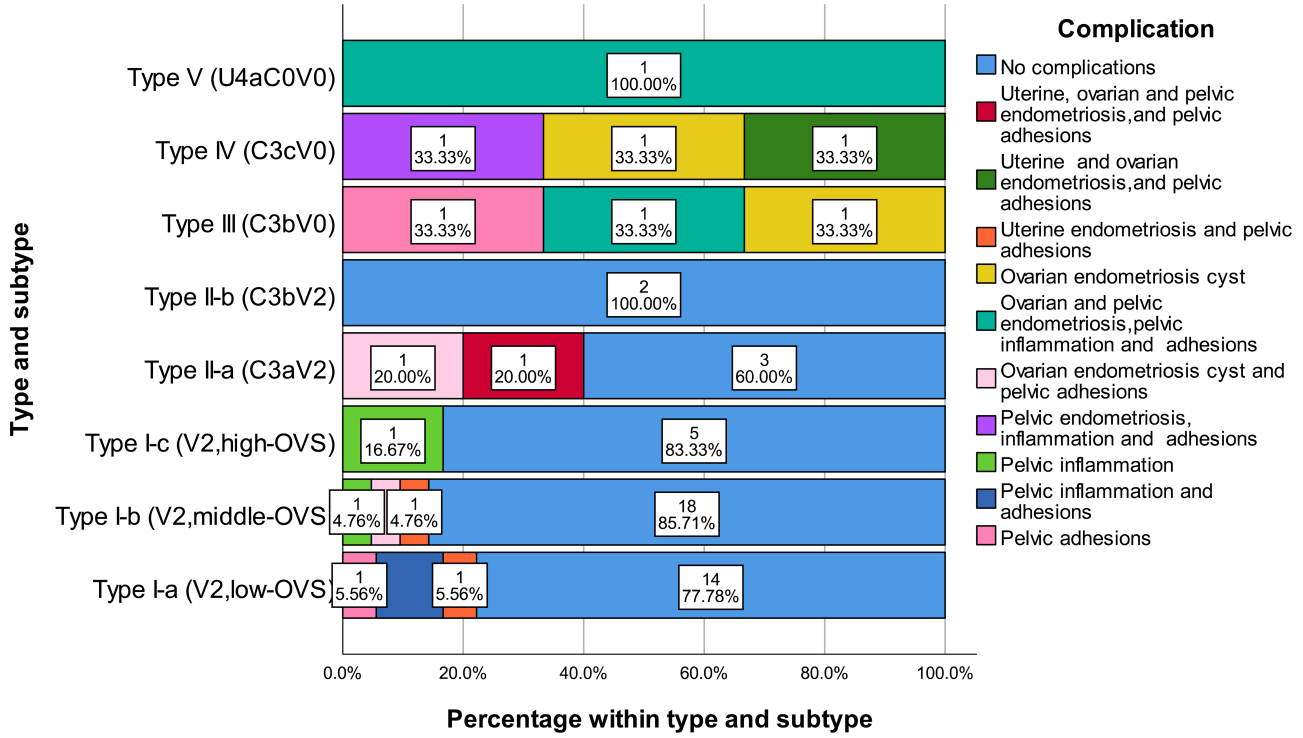

Figure 10 The number and incidence of different complications in different types and subtypes of UGTOIRA syndrome (n=59).

Discussion

Definition

In the literature, various terms such as Herlyn-Werner syndrome, HWW syndrome, OHVIRA syndrome, obstructed uterovaginal duplication, vaginal oblique septum syndrome have been used to define the syndrome that involves the association of renal agenesis with ipsilateral obstructed hemivagina.[2,3,5,11–13] These definitions highlight hemivaginal obstruction, but in our study, only type I involves simple vaginal obstruction. Type II involves cervical obstruction in addition to vaginal obstruction; type III and IV involve cervical obstruction with a normal vagina, while type V involves obstruction of the lower segment of the uterine body with a normal cervix and vagina. Such cases are also documented in the literature.[5] We propose a new term, "unilateral genital tract obstruction and ipsilateral renal agenesis (UGTOIRA) syndrome", to describe the syndrome characterized by unilateral obstruction of the genital tract with various anatomical types and concurrent absence of the kidney on the same side. The term encompasses the shared characteristics of all anatomical variations of this type of disease.

