Case Report

Intraoperative Endoscopic Ultrasound Guided Surgical Treatment of Herlyn-Werner-Wunderlich Syndrome. Case Report and a Systematic Literature Review

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Abstract

Aim: Herlyn-Werner-Wunderlich (HWW) syndrome is a rare congenital anomaly characterized by uterus didelphys, obstructed hemivagina, and ipsilateral renal-ureteral agenesis, due to an embryogenesis defect. Clinically, HWW results in hematometrocolpos on the obstructed hemivagina side, which produces a mass effect with pain. The diagnosis is difficult because this syndrome is infrequent, and its clinical presentation is variable. Early detection and treatment are important to prevent further complications that could affect the reproductive performance. Ultrasound (US) is the first step when a Müllerian anomaly is suspected but MRI has a higher accuracy to manage surgery. Surgical treatment consists in vaginal septum excision. This review provides information about HWW syndrome and about its diagnosis and treatment. The main objective of this report is to illustrate the clinical presentation, the ultrasound features of a rare syndrome and the use of a

laparoscopic ultrasound guidance to allow a fertility sparing treatment without complications.

Material and Methods: A search of PubMed Database identified articles published from the inception to February 2019.

Results: 186 articles were identified: 125 articles were excluded for any reason. Overall, 63 articles were incorporated for further assessment.

Conclusions: The case reported was treated successfully by minimally invasive surgical drainage procedure supported by full time intraoperative ultrasound guidance. Only few researches described transvaginal and transabdominal probe use during surgery; this is the first case in the literature in which a laparoscopic ultrasound probe was used to guide surgeons in the excision of the vaginal septum to prevent complications and to preserve future fertility.

Keywords: Hematocolpos; Intraoperative Endoscopic Ultrasound; Müllerian Congenital Anomalies; Ultrasonography; Uterine Anomalies

1. Introduction

Herlyn-Werner-Wunderlich (HWW) syndrome is a rare congenital anomaly involving Müllerian and Wolffian structures, anatomically characterized by a triad of uterus didelphys, obstructed hemivagina, and ipsilateral renal-ureteral agenesis, with the right side twice more frequently affected than the left [1, 2]. In the general population, the reported incidence of uterine didelphys with renal agenesis is 0.1% to 3.8%; out of these, two thirds have a complete vaginal septum [3]. New classification proposed by Zhu et al. includes two types. Type 1, with a completely obstructed hemivagina and type 2, with an incompletely obstructed hemivagina [4]. Clinically, HWW syndrome results in hematometrocolpos on the obstructed hemivagina side, which produces a mass effect with pain [5]. Patients usually present symptoms shortly after menarche. Delays can occur in case of incomplete hemivagina obstruction or partial blood absorption between menstruations [6, 7]. The diagnosis is often difficult due to syndrome infrequency and clinical presentation variability. Early detection is important because surgical resection of the obstructed vaginal septum can provide pain relief and prevent further complications [2]. Delayed diagnosis could affect the reproductive performance of these patients, because retrograde blood flow destroys tubal function and leads to endometriosis [8]. Radiologic imaging is a fundamental tool in HWW syndrome diagnosis. Ultrasound is the first step when a Müllerian anomaly is suspected, but the technique is not able to clearly identify this anatomical abnormality. MRI depicts structural abnormalities with high-level accuracy and results are necessary to precisely plan surgery [7]. Surgical treatment consists in vaginal septum excision, showing good results. Around 80% of patients are able to conceive after surgery. Renal abnormalities and endometriosis are often associated with HWW syndrome. Therefore, it is important that physicians pay attention to these two indicator conditions, to guarantee a timely diagnosis and to avoid complications [8]. We present an HWW syndrome case, type 1.1 according to Zhu classification 4, with unusual late symptom onset. The minimally invasive surgical drainage procedure was supported by intraoperative ultrasound guidance carried out by an experienced ultrasonographer who helped the surgeon through a real-time visual ultrasonographic feedback to minimize surgical risks and to preserve fertility. The goal of this report is to review the published literature on HWW

syndrome diagnosis, treatment and discuss the potential future role of laparoscopic ultrasound guidance to improve fertility-sparing surgery in female genital anomalies.

2. Case Report

A twenty-year-old woman was admitted to our department with 1-month history of lower abdominal pain, not responsive to medical treatment. No associated menstrual irregularity, urinary or bowel symptoms, or loss of appetite/weight was evident, and menarche started at the age of twelve. No significant family and personal medical history were referred. No external genitalia abnormalities were noted, and secondary sexual characteristics were well developed. Physical examination exposed a tender and mobile mass in the pelvic region up to the umbilicus level. Gynecologic examination revealed a bulge occupying the upper part of the vaginal canal. Laboratory exams revealed normal white blood cells count and negative serum beta HCG. The CA 125 serum level was elevated (155 UI/mL; normal range= 0-34 U/mL). Abdominal and pelvic ultrasonography revealed a 197x83x120 mm regular neoformation, tender to the push of the ultrasound probe, with a "jelly like" content and absent flow at Doppler examination. The mass seemed to be connected to the uterine body, which appeared dislocated in the right hypochondrium (Figure 1). Only the right ovary was identified. The right kidney was not visualized. The left kidney was normal with a distal ureteral dilation (mm 49x20).

Magnetic resonance imaging (MRI) of the pelvis revealed uterus didelphys with two separated vaginas. The right vagina was inferiorly obstructed and distended, with blood as hematocolpos, suggesting a longitudinal obstructing vaginal septum. Both ovaries were described as normal. The right kidney was not visualized. Herlyn-Werner-Wunderlich syndrome was hypothesized in consideration of the right renal agenesis, uterus didelphys, and unilateral obstructed hemivagina with resultant hematocolpos. The patient was scheduled for combined laparoscopic and hysteroscopic treatment under laparoscopic ultrasound guidance. Prior to the surgery the patient underwent a gynecologic examination under anesthesia confirming the bulge on the right anterolateral vagina wall and confirmed the cervix in the left portion. Laparoscopy was performed in lithotomic position, after a 10-mm trocar insertion in the umbilicus. Two 5-mm ancillary trocars were introduced in the lower abdomen. Continuous CO2 pneumoperitoneum was induced keeping an intra-abdominal pressure below 12 mmHg. A 0° optic was introduced in the umbilical 10-mm trocar. Diagnostic laparoscopy revealed normal ovaries and fallopian tubes, but two uterine bodies as uterus didelphys, dislocated in the mesogastric and hypochondriac region and the presence of 100 mm mass, tender to the touch by laparoscopic forceps (Figure 2). Moreover, peritoneal brown patches were present suggesting early peritoneal endometriosis due to retrograde menstruation. An intraoperative ultrasound exam was required to clarify the origin of the formation. A 10 mm-suprapubic trocar was positioned to enter with a laparoscopic probe (model Toshiba PET-805LA, Toshiba Aplio i800 ultrasound machine), covered with a sterile cover. The probe was inserted in the 10 mm suprapubic trocar and positioned in direct contact with the uterus (Figure 3). The laparoscopic ultrasound guidance revealed an obstructive longitudinal vaginal septum with a massive hematocolpus in the right blind hemivagina and allowed surgeon to incise the septum using a transvaginal approach, spilling out a large amount of chocolate-like fluid (900 cc) (Figure 4). The

septum was resected revealing a second cervix (Figure 5).

