

## Herlyn-Werner-Wunderlich Syndrome: A case report and a comprehensive review of literature

Nguyen Tuyet Trinh<sup>1\*</sup>, Dang Van Tan<sup>2</sup>, Tran Minh Thang<sup>2</sup>, Le Viet Hung<sup>2</sup>, Cao Ngoc Thanh<sup>1</sup>

<sup>1</sup> Hue University of Medicine and Pharmacy, Hue University

<sup>2</sup> Hue Central Hospital

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Corresponding author: Nguyen Tuyet Trinh, Email: nttrinh95@gmail.com

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### Abstract

*Herlyn - Werner - Wunderlich is a very rare congenital malformation of the urogenital tract involving both the Müllerian (paramesonephric duct) and Wolffian duct (mesonephric duct), which is characterized by the triad of didelphys uterus, ipsilateral obstructed hemivagina, and ipsilateral renal agenesis. We report the clinical case of a 25-year-old female patient diagnosed with Herlyn - Werner - Wunderlich syndrome (HWWS) as well as an overview of HWWS to discuss the approach, diagnosis and treatment by classification.*

**Keywords:** *Herlyn-Werner-Wunderlich (HWW) syndrome, didelphys uterus, ipsilateral obstructed hemivagina, ipsilateral kidney agenesis.*

### 1. INTRODUCTION

Herlyn - Werner - Wunderlich Syndrome (HWWS) is a very rare congenital malformation of the urogenital tract involving both the Müllerian (paramesonephric duct) and Wolffian duct (mesonephric duct), which is characterized by the triad of didelphys uterus, ipsilateral obstructed hemivagina, and ipsilateral renal agenesis. The first case of uterine didelphys, together with hemivaginal obstruction was reported in 1922 while the triad was first reported in 1971 by Herlyn and Werner and re-reported in 1976 by Wunderlich [1]. Therefore, this syndrome is called Herlyn - Werner - Wunderlich.

The incidence of didelphys uterus, related to HWWS, is approximately 1/2,000 to 1/28,000, and it is accompanied by unilateral renal agenesis in 43% of cases. The incidence of unilateral renal agenesis is 1/1100, and 25 - 50% of affected women exhibits associated genital abnormalities [2]. A complete or partial vaginal septum is present in 75% of women with didelphys uterus [3]. HWWS involves the abnormal development of two embryological structures: the mesonephric and paramesonephric ducts, but the exact mechanism remains unknown [4]. HWWS is often diagnosed after menstruation with clinical manifestations of dysmenorrhea, recurrent abdominal pain and irregular menstruation. There are currently two main classifications for HWWS, which are the classical classification according to Rock and Jones and the classification by Chinese experts in 2015. The latter has added a new group to the classification, which is cervicovaginal atresia, without communicating uteri.

The clinical presentation of female genital tract malformations is different and the possible

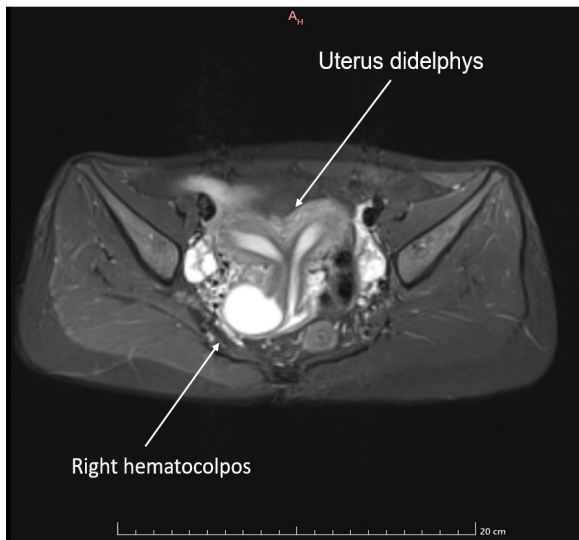
combinations of other malformations, it is nearly impossible to outline a single uniform treatment and management plan. Therefore, selecting the appropriate management and therapeutic strategy presents a challenge for gynaecologists. Based on our experience and the updated literature review, we report the clinical case as well as mention an overview of HWW syndrome to provide information for clinicians in early diagnosis and treatment strategies.

### 2. CASE REPORT

A 25-year-old female patient, not yet sexually active, was admitted to the hospital with lower abdominal pain. She attained menarche 10 years back. The patient had regular and scanty menstruation associated with dysmenorrhoea. Physical examination showed no palpable mass in the abdomen. Secondary sexual characters were well developed. Routine investigations were normal. From vaginal inspection, vaginal introitus was seen and with an intact hymen.

Abdominopelvic ultrasound images revealed uterus didelphys, obstructed right hemivagina, and a voluminous cystic mass in the left corresponding to hematocolpos, measuring 36 x 24 mm. The right kidney was not visualized.

MRI illustrated right renal agenesis, image of a uterus didelphys with two uterine chambers and two separate cervixes. The vagina has a wall that separates the two vaginas and the two uteruses. The right vaginal chamber has a large cyst with thick fibrous walls, measuring #77 x 47 x 25 mm. Both ovaries were of normal size. Image of a hydrosalpinx was next to the right ovary.



(a)



(b)

**Figure 1.** MRI showing uterus didelphys (a) and right hematocolpos (b)

The patient was diagnosed with Herlyn - Werner - Wunderlich syndrome and was prescribed diagnostic laparoscopy and vaginal surgical approach to resect the vaginal septum.

Our surgical protocol was as follows:

Laparoscopic surgery was performed first and confirmed that the entire peritoneal cavity has normal morphology. The image of 2 uteruses of a double uterus is observed, the size is equivalent, about 7 x 4 x 3 cm. The right fallopian tube is slightly dilated. The ovaries on both sides did not show any abnormal images.