Embryological Origin, Pathogenesis, and Anatomical Characteristics

Its etiology, embryological basis, and pathogenesis are still being discussed. It is widely accepted that the development of the urinary system is closely related to the development of the reproductive tract between the 6th and 9th weeks of embryonic development. The full development of the caudal parts of the mesonephric (Wolffian) duct, extending from the urogenital ridge to the urogenital sinus, induces the development of the ureter and kidney. It also leads to the complete development, fusion, and septal absorption of the paramesonephric (Mullerian) duct parallel to the mesonephric duct. The caudal parts of the paramesonephric duct fuse to form the uterus. On the affected side, abnormal development of the mesonephric tube leads to failure in normal ureter sprouting and kidney differentiation (resulting in renal agenesis and other abnormalities), as well as failure in development, fusion, and septal absorption of the paramesonephric duct.

The vagina is the female genital organ that has the most controversial embryology. The most widely accepted theory suggests that the superior part of the vagina derives from the fusion of the paramesonephric duct, while the inferior part

arises from the urogenital sinus (sinus vagina).[14–17] However, this theory cannot explain well the different heights of the OVS, especially the lower OVS. Acien proposed that the whole vagina has a mesonephric nature.[18] This view can effectively explain various abnormalities in vaginal development.

The authors agree that the upper genital tract (consisting of the cervix, uterus, and fallopian tube) originates from the paramesonephric duct, while the lower genital tract (the vagina) originates from the mesonephric duct. The bulge and expansion of the upper part of the vagina form a fornix that surrounds the lower part of the cervix and merges with it. Based on the embryological basis of the urogenital system and in combination with various anatomical features observed in UGTOIRA syndrome cases in our study, the authors propose a hypothesis regarding the pathogenesis of UGTOIRA syndrome.

This hypothesis includes three aspects: the pathogenesis of vaginal obstruction, the pathogenesis of cervical or uterine body obstruction and anomalies, and the pathogenesis of renal and ureteral dysplasia. Around the 6th week of embryonic development, the developmental arrest of the caudal portion of the unilateral mesonephric duct leads to a failure in ureteral bud and kidney development. This results in ipsilateral vaginal developmental arrest, which subsequently leads to abnormal development of the uterus due to a lack of induction for a fully developed vagina. Failures in unilateral ureteral bud and kidney development can result in ipsilateral renal agenesis or the presence of ureteral remnant cysts with vaginal or cervical insertion. The development of the vagina occurs from top to bottom. If ipsilateral developmental arrest of the vagina is combined with septal absorption disorders after bilateral fusion, OVS will form. Different segments of the ipsilateral vaginal developmental arrest result in varying lengths or heights of OVS. If the ipsilateral vagina is completely undeveloped, the vagina appears to be a normal vagina. The development of a bilateral uterus occurs from top to bottom, and the fusion occurs from bottom to top. If the bilateral uterus is not fused at all, a double cervix will be formed along with a complete bicorporeal uterus. The fusion stopping at different parts will result in the formation of a normal cervix with a complete bicorporeal uterus or a normal cervix with a partial bicorporeal uterus, respectively. After the fusion of the bilateral uterus, the septum is absorbed from the internal orifice of the cervix. The uterine septum and cervical septum are respectively absorbed upward and downward from the internal orifice of the cervix. The length of the septum depends on the segment at which septal absorption ceases. If the septum is not absorbed, is only absorbed at the internal orifice, or is partially absorbed, it then forms a complete septate uterus and a normal cervix or septate cervix, a complete septum with a communicating internal orifice or a partial septate uterus, or a normal cervix or septate cervix, respectively. If incomplete uterine fusion occurs in combination with septal resorption failure, a bicorporeal septate uterus is formed. If the ipsilateral cervix is hypoplastic to varying degrees, this leads to the formation of a unilateral small cervix, a unilateral obliterated cervical orifice, or partial non-development of the unilateral cervix with a blind end. If the ipsilateral cervix is completely undeveloped, it will appear as a normal cervix. If the lower segment of the ipsilateral uterine body is underdeveloped, it will result in unilateral isthmus atresia without communication with the contralateral uterus. Patients with UGTOIRA syndrome do not exhibit fusion disorders of the lower and upper genital tracts in the vertical direction. The obstructed site is the part where the development of the reproductive tract stops, and blood accumulates in the reproductive tract above this part. The different communication sites of UGTOIRA syndrome may be caused by local absorption of the septum during embryonic development or the formation of a spontaneous breach due to inflammation and massive blood accumulation after birth.