Hysteroscopy was performed with a vaginoscopic approach, using a 5-mm diameter continuous-flow hysteroscope with oval profile, a 30° fore-oblique telescope and a 5 Fr operating channel (Office Continuous Flow Operative Hysteroscopy 'size 5'; Karl Storz, Tuttlingen, Germany). Saline solution (NaCl 0.9%) was used as distension medium, which was introduced with an electronic irrigation and aspiration system (Endomat; Karl Storz, Tuttlingen, Germany). A stable intrauterine pressure of about 40 mmHg was obtained. The hysteroscopic view showed a left external uterine ostium with a regular cervix. A left hemicavity with a single fallopian tube ostium was visualized examining the left cervical canal. On the right side, after the incision of the septum, a right external uterine ostium with a regular cervix was found. This right cervical canal led to a right hemicavity with a single fallopian tube ostium. The procedure took 30 minutes. No significant bleeding nor postoperative complications were encountered. Our case is classified as U3bC2V2 congenital anomaly according to the ESHRE/ESGE classification established by the CONUTA working group [9]. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

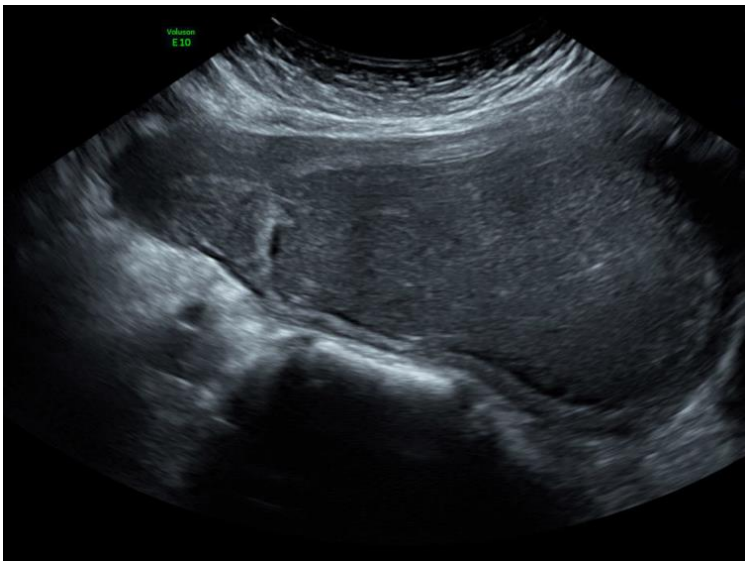

Figure 1: Ultrasound image of the hematocolpos.

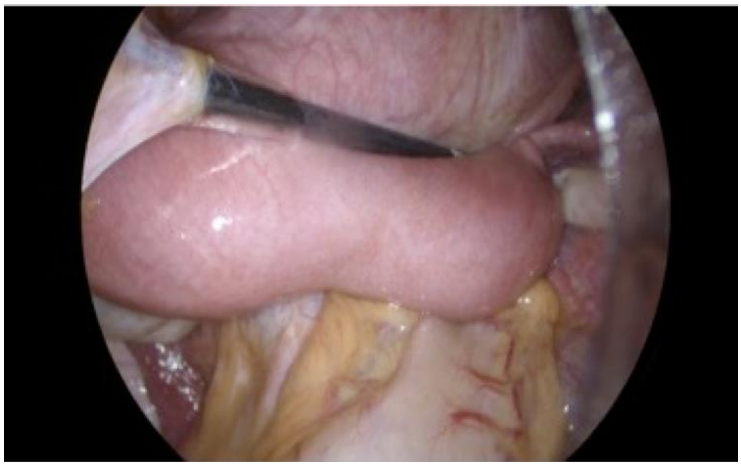

Figure 2: Laparoscopic view of two two uterine hemicorpi and hematocolpos.

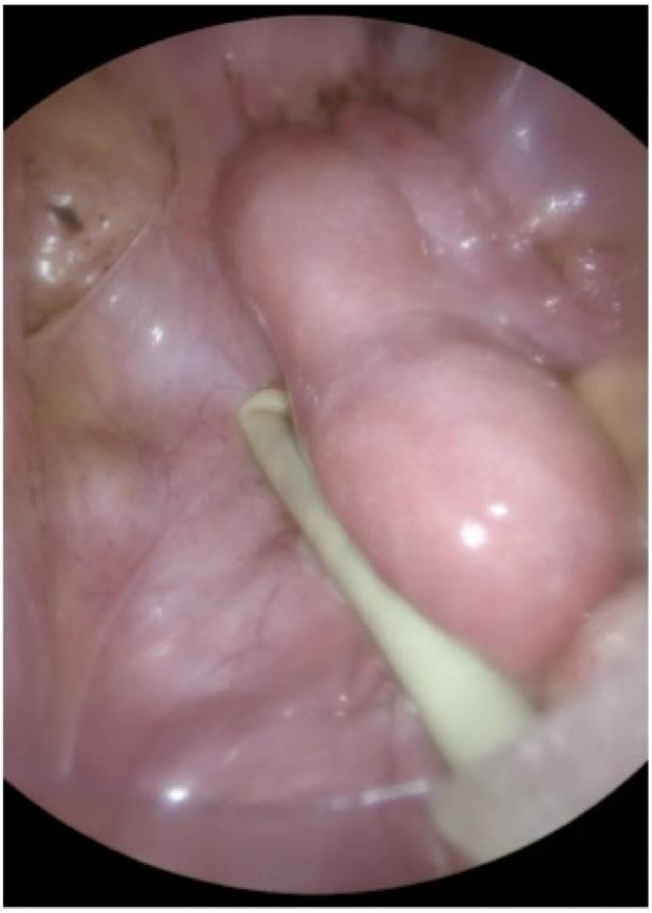

Figure 3: Laparoscopic probe in contact with the uterus.

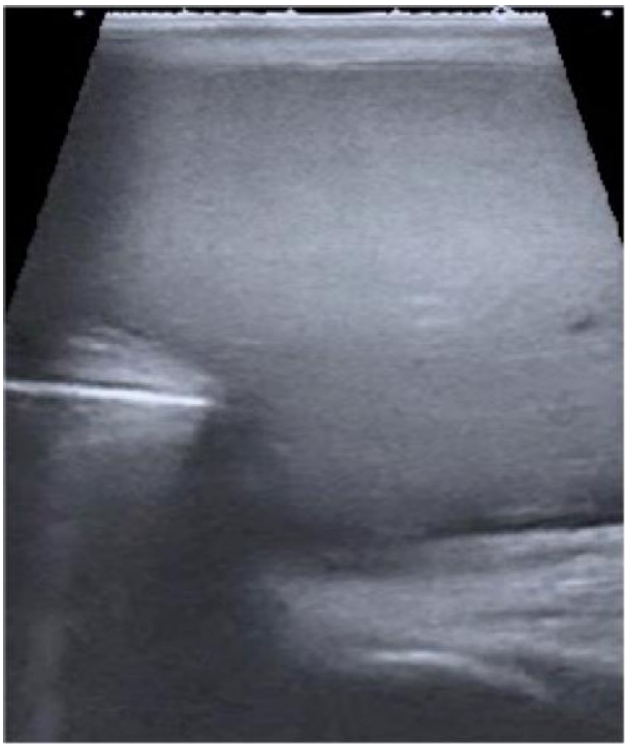

Figure 4: Laparoscopic ultrasound guidance during hematocolpos incision.