Before starting the vaginal approach, a small hymenotomy was performed to have access into the

vagina. We observed that the ipsilateral obstructed hemivagina was bulging at the top-right side, pushing out and filling the space in the vagina, a small fistula about 1cm from the cervix on the right. Two traction sutures were passed through the vaginal mucosa, above and under the greatest bulging, at a 5 cm distance, and the vagina wall was incised about 5 cm distance on the bulge and draining about 70 ml of "chocolate-like" fluid. Above the hemivagina, a separate complete cervix was found. Stitched the edge of the incision by knotless suture about 1 cm apart by vicryl 2.0. Antibiotic therapy (amoxicillin and clavulanic acid) also commenced.



**Figure 2.** A laparoscopic view shows two hemi uteri, corresponding to uterine didelphys.

The patient was discharged from the hospital 3 days after surgery. Then, she was referred to a gynecological outpatient clinic for further follow-up after 3 months and

6 months. During the observation, the patients did not report any pain that had already subsided during hospital treatment. No blood was found in the reproductive tract.

### 3. DISCUSSION

Herlyn - Werner - Wunderlich syndrome is a congenital genital malformation due to abnormalities in the development of the Müllerian duct and the Wolffian duct, characterized by the triad of didelphys uterus, ipsilateral obstructed hemivagina, and ipsilateral renal agenesis. Clinical presentation is usually with abdominal pain, dysmenorrhea, urinary retention, hematosalpinx, endometriosis, and rupture of a tubo-ovarian abscess [2].

During embryogenesis, at about the 6th week, embryos in both sexes have 2 pairs of gonadal ducts: 2 mesonephric ducts (Wolffian ducts) and 2 paramesonephric ducts (Müllerian ducts). The Müllerian ducts form the fallopian tubes and uterus up to the external cervical os but without reaching the urogenital sinus. The Wolffian ducts open into the urogenital sinus, and the ureteral bud sprouts from the caudal tip of their opening [3]. The kidneys originate as ureteric buds from the Wolffian ducts, and the lower third of the vagina derives from the urogenital sinus [3].

The exact etiology and pathogenesis of HWWS is still unclear, but experts suggest that this syndrome occurs due to defects in the development and fusion of the caudal portion of the Müllerian duct during the 8th to 12th week of gestation, accompanied by abnormalities in septal resorption failure at 20 weeks of pregnancy [4], [5], [6]. The mesonephric ducts, besides giving origin to the kidneys, are also inductor elements for adequate Müllerian duct fusion. Therefore, a developmental anomaly of the caudal portion of one of the Wolffian ducts may be the cause of unilateral renal agenesis associated with imperforate hemivagina [7]. On the side where the Wolffian ducts is absent, the Müllerian duct is displaced laterally and cannot fuse with the contralateral duct, resulting in a didelphic uterus. The contralateral Müllerian duct gives rise to the vagina, whereas the displaced Müllerian duct that cannot come into contact with the urogenital sinus centrally forms a blind sac, leading to an imperforate or obstructed hemivagina [2].

The most common symptom is recurrent and progressive pelvic pain, and the severity of the symptoms is greatly influenced by the shape of the vaginal obstruction [8] [9]. Pain usually occurs due to the presence of hematocolpos, hematometra, hematosalpinx, and or hemoperitoneum [1, 6]. However, the course of HWWS can be asymptomatic, which is associated with the normal outflow of menstrual blood through a patent collateral hemivagina [10]. At the same time, such a long time of blood retention in the blocked vagina could contribute to the development of bacterial infection. Long-term continual reverse menstrual flow may result in hematocolpos, hematometra, and hematosalpinx, leading to long-term complications such as pelvic adhesions, endometriosis, infertility, and increased risk of abortion [11]. Furthermore, the female reproductive tract

and urinary tract develop in close relationship with one another. Thus, Müllerian anomalies are often associated with urinary tract anomalies such as horseshoe or pelvic kidney, renal agenesis, duplication of the collecting system, or ectopic ureters [12].

Due to the normal appearance of the external genitalia, this syndrome often remains undiagnosed and asymptomatic in early childhood [13]. A study conducted in the United States in 2004 found that: The mean age at diagnosis was 14.5 years; menarche ranged from 10 to 15 years of age, with a mean age of 12.5 years [14]. As demonstrated by the case presented here, the patient was diagnosed and treated after 9 years of menstruation (at 25-year-old). This may be due to several factors. Since only one uterine horn is obstructed, the patient menstruates regularly from the other horn delaying the diagnosis of outflow obstruction that would more readily be made had she presented with amenorrhea and cyclic pain. Second, it is an uncommon condition, and therefore not often thought of as a diagnostic possibility [14]. In addition, the patient's tolerance to pain and the use of painkillers may also may delay the diagnosis. Diagnosis is determined on the basis of radiological examinations. Although MRI usually allows for unequivocal diagnosis of an anomaly, it is not as accessible as ultrasound. Ultrasound is therefore usually helpful in establishing a diagnosis, allowing the evaluation of the uterine morphology, detecting the level of characteristic fluid contents in the proximal vagina and uterine cervixes [5]. Ultrasound of our patient revealed uterus didelphys associated with complicated fluid echoes at the level of the proximal vagina or cervixes. However, the vaginal septum is difficult to visualize on ultrasound and is best shown on MRI. MRI is more sensitive in detecting the uterine contour, the shape of the intrauterine cavity, and the character of the septum compared to the other imaging modalities, but it is less adequate in diagnosing endometriosis, pelvic inflammation, and adhesions, so it has been suggested that