The anatomical characteristics of the cases form the basis for this hypothesis. In turn, the hypothesis can effectively explain the embryological basis and pathogenesis of the different anatomical characteristics observed in all 59 cases in our study.

The syndrome does not preferentially affect one side of the body. In this study, 29 cases (49.2%) were diagnosed with left UGTOIRA syndrome, and 30 cases (50.8%) were diagnosed with right UGTOIRA syndrome. Another study has shown similar findings to ours,[11] but it has also been reported that the frequency of UGTOIRA syndrome on the right side of the body is twice that on the left side.[19]

Baseline Characteristics, Clinical Manifestations, and Complications

Our relatively large sample size provides new evidence on the heterogeneity of UGTOIRA syndrome. The age of symptom onset, diagnosis, and operation for patients without communication were significantly lower than those for patients with communication, which is consistent with another study.[6] In our study, all 59 patients (100%) presented with ipsilateral renal agenesis, and we observed the combination of an ipsilateral ureteral vestige cyst with insertion into the obstructed

hemivagina in three patients. However, some other renal anomalies, such as ipsilateral dysplastic or polycystic kidneys, a pelvic kidney, a duplicated ureter, an ectopic ureter, and ureterocele, have been reported in several studies.[7,11,20] A case series has reported rare cases of patients with two normal kidneys.[11]

Most patients with UGTOIRA syndrome are asymptomatic until puberty. Most of the patients visited the hospital before puberty due to a pelvic mass discovered prior to delivery or suspected after delivery. If there is an ectopic ureter or a ureteral remnant inserted into the vagina or cervix of the obstructed side, it will cause a significant accumulation of fluid in the vagina, cervix, and uterine cavity on the obstructed side, resulting in abdominal pain and a pelvic mass. A 5-year-old girl in our study was found to have lower abdominal distension when she was born at the local hospital. Subsequently, an ultrasound examination revealed a deficiency of the left kidney and a cystic mass behind the bladder; however, she did not receive any treatment at that time. The mass grew slowly and progressed over a period of 5 years, during which the patient occasionally experienced vaginal pain and a lack of vaginal secretion. In patients who were asymptomatic before puberty, dysmenorrhea can worsen after menarche due to increased blood accumulation in the obstructed genital tract, leading to persistent lower abdominal pain. In patients with communication, dysmenorrhea and lower abdominal pain may be delayed or only mild.[21] The findings led us to the same conclusion, namely that patients without communication mainly presented with unbearable dysmenorrhea. Symptoms of vaginal drip bleeding and irregular bleeding were common in patients with communication. If there is no timely and correct diagnosis and operation, the presence of blood in the vaginal/cervical/uterine cavity provides a culture medium for microbial growth, which may lead to genital and pelvic empyema. This can result in acute exacerbation of lower abdominal pain and the development of peculiar-smelling vaginal secretions, as well as chronic inflammation in the genital tract and pelvis. In our study, two cases developed vaginal, uterine, fallopian tube, and pelvic empyema with symptoms of an odorous yellow vaginal discharge and severe lower abdominal pain. The ages at which symptoms started were 52 years and 35 years respectively. If left untreated, the natural progression of UGTOIRA syndrome can lead to the development of endometriosis in the uterus, ovaries, pelvic cavity, and even the bowel, which will exacerbate dysmenorrhea. Inflammation and endometriosis may result in pelvic adhesions. Genital tract and pelvic endometriosis, inflammation, and adhesion are high-risk factors for infertility. Acute complications may include uterine cavity empyema, fallopian tube empyema, adnexal abscesses, and pelvic empyema, while long-term problems can consist of endometriosis, pelvic adhesions, infertility, and obstetric complications.