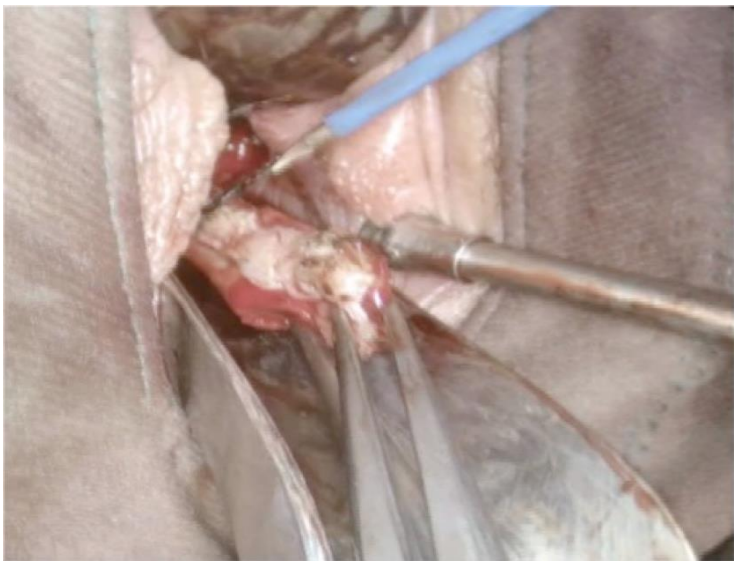

Figure 5: Vaginal septum resection.

3. Methods

A systematic review was therefore undertaken following the Preferred Reporting Items for Systematic reviews and Meta-Analyses "PRISMA" guidelines [10]. The clinical question was developed based on the PICOS format for this review (Table 1) [10]. Studies with patients with HWW syndrome were considered for the inclusion. Case reports were included in the selection. We searched PubMed (all from inception to 20 February 2019) to identify previous HWW syndrome case reports and reviews. No language restrictions were initially applied. We made an advanced search using in "all fields" the following key words: "Herlyn-Werner-Wunderlich", "didelphys uterus, obstructed hemivagina, ipsilateral renal agenesis" and "congenital vaginal oblique septum syndrome". This process was performed collaboratively by 2 authors (AM, MMC).

4. Results

The electronic database search provided 186 results. 159 records were screened after 27 duplicates were removed and of which 15 were excluded for linguistic reasons and 17 were excluded because full text was not available. 127 full text articles were screened and of which 20 were excluded because of ante menarche age of patients, 14 because related to pregnancy, 3 because presenting with cervical carcinoma, 20 because considered not relevant for the review, 9 because patients did not have all HWWS characteristics. 61 articles were considered eligible and of which reference lists were analyzed finding 2 additional eligible studies. Overall, 63 articles were incorporated in our review and patient features are summarized in Table 2. The main bias of the review is that many studies include few patients or single case report.

	Definition	**Search Keywords**
Participants	Patients with HWW syndrome. Patient with cancer, ante menarchal and pregnant were excluded.	"Herlyn-Werner-Wunderlich", "didelphys uterus, obstructed hemivagina, ipsilateral renal agenesis" and "congenital vaginal oblique septum syndrome"
Intervention	Any intervention	Not set
Comparison	Any intervention	Not set
Outcome	To assess the accuracy of the diagnosis and to identify the best treatment approach to avoid complications and improve the fertility outcome	Not set
Study Design	Any type of study including case report	Not set

Table 1: PICOS Format and Search Keywords.

Author (year)	Nr. of patients	Age or median age at menarche (years)	Age or median age at presentation (years)	Side	Clinical presentation	Ultrasound Findings	MRI findings	Surgery
Zurawin [31]-2004	8	12.5	14.5	6 RT	Cyclic pelvic pain	US used for initial imaging (75% of the time).	MRI was used in only four cases, and of these four, MRI was used as a second choice imaging modality in two cases.	3 VSR
				2 LT				
								3 LPS+VSR
Gholoum [1]-2006	12	Unknown	13		Menstrual irregularity 4	11/12 preoperatively assessed patients with an abdominal and pelvic US examination	MRI was performed in 2 patients	11 VSR
					Abdominal pain 11			1 laparotomy and salpingectomy for pyosalpinx
					Intraabdominal abscess 2 Menstrual bleeding 7			

	1	Unknown	11	RT	Amenorrhea and a 2-month history of lower abdominal pain	Absent right kidney, dilated right hemiuterus and hemivagina	Hematometrocolpos,suggesting the presence of a transverse vaginal septum with a dilated proximal vagina	VSR
	1	13	14	RT	Dysmenorrhea	Cystic mass in the pelvis, didelphic uterus, right renal agenesis	Confirmed the US findings, with the right hemiuterus filled with old menstrual blood	VSR
Orazi [23]-2007	5	6 months before	12	RT	Foul-smelling clots in vaginal discharge	Didelphic uterus, slightly dilated right hemivagina, absent right kidney	Didelphic uterus, dilated right hemivagina, absent right kidney	VSR
		2 months before	12	RT	Dysmenorrhoea	Didelphic uterus, right hemihaematometrocolpos, absent right kidney	Didelphic uterus, right hemihaematometrocolpos, periadnexal fluid collection, absent right kidney, hypertrophic left kidney	VSR
		11	12	RT	Dysmenorrhoea	Didelphic uterus, right hemihaematocolpos, absent right kidney	Didelphic uterus, divergent hemihaematocolpos, absent right kidney, hypertrophic left kidney	VSR

		12	12	LT	Dysmenorrhoea	Didelphic uterus, left hemihaematometrocolpos, absent left kidney	Didelphic uterus, left hemihaematometrocolpos, haematosalpinx, haemoperitoneum, absent left kidney, hypertrophic right kidney, left paravaginal Gartner's cyst and blind ectopic ureter	VSR
		12	13	LT	AUB	Didelphic uterus, left hemihaematocolpos, absent left kidney	Didelphic uterus, diverging horns, left hemihaematocolpos, absent left kidney, hypertrophic right kidney	VSR
Smith [32]-2007	27	unknown	14	16 RT	23/27 pain	Ultrasound performed in 16 cases, with a correct diagnosis in 5 cases.	Seven underwent magnetic resonance imaging (MRI) prior to referral, and a correct diagnosis was suggested in four cases. Sixteen MRI studies were performed after referral, of which 15 suggested a correct diagnosis.	26 VSR
				11 LT	6/27 AUB			1 hemihysterectomy
					2/27 fever			

Kim [33]-2007	1	8 months before	14	LT	Persistent vaginal spotting following menstruation	Two distinct uteri and a cystic mass along the left lateral wall of vagina	uterus didelphys, obstructed hemivagina and ipsilateral agenesis of the left kidney	VSR
Asha [34]-2008	1	15	17	LT	Recurrent swelling in the perineal region of her left side	An elongated lobulated lesion with thickened walls that extended from the perineal surface on left side into the pelvic cavity in close proximity to the uterus. The uterus along with the cervix was deviated to the right side. Left hematosalpinx. Left kidney was absent.	Unknown	LPS+HSC+ VSR
Kimble [35]-2009	4	12	15	RT	Menorrhagia and dysmenorrhoea	Unknown	Performed	LPS+VSR
		10	12	RT	Abdominal pain	Unknown	Performed	LPS+VSR
		14	17	RT	Urinary frequency Abdominal pain	Unknown	Performed	LPS+VSR
		11	12	LT	Vomiting Abdominal pain	Unknown	Performed	LPS+VSR

Sarac [36]-2009	1	13	25	RT	Primary infertility and episodes of mild lower abdominal pain during menstruation	Unknown	A large, well-defined and regularly bordered mass in the lower pelvis. Two distinct endocervical canals and clear separation of the uterine horns. The right endocervical canal was in contact with the upper portion of the mass. No direct communication could be established between the mass and the left hemivagina. Absent right kidney.	Unknown
Jindal [37]-2009	1	12	14	RT	Abdominal-pelvic pain	Uterus didelphys with unilateral obstructed hemivagina with resultant hematometrocolpos and hydrosalpinx with ipsilateral renal agenesis	Unknown	LPS+VSR

Takagi [38]-2010	2	12	14	RT	Recurrent pelvic pain	Unknown	An elongated lobulated lesion with thickened walls that extended from the perineal surface on the left side into the pelvic cavity in close proximity to the uterus. The uterus along with the cervix was deviated to the right side. Her right and left ovaries appeared normal. Absent left kidney.	VSR
		Unknown	52	LT	Recurrent pelvic pain	Enlarged lobulated lesion with thickened walls extending from the perineal surface on left side into the pelvic cavity in close proximity to the uterus	Uterovaginal duplication with an enlarged left uterovaginal cavity. Absent left kidney.	VSR

Arikan [39]-2010	1	13	17	RT	Right pelvic pain and dysmenorrhea	A right pelvic mass (5x5 cm), double endometrial echoes, and hematocolpos.	A right pelvic mass, agenesis of the right kidney, double uterus, and blind hemivagina with hematocolpos were detected by magnetic resonance imaging (MRI)	LPS+VSR
Khong [25]-2011	1	11	12	RT	6-month history of dysmenorrhoea	Uterine didelphys, with the ipsilateral hemiuterus distended to 5 cm in cross section, an absent right kidney, and a hypertrophic left kidney with a length of 12.5 cm.	Although preoperative magnetic resonance (MR) imaging of the pelvis would have been useful, obtaining a scan at short notice was difficult and would have delayed surgical management.	US guided VSR
Aveiro [13]-2011	1	5 months before	13	RT	4-day history of increasing right lower quadrant (RLQ) and hypogastric pain, nausea and sporadic vomiting	Absent right kidney Two uterine bodies	Two separate uteri with two separate cervices and two proximal vaginas, right distended vagina filled with a slightly hypointense material suggesting blood collection (haematocolpos). Although a longitudinal vaginal septum was not directly visualised, its presence was	VSR

							admitted.	
Nigam [40]-2011	1	15	22	LT	Foul smelling discharge for 2 years	Bicornuate uterus bicollis with an area of heterogenous collection, below and left to the uterus in the region of the vagina. Absent left kidney	Uterus didelphys with septae in the upper part of the vagina. Collection on the left side of the vagina was observed. Absent left kidney.	VSR
Dhar [41]-2011	1	Unknown	25	RT	Frequent, heavy, painful menstruation and foul smelling vaginal discharge	Two widely divergent uterine horns with two cervical canals. The right cervix was distended with fluid up to the right lateral vaginal wall.	Uterus didelphys with right hemivagina, a right lateral vaginal wall swelling with ipsilateral renal agenesis	LPS+VSR
Cox [42]-2012	1	12	17	LT	Progressive painful distention of the lower abdomen	A 7 cm fluid collection with diffuse low level internal echoes, which appeared contiguous with the endocervix	Didelphic uterus. Left hematometrocolpos. Left renal agenesis.	VSR
Guducu [43]-2012	1	Unknown	21	LT	Foul-smelling vaginal discharge after menstruation	Hematocolpos	Confirmed the diagnosis of blind hemivagina on the left side	VSR
	1	12	13	RT	Dysmenorrhea Dyspareunia	Right renal agenesis and right hematometrocolpos	Confirmed the US findings	Right hemi-hysterectomy

Mandava [44]-2012	1	11	14	LT	Acute retention of urine, fever, vomiting, and lower abdominal pain.	A large, well- defined cystic lesion with low-level internal echoes in the pelvis.The left kidney was not visualized.	The left uterus, cervix, vagina, and fallopian tube were distended with fluid, with an obstructing longitudinal vaginal septum, suggestive of hematometrocolpos and hematosalpinx. The left kidney was not visualized.	LPS+ VSR
Delvescovo [45]-2012	3	13	16	RT	Abdominal-pelvic pain	Absent right kidney, possibility of uterine anomaly	Didelphys uterus and double vagina, one of which was obstructed. Right renal agenesis.	Unknown
		14	15	RT	Abdominal-pelvic pain	Unknown	Didelphys uterus communicating with a double vagina, of which the right vagina was obstructed. Right renal agenesis.	Unknown
Bajaj [46]-2012	1	13	14	RT	Abdominal-pelvic pain	Two uterine horns. The right horn was seen to communicate caudally with a large, ovoid fluid collection with internal echoes. Absence of the right kidney.	Confirmed the findings. In addition, it clearly demonstrated 2 vaginal cavities.	VSR

Schutt [27]-2012	2	Unknown	15	LT	Dysmenorrhea	9-cm complex cystic abdominal mass	Well-circumscribed vagina filled with a 12□7 x 8 cm fluid collection. Superior to this fluid collection, a nondistended uterus communicated with the vagina. A second uterus was identified, which also appeared nondistended.	VSR
		Unknown	14	LT	6 weeks of pelvic pain	A uterine didelphys with duplicated vagina as well as hematometra and hematocolpos of the left hemivagina and left uterine horn secondary to an obstruction of the left hemivagina. Ipsilateral renal agenesis.	Unknown	VSR

		10	11	LT	1 month of pelvic pain	A cystic pelvic mass (9.7 cm). A connected tubular structure, measuring 6.1x 3.1 cm, was noted to extend from the cephalad corner of the mass. This appeared to represent a hydrosalpinx emanating from a noncommunicating hematometra. There also appeared to be a second uterine horn, which was displaced and compressed along the mass. The left kidney was absent.	The left horn of the uterus was markedly dilated, measuring greater than 10 cm in length, with a second lobule seen superiorly.	LPS+VSR