Diagnosis

Prompt and accurate diagnosis of UGTOIRA syndrome is essential for promptly relieving symptoms and preventing complications such as endometriosis, pelvic adhesions, and infection.[22] The purpose of preoperative diagnosis for UGTOIRA syndrome is to determine whether it is a case of UGTOIRA syndrome, specifically if there is obstruction in the unilateral genital tract combined with ipsilateral renal and ureteral abnormalities, as well as identifying the specific type of UGTOIRA syndrome present.

The diagnostic contents include the affected side, the type of abnormality in the kidney and ureter, the site of obstruction, the location of blood accumulation, the size of the ipsilateral genital tract, whether there is communication and its site, the type based on the obstruction site, and the presence and type of complications. The specific diagnosis is related to kidney agenesis or pelvic ectopic kidney, renal dysplasia, polycystic kidney, and whether there is a duplicated ureter or a ureteral remnant cyst with ectopic insertion into the vagina or cervix on the obstructive side. The key point related to the diagnosis is the specific diagnosis of an ipsilateral genital tract obstruction, including whether there is OVS, the distance between the lower edge of the OVS and the external opening of the vagina, the thickness of the OVS, whether there is a hole on the OVS, the amount of blood that has accumulated in the posterior cavity of the OVS; whether the cervix is double, septate, or normal, whether there is an ipsilateral cervical obstruction including a small, obliterated cervical orifice, or partial non-development of unilateral cervix with a blind end, and the amount of blood accumulated in the cervical canal; whether the ipsilateral uterine body is a completely bicorporal, partially bicorporal, bicorporal-septate, completely septate, partially septate uterus, or a unilateral isthmus atresia, also depending upon the amount of blood accumulated in the ipsilateral uterine cavity; whether the ipsilateral fallopian tube is thickened, dilated, or keratocele; and finally, whether there is a pelvic hematocele. At the same time, clinicians should also diagnose

complications such as endometriotic cysts in the ipsilateral ovary, deep invasive endometriosis, acute and chronic pelvic inflammation, and pelvic adhesions.

Diagnostic methods include a clinical consultation and examination by a gynecological specialist, SSUS, magnetic resonance imaging (MRI), computerized tomography (CT), hysteroscopy, laparoscopy, colposcopy, and laparotomy exploration. Based on the patient's age, relevant clinical manifestations, and gynecological examination, a preliminary diagnosis can be made. An ultrasound doctor with extensive experience in diagnosing malformations of the female genital system and urinary system can accurately diagnose urinary and genital malformations using high-resolution ultrasound instruments, a combination of various ultrasound technologies (2D or 3D), and different examination approaches (transabdominal/vaginal/perineal/rectal). Most of the diagnostic contents mentioned in the above paragraph can be accurately diagnosed. Ultrasonography is cheap, noninvasive, and useful. It is the first choice for imaging diagnoses of genital tract malformations in our hospital. However, it is difficult to observe ectopic insertion of the ureter or ureteral remnant cysts in the vagina or cervix on the obstructive side via ultrasound. When high OVS is combined with an ipsilateral obliterated cervical orifice, it is difficult to observe the presence of OVS via ultrasound because there is no blood accumulation in the posterior cavity of OVS. It is also a great challenge for doctors to observe deep invasive endometriosis and pelvic adhesions using ultrasound. However, MRI can compensate for the limitations of ultrasound due to its ability to capture images from multiple angles, its wide field of view, and its excellent resolution for visualizing soft tissues.[23] MRI can provide diagnostic information for the three points mentioned above that are difficult to observe via ultrasound and can offer greater diagnostic confidence for the content observable using ultrasound. However, MRI can only be used when the ultrasound diagnosis is unclear due to the need for expensive equipment, the high cost of detection, difficulty in making appointments, and a lack of doctors with rich experience in gynecological disease diagnosis. In our study, two patients underwent a CT examination. One patient underwent a CT examination at another hospital due to lower abdominal pain. Another patient was diagnosed with left type II-b UGTOIRA syndrome, which presented with a left obliterated cervical orifice and a sinus on the cervical septum, through SSUS in our hospital. The surgeon requested a CT examination to increase the diagnostic confidence, but the surgical confirmation revealed that the CT diagnosis was less accurate than the ultrasound diagnosis. CT does not easily depict pelvic anatomy and involves the use of ionizing radiation, so it is not recommended for differential diagnosis of congenital uterine anomalies.[24] Hysteroscopy allows for direct visualization of the intrauterine cavity and ostia, but it does not enable evaluation of the external contour of the uterus. Its results may require further investigation as well. Additionally, this procedure is invasive, usually requiring anesthesia, and is less appropriate for preoperative diagnosis in children.[25] Although ultrasound and MRI have been able to accurately diagnose genital tract malformations, some authors advocate laparoscopy or laparotomy as the gold standard for diagnosing uterine contour malformations. They argue that these methods can better identify endometriosis, pelvic inflammation, and adhesions.[26] However, this is a highly expensive and invasive procedure, and it has been argued that the risks associated with anesthesia and surgery involved in using laparoscopy or laparotomy are too high to justify their use for preoperative diagnoses.[27] The authors agree with this view and thus suggest that hysteroscopy and laparoscopy should only be performed for preoperative diagnosis when other imaging methods cannot be used to make a clear diagnosis, and when the unclear diagnosis directly affects the formulation of the operation plan.