Moshiri [47] -2012	1	Unknown	31	RT	18 months of primary infertility	Unknown	Two uterine horns, two individual cervices. A longitudinal vaginal septum divided the upper vagina into two cavities, with one cervix entering each hemivagina. A defect in the proximal end of the vaginal septum allowed direct communication between the two hemivaginas. The right hemivagina was moderately distended and contained blood products, consistent with hematocolpos. The right hemivagina terminated blindly approximately 4 cm cranial to the introitus.	Unknown
Beer [6]-2013	1	Unknown	19	RT	Severe vaginal pain	Unable to clearly identify the etiology of the mass	Uterine didelphus and absence of the right kidney	VSR
Zhou [48]-2013	1	19	26	RT	Dysmenorrhea	Didelphic uterus and a si-ngle cervix contiguous with the left uterine cav-ity. Right hematometra.	Unknown	VSR

Ahmad [49] -2013	1	13	22	LT	Infertility	Absent left kidney, a bicornuate uterus, bilateral cystic adnexal lesions, and left hydrosalpinx.	Two separate uterine cavities, cervices, and vaginas, suggestive of uterus didelphys. The right uterine cavity, cervix, and vagina were normal. The left uterine cavity and cervical canal were dilated and filled with fluid suggesting blood products. Left hemivagina was dilated with blood products within, implicating the presence of an obstructing left vaginal septum. Multiloculated left adnexal cystic lesions with blood products were seen suggestive of endometriotic cysts. In addition, a tubular structure was noted in left adnexal location extending laterally from left uterine cornu with hemorrhagic fluid within, indicative of left	VSR

							hematosalpinx. Absent left kidney with loculated hemorrhagic fluid collections in bilateral paracolic gutters, suggestive of peritoneal endometriosis	
Fedele [18]-2013	67	Unknown	20.7		Dysmenorrhea 94% Acute abdomen pain (2%)	Not performed	Unknown	VSR ± isteroscopic metroplasty ± cervicoplasty
Nabeshima [50]-2013	1	Unknown	12	LT	A history of severe pain in the lower abdomen and dysmenorrhea since menarche	A uterus bicornis unicollis with a dilated left uterine horn and sus- pected hematocolpos	A uterus didelphys and a cystic lesion of the cervix connected to the left uterine cavity	LPS Strassman metroplasty

Attar [51]-2013	1	11	13	RT	Abdominal-pelvic pain	Two disfinct hemiuteri. Right haematometra and haematocolpos. A single left kidney.	Confirmed the findings.	LPT+VSR+ Strassman metroplasty
Lin [52]-2013	1	12	19	RT	Frequent, copious amounts of blood-tinged, foul-swelling vaginal discharge.	Large, well-defined cystic lesion with a hypoechogenic elliptical cystic mass. A double uterine fundus with its corresponding endometrial canals. Both ovaries appeared normal. In addition, absence of the right kidney and a left cystic kidney were noted.	Two uterine horns, two cervices, and two vaginal cavities. The right hemivagina was markedly distended.	VSR
Ugurlucan [26]-2014	1	6 months before	13	RT	Acute severe abdominal pain Dysmenorrhea	Cystic lesion with well-defined borders and internal echoes in the pelvis and left lower abdomen posterior to the uterus. Right kidney not visualized.	Uterus didelphys and a single vagina, 5 cm mass filled with fluid suggestive of hematometrocolpos between the cervix on the right side and the proximal vagina on the left, absent right kidney	Unilateral hysterectomy after a TV US guided spetum incision
Sabdia [12]-2014	10	12		7 RT	6 progressively worsening	Unknown	Unknown	8 VSR

					dysmenorrhea			
				3 LT	3 patients acute abdominal pain			2 LPS Hemihysterectomy
					1 incidental finding			
Tong [21]-2014	70	Median time between menarche and symptom onset was 1 year	17.03	42 RT 28 LT	45 dysmenorrhea	A 100% accuracy rate, using ultrasonography.	Thirty-seven patients underwent MRI.	9 LPS/LPT +VSR
					28 intermittent mucopurulent discharge 18 metromenorrhagia			61 VSR
					14 combinations of these symptoms.			

Van Der Byl [7]-2014	1	6 months before	10	LT	Severe abdominal pain	Uterus didelphys.The left uterine cavity and cervical canal were dilated and filled with fluid that was hypoechoic with few hyp-erechoic areas . A tubular structure was noted in left adnexa location extending laterally from left uterine corn with fluid within, suggestive for left hema-tosalpinx. Renal agenesis of the left kidney.	Two separate uterine cavities, cervices and vaginas. Left uterine cavity, cervical canal and salpinx were dilated and filled with fluid suggesting blood products.	VSR
Wang [16]-2014	61	Median time between menarche and symptom onset 5.6 years	18.1	39RT	Dysmenorrhea	Unknown	Unknown	6 LPS+VSRT
				22 LT	Cystic mass in vaginal wall			52 VSR
					Abnormal vaginal discharge			3 Hysterecto-my
Wozniakowska [53] -2014	1	13	14	RT	Chronic, purulent, foul-smelling vaginal discharge	A double uterus with a double cervix, an echogenic structure on the right side of the vagina.	Didelphic uterus, largely distended right hemivagina (2.6 cm 4.3 cm 2.5 cm) suggestive of hematopyoc-olpos. Right renal agenesis.	VSR

Pereira [30] -2014	1	Unknown	25	RT	Dysmenorrhea	Uterine didelphys	A uterine didelphys with dilatation of the endometrial and endocervical canals bilaterally. The left uterus led to a normal-appearing vagina, while the right uterus led to a proximally dilated hemivagina measuring 4.7 × 3.3 × 4.2 cm. Absent right kidney.	VSR
Mishra [11]-2014	2	11	13	RT	worsening lower abdominal pain	Uterine didelphys, right hematometrocolpos and probable right haematosa-lpinx.The right kidney was absent.	Not performed	LPS+HSC + VSR
		12	13	LT	Dysmenorrhoea	Uterine didelphys, haema-tometra of the left uterine cavity, haematocolpos and absent left kidney.	Not performed	VSR
		9 months before	14	RT	Abdominal pain Dysmenorrhea worsening	right fallopian tube pathology	Two separate uterine horns with a hematometrocolpos.	LPS+***HSC + US guided VSR

Karaca [5] -2015	1	unknown	13	RT	2 days severe pain in the right lower quadrant of the abdomen	A cystic lesion in the right adnexial region and absence of the right kidney	Didelphys uterus communicating with a double vagina; the right vagina was obstructed. There was a collection of fluid, both in the right uterus, and in the right obstructed vagina referred to as hematometrocolpos	VSR
Piccinini [8] -2015	1	11	13	LT	5-month history of episodic perineal and rectal pain and abdominal fullness unrelated to eating	Unknown	Unknown	Hymenectomy +VSR

Mehra [14] -2015	1	2 months before	13	LT	3 months cyclical pain in the lower abdomen	Absence of left kidney with two structures in the pelvis demonstrating the shape, contour and echo pattern of a uterus. The endometrial cavity of the left uterus was distended with fluid contents. The vagina was not clearly appreciated in continuity with this structure.	Absence of left kidney was confirmed. The endometrial cavity of the left uterus and upper part of left hemi vagina was distended with fluid suggestive of hemorrhagic contents. Two separate uteri each with a separate cervix and vagina with no communication between the two at any level. A septum just below the hematometrocolpos in the mid left hemi vagina. A diagnosis of left renal agenesis with didelphys uterus and left hemivaginal septum causing obstruction and left hematometrocolpos was arrived at, based on the MR imaging.	VSR

Yavuz [54]-2015	13	detected from about 4 months to 20 years after menarche.	17.2	7 RT	Severe pelvic pain, progressive dysmenorrhea, and irregu- larity in menses with discharge of longstanding, partially clotted menstrual blood at initial presentation.	Uterovaginal duplication (didelphic or bicornuate-bicollis uterus) and hematocolpos/hematometrocolpos due to obstructed hemivagina in all cases. Agenesis of the ipsilateral kidney.	signal of fluid collections showed variances on the basis of the content and duration of blood. Hyperintense fluid on both T1- and T2-weighted images was established in both uterovaginal cavities (hematometrocolpos) in four patients and solely in the uterine cavity (hematometra) in 8 patients. In addition, distinct fluid-fluid levels were detected in cavities in 6 patients. Ipsilateral renal agenesis was also confirmed in all patients.	4 refused the procedure
				6 LT				1 Hysterectomy with unilateral colpectomy

Kumar [55]-2015	1	12	14	LT	Acute retention of urine	Bicornuate uterus with haematocolpos	Two widely divergent, symmetrical uterine corpii, partially fused at the cervix without any communicati-on between their endomet-rial cavities. Left hemivag-inal septum with a large ipsilateral haematocolpos. Left haematosalpinx. Left renal agenesis.	LPS+VSR
Tug [56]-2015	1	12	21	LT	Abdominal-pelvic pain and distention for one year.	Haematometrocolpos, obstructed hemivagina and renal agenesis	Haematometrocolpos, obstructed hemivagina and renal agenesis	VSR
Zhu [4]-2015	79	Duration between menarche and	16.4	45RT	Dysmenorrhea	Unknown	Unknown	11 LPS/LPT+V SR
		onset of symptoms 1,6 years		34 LT	Intermittent mucopurulent discharge			68 VSR

Mittal [57]-2016	1	unknown	16	RT	Pain lower abdomen for 1–2 years	Bicornuate uterus. Hematometra and hematosalpinx with free fluid in peritoneal cavity and the absence of right kidney.	confirmed the findings of USG, i.e., uterus didelphys with two cervix with right-sided he- matometra and hematosalpinx with free fluid in peritoneal cavity and the absence of right kidney.	Right hemi-hysterectomy
Khaladkar [2]-2016	1	12	13	LT	pain in the lower abdomen	Absence of the left kidney. Uterus didelphys. Haematometra and haematocolpus.	Absence of the left kidney, uterus didelphys. The left uterus was enlarged due to fluid collection,suggestive of blood, in the uterine cavity and cervical canal measuring 8.7 (L) ×4.3 (AP) ×4.1 (T) cm	****LPT hemihysterectomy
Sharma [58]-2016	1	5 months before	13	RT	4-day history of increasing right lower quadrant and hypogastric pain, nausea, sporadic vomiting without fever, diarrhoea and urinary symptoms.	Absent right kidney, right haematocolpos and two uterine bodies	Uterus didelphys and two proximal vaginas. Right haematocolpos.	VSR

Bhoil [59] -2016	1	16	19	RT	Abdominal pain gradually increasing in intensity and scanty periods since the last 6 months	Uterus didelphys, haematocolpos Absent right kidney.	Confirmed the US findings	VSR
Unal [60] -2016	1	12	13	RT	Pelvic pain and dysmenorrhea	A right pelvic mass, agenesis of the right kidney, double uterus and blind hemivagina with hematocolpos	Confirmed the US findings.	LPS+HSC+ VSR
Tsai [61] -2016	1	unknown	43	RT	Fever with chills and left flank pain	Unknown	Unknown	Antibiotics and insertion of Foley
Ylmaz [15] -2017	2	3 months before	13	LT	Dysmenorrhoea	Uterus didelphys, haematocolpos and agenesis of the left kidney.	Uterus didelphys and two proximal vaginas distended and filled with hyperintense fluid, suggesting a blood collection (haematocolpos).	Unknown
		13	15	RT	Cyclic pelvic pain	Uterus didelphis, left dilated hemivagina. The right kidney was absent.	Uterus didelphis, a distended left hemivagina with fluid consistent with haemorrhage was depicted.	VSR

Ellspermann [62] - 2017	1	10	12	RT	Abdominal-pelvic pain	Hypoechoic structure of indeterminate etiology in the right lower quadrant, to the right of the uterus, filled with hypoechoic material. There was consideration for fluid collection, hemorrhage, and even for malformed kidney in the pelvis.	Not performed	VSR
Sleiman [63]-2017	2	12	16	LT	Chronic pelvic pain and progressive painful distention of the lower abdomen	Two endometrial cavities, the left side being dilated with a fluid collection. Left hematosalpinx, and a vaginal collection of 6x4 cm^2. Absence of a left kidney.	Didelphic uterus was demonstrated. Left hematosalpinx. The left endometrial cavity distended, and contiguous with the left obstructed hemivagina	VSR
	13	20	RT	Primary infertility and dyspareunia	Didelphic uterus with a 3x4 cm^2 homogenous collection in the vagina. Absence of a right kidney	a bicornuate uterus, with two crevices, the right one communicating with a right vaginal collection due to a longitudinal hemi vaginal septum	LPS+VSR	13

Jung [64]-2017	1	13	22	RT	Foul-smelling vaginal discharge with intermenstrual bleeding	Uterus didelphys with a hypoechoic heterogeneous cystic mass measuring 4.8 x 5 cm behind the bladder. Absent right kidney.	Uterus didelphys with a distended right hemivagina measuring 3.1×3.5×4.8 cm, suggesting a turbid fluid collection and right renal agenesis	LPS+VSR
Al ghafri [19]-2018	1	Unknown	15	RT	Abdominal discomfort	Absent right kidney Distended right vagina	Uterus didelphys, Right hematocolpos. Right kidney absent	*LPS+ **VSR
Gai [20]-2018	21	Mean duration from the first menstruation to operation: 6.67+-2.06 in type I 134 months in type III	17.29	14 RT 7 LT	Dysmenorrhea	All 21 patients exhibited a double uterus and cervix with ipsilateral renal agenesis and oval cystic masses of various sizes with dense floating echogenic debris	Unknown	VSR
Gupta [3]-2018	1	14	16	RT	2 days history of increasing lower pelvic pain	Hematometra, hematocolpos, right kidney absent	Uterus didelphys, right cervical atresia resulting in distended right endometrial and right endocervical cavities	Right hemi-hysterectomy