In conclusion, a correct diagnosis can typically be made based on the patient's medical history and a gynecological examination, in combination with appropriate imaging. US and MRI are the most commonly used methods for diagnosing UGTOIRA syndrome.[28]

Differential Diagnosis

According to our clinical experience, the diagnosis of UGTOIRA syndrome needs to be distinguished from three types of genital tract malformations.

First, it should be distinguished from a complete bicorporeal uterus, double cervix, and septate vaginal malformation combined with inflammatory adhesion or stenosis of the lower segment of the unilateral vagina, resulting in empyema of the unilateral vagina, cervix, uterine cavity, and fallopian tube. The distinguishing point is that these patients have no history of congenital vaginal malformation surgery, previous genital tract obstruction or dysmenorrhea, and two external vaginal openings can be seen in the gynecological examination. Additionally, ultrasound examinations confirm normal

ipsilateral kidney function. We suggest reexamining ultrasound and gynecological examinations after completing anti-inflammatory or surgical treatment.

Secondly, UGTOIRA syndrome should be distinguished from cases involving a complex mesonephric cyst in the vaginal wall. The distinguishing point is that the tortuous duct in the vaginal wall mostly runs longitudinally along the long axis of the vagina and does not communicate with the cervical canal. In these cases, the uterus can be normal or abnormal, and the ipsilateral kidney remains normal.

Third, UGTOIRA syndrome should be distinguished from a hemi-uterus with a rudimentary (functional) cavity characterized by the presence of a communicating or noncommunicating functional contralateral horn, but not combined with ipsilateral kidney malformation. The distinguishing factor is the absence of ipsilateral kidney malformation.

Strengths, Limitations, and Future Research

The innovation of our research lies in the authors' proposal of a new term, "unilateral genital tract obstruction and ipsilateral renal agenesis (UGTOIRA) syndrome", which encompasses the common features of all anatomical variations involving unilateral genital tract obstruction and ipsilateral renal agenesis. We have proposed a new typing method that can serve as the foundation for clinical management, and a new embryological hypothesis that can elucidate the pathogenesis of each type. However, the number of cases used in this study is limited. Therefore, future research should include a larger sample size to verify the hypothesis related to embryological pathogenesis.

Conclusions

In conclusion, UGTOIRA syndrome can be classified into five types based on the location of obstruction. This classification can encompass the anatomical characteristics of all cases reported in the current literature and our study. Only by fully understanding the definition, embryological origin, and anatomical characteristics of this syndrome, as well as identifying its clinical manifestations and complications comprehensively, can doctors - including gynecologists, pediatric surgeons, sonographers, and radiologists - make accurate diagnoses at the earliest possible stage and provide individualized management.

Data Sharing Statement

The data set used in the current study will be made available upon request from Ling Zhang via email at zhangling0709@tjh.tjmu.edu.cn.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. It received approval from the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology (approval number:TJ-IRB20220917). This is a retrospective and descriptive analysis based on prospectively collected data for routine clinical services. It does not involve any private patient information, and obtaining informed consent to participate is exempt.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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