Hamidi [17]-2018	1	Unknown	19	RT	Chronic pelvic pain and a palpable mass at the lower pelvic midline region	A cystic structure in the lower pelvic region communicating with the uterus (likely dilated vagina) with endometrial cavities and absent right kidney	Duplication of the uterine bodies, endometrial canals, uterine cervices and vaginal canals, significantly dilated right vaginal canal, communication between the two cervices, small tubular structure with internal fluid signal along the anterolateral aspect of the dilated right hemivagina represented blind ectopic ureter, absentright kidney heterogeneous cystic structure in the left ovary with hemorrhagic components	VSR
Ilyas [65]-2018	4	unknown	18	LT	Secondary amenor-rhea, abdominal pain and lower abdomen swelling	Not performed	Left haematometra, haematocolpos, and haematosalpinx, absent left kidney	unknown
		13	14	RT	Increasing pelvic pain	Absent right kidney and uterus didelphys with right cavity dilated	Uterine didelphys and absent right kidney	unknown

		unknown	26	RT	irregular menses gradual supra-pubic swelling	Not performed	Uterus didelphys with right haematocolpos and haematometra with absent right kidney	unknown
		unknown	13	RT	Primary amenorrhoea, lower abdominal pain, increasing suprapubic swelling.	Not performed	Uterus didelphys with grossly dilated right hemivagina with blood products and normal left uterine cavity, absent right kidney and normal left kidney	unknown
Kapczuc [28]-2018	16	12	13	59.1% RT 40.9% LT	1 asymptomatic 2 dysmenorrhea 4 spontaneous perforation of the vaginal septum	Unknown	Unknown	VSR

Widyakusuma [22]-2018	1	12	23	RT	Dysmenorrhoea	Two anteflexed uteri fused at the precede to the cervix haematocolpos. There was no right kidney.	Two complete sets of uteruses were found, each with its own corpus and cervix. The results also showed a cystic mass connected with the uterine cavity and cervical canal, obstructing the distal part of the vagina	VSR
* *LPS: laparoscopy surgery*								
** *VSR: vaginal septum resection*								
*** *HSC: hysteroscopy*								
**** *LPT: laparotomy surgery*								

Table 2: Sistematic literature review about cases of HWW syndrome.

5. Discussion

5.1 Definition

Herlyn-Werner-Wunderlich syndrome represents currently a combination of two different syndromes: Herlyn-Werner syndrome, described in 1971, consisting of renal agenesis and ipsilateral blind hemivagina, and Wunderlich syndrome, described in 1976 that broadened the syndrome adding uterus didelphys [1, 7]. The first article in English using the term Herlyn-Werner-Wunderlich syndrome described the triad of uterine didelphys with obstructed hemivagina and ipsilateral renal agenesis and was published in 2006. The acronym OHVIRA (obstructed hemivagina and ipsilateral renal anomaly) syndrome was proposed in 2007 to allow the inclusion of other uterine and renal anomalies [4].

5.2 Etiopathogenesis

HWW syndrome occurs at the eighth week of gestation due to an embryogenesis defect affecting both the paramesonephric (Müllerian) and mesonephric (Wolffian) ducts [11]. The close embryological relationship between the Müllerian and Wolffian ducts results in a strong association between renal and genital tract abnormalities. Indeed, renal agenesis is a predictor for ipsilateral obstructive Müllerian anomaly in more than 50% of cases [12, 13]. During the 6ed week of embryogenesis, the absence of Müllerian Inhibiting Factors promotes in female embryos bidirectional growth of paired Müllerian ducts [14]. At the 8th week, the Müllerian ducts migrate to the midline where they fuse to develop the uterus, the cervix, and the upper part of the vagina [6]. The lower third of vagina is formed from sinovaginal bulbs, which are protrusions of the urogenital sinus [15]. Wolffian ducts induce kidneys development and play an important role in the internal genital organ development, as adequate fusion inductor of the Müllerian ducts [2]. Failure of fusion leads to uterine duplication with two uterine bodies, two cervices, and a vaginal septum [16]. The absence of one Wolffian duct leads to kidney and ureteral agenesis on the absent side, and to lateral displacement of the Müllerian duct, which cannot fuse with the contralateral duct, resulting in uterus didelphys. The contralateral Müllerian duct induces vagina development, whereas the displaced duct cannot come into contact with the urogenital sinus and centrally forms a blind sac, leading to an imperforate hemivagina

5.3 Classification

Zhu et al. [4] reviewed the characteristics of 79 HWW patients at the Peking Union Medical College Hospital and suggested a new syndrome classification based on complete or incomplete obstructed vaginal septum presence. Each of these two groups included two classification types. Type 1.1: The affected hemivagina is completely obstructed and hematocolpos usually occur a few months after menarche, alongside abdominal pain, fever, and vomiting. Type 1.2: The hemivagina is completely obstructed, the cervix behind the septum is maldeveloped/atresic and menses cannot outflow from the uterus behind the septum through the atresic cervix. Type 2.1: A small connection exists between the two hemivaginas, which obstructs the vaginal cavity behind the septum incompletely. Type 2.2: The hemivagina is completely obstructed and a small connection exists between the duplicated cervices. In the two last classifications, menses can outflow through a small connection, therefore patient symptom onset occurs later in life [4]. We classified our case according to Zhu et al. [4] as a 1.1 type, since a completely obstructed hemivagina was evident and in absence of cervical atresia or communication between the two cervices. However, the late symptom onset

(seven years after menarche) makes our case unusual.

5.4 Clinical presentation

Herlyn-Werner-Wunderlich syndrome is usually diagnosed at puberty, shortly after menarche, compared to most frequent congenital anomalies of the female genital tract, such as imperforate hymen or vaginal atresia, presenting symptomatic amenorrhea, Initially, the syndrome may remain unrecognised as regular menstrual flow, from the unobstructed hemivagina appears as normal menses. Additionally, dysmenorrhea, if present, is a common complaint in this age group [1, 3, 11]. Clinical symptoms may vary and non-specific features such as acute abdominal, pelvic or vaginal pain, dysuria, urinary retention, vaginal discharge and infertility have been reported. Associated complications include infectious collections and long-term sequelae such as endometriosis, pelvic adhesions, and infertility [11]. In case of infected hematocolpos, fever, chills, nausea and vomiting may be present [8]. In extremely rare cases, hematocolpos can lead to hematosalpinx and rupture, resulting in peritonitis, while incomplete obstruction could cause mild intermittent symptoms that do not get worse until complete obstruction with hematocolpos occurring later in life [6]. Rarely, adenocarcinoma of the obstructed uterine cervix and clear cell carcinoma of the obstructed vagina portion are also reported [3]. Clinical symptoms are mainly related to the abnormality type. In classification I, the common clinical presentation can be pelvic pain shortly after menarche, associated with vaginal or pelvic mass. In classification 2, the clinical presentation may be delayed as the obstructed side can be drained through the contralateral vagina [17]. Fedele et al. conducted a large institutional case series including 87 patients with OHVIRA syndrome, of which 67 patients were diagnosed with didelphys uterus, obstructed hemivagina and ipsilateral renal agenesis. Clinical characteristics, in particular main symptoms, were underlined like dysmenorrhea (94%), spotting (41%), chronic pelvic pain (24%), vaginal discharge (14%), dyspareunia (14%), fever (3%) and acute abdomen pain (2%) [18].

5.5 Diagnosis

Sonography and magnetic resonance imaging (MRI) are extremely useful to diagnose and classify Müllerian duct anomalies [4]. Ultrasound is frequently the initial imaging modality due to its wide availability and relatively low cost [19]. Recently Gai et al. investigated ultrasound features of 21 patients affected with HWW and compared them with surgery results. All 21 HWW syndrome cases were diagnosed with ultrasonography prior to surgery. Based on these results, he suggested that a sonographic type 1 HWW syndrome diagnosis might be possible in evidence of a double uterus, with or without uterine cavity hemorrhage, featuring an echo-free area below one cervix, with dot-like hyperechoic regions, mimicking endometriotic ovarian cysts and ipsilateral renal agenesis. Type 2 HWW syndrome ultrasonographic features are the same as for type 1, apart from a smaller and lower mass tension, due to partial menstrual blood drainage [20]. In a retrospective analysis, including 70 patients with hemivaginal septum, uterus didelphys and ipsilateral renal agenesis, a high ultrasonography accuracy rate to diagnose HWW syndrome was reported. Only 37 out of 70 patients required MRI or further confirmation of uterine and cervical development [21]. Ultrasound achieved 90-92% accuracy to diagnose HWW syndrome. However, vaginal septum visualization is often difficult and requires an MRI. This modality has long been considered as the gold standard to diagnose and plan surgical treatment, especially in a tertiary center with experience in Müllerian anomaly interpretation [18, 15,

22]. MRI with multiplanar image provides more detailed information regarding uterine morphology (uterine horns disposition), vaginal channels continuity (obstructed/not obstructed) [22], vaginal septum thickness and location, obstructed cavity contents (e.g. blood versus simple fluid) and coexisting urinary tract malformations [11, 19].

MRI accuracy, to diagnose uterine malformations, is well established and even 100% accuracy has been reported [23]. Laparoscopy has been advocated as the gold standard for HWW syndrome evaluation and associated complication treatment, specifically for those cases where a clear MRI diagnosis is impossible, an MRI is not available or when suspected concurrent intraperitoneal pathologies such as endometriosis, adhesions and pelvic infection are present [3, 11]. Intraoperative ultrasound guidance can be very helpful in HWW syndrome surgery in order to gain access to the obstructed hemivagina, especially when the vaginal bulges are not obvious, avoiding bladder, rectum and blood vessels damage [24]. We performed full time intraoperative ultrasound guidance using a laparoscopic probe, to identify first the origin of the pelvic mass, then to guide the surgeon to drain the hematocolpus and finally to identify the two different hemicavities during the hysteroscopic procedure. We could not identify any HWW case reports in which the use of a laparoscopic ultrasound probe was described. We identified three case reports describing intraoperatively ultrasound guidance. Khong et al described a transabdominal ultrasound guidance of vaginal septum resection [25]; Gungor Ugurlucan et al. [26] and Schutt et al. [27] described a transvaginal ultrasound guidance, Alur et al described an intraoperatively ultrasound guidance but without reference to the approach they used [24].

5.6 Treatment

HWW syndrome treatment aims at complication prevention to avoid hematocolpos and hematometra in order to restore genital system functionality, achieving normal fertility potential [1, 3]. Currently, the preferred surgical approach for patients with 1.1, 2.1, and 2.2 classification is the full excision and marsupialization of the vaginal septum applying a transvaginal approach in order to reestablish the continuity of the obstructed hemivagina. This approach is better executed under ultrasound guidance and during menstruation as large distended hematocolpos are easier to visualize and to palpate [1]. Although not yet reported in literature, the grossly distorted uterovaginal anatomy could increase the risk of resecting normal vaginal tissue or even lead to bladder perforation, particularly when the obstructed vagina reaches the hymeneal ring. Intraoperative ultrasound guidance is very useful to identify anatomical structures to decrease this risk. Treatment for patients with 1.2 classification differs from the treatment of patients with other classifications because surgical cervical agenesis correction is difficult and laparoscopic or transabdominal resection of the atresic hemi-uterus is suggested [4]. Complete vaginal septum excision was performed in all 16 HWW syndrome patients described by Kapczuk et al. The surgery was for 15 patients uneventful. Vaginal septum excision was complicated by urinary bladder injury in one patient, with spontaneous perforation of the vaginal septum a week before hospital admission [28]. Hur et al. suggested not omitting laparoscopic evaluation in patients with obstructed vaginal septum, which may inevitably result in massive menstrual regurgitation or even endometriosis and pelvic adhesions, which cannot be detected by ultrasonography or MRI [29]. Postoperative vaginal adenosis should be considered in patients with previously obstructed vagina. No

definitive guidelines are yet existing, although some authors recommend yearly Papanicolaou tests and colposcopy [1].

5.7 Prognosis

Untreated HWW syndrome can lead to endometriosis, pelvic adhesions, and pyosalpinx or pyocolpos [1]. Endometriosis occurs in 17%–35% of patients with uterus didelphys. The rate of endometriosis was higher among patients with complete hemivaginal obstruction compared to those with incomplete obstruction, possibly because of consistent and severe retrograde menstrual flow [21]. Women with uterus didelphys have a reasonable chance of getting pregnant, but the abortion rate is high (74%) and premature delivery is common (22%). In 82% of pregnancies a caesarean section is required [13]. Zhu et al. performed a retrospective long-term follow-up study on surgical prognosis and pregnancy outcomes. They found that full resection of the vaginal septum was associated with good outcomes and fertility. No pathologic pregnancies or pregnancy complications were documented [4]. Gholoum et al. performed a review including 12 HWWS patients who were treated surgically with vaginal septectomy and hematocolpos/hematometrocolpos drainage. The median follow-up was 3 years in which 11 patients were asymptomatic after treatment and only one patient complained irregular menses [1]. MRI evaluation of the genital tract is recommended in all young women with known renal abnormalities, to carry out surgical corrections of the obstruction before menarche and therefore before any damage has occurred [13]. In conclusion, HWW syndrome prognosis is good for early diagnosed and treated patients, except for those with 1.2 classification. Ipsilateral hysterectomy is suggested in HWW syndrome cases complicated by cervical atresia, because septum resection would not relieve obstructions [4].

6. Conclusions

Although rare, HWW syndrome should be considered in young patients presenting symptoms like dysmenorrhea, abdominal pain, pelvic mass and renal agenesis because early detection and management is important for symptom relieve, to prevent complications and to preserve future fertility. The current study is the first literature review on HWW syndrome; moreover, we present the first case in which the use of laparoscopic ultrasound probe is fundamental to diagnose and treat a uterine defect. Only few cases are described using transvaginal and transabdominal probes during surgery [24, 25, 26, 30]. We think that our technique allows a precise intraoperative definition of some complex uterine malformations, supporting a precise and safe surgical procedure and avoiding intraoperative complications; albeit just one case, we propose intraoperative laparoscopic ultrasound guidance as an innovative approach to be used in complex female genital malformations, waiting at least larger case series to have solid results about surgical outcomes and fertility.

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Disclosure

No disclosures to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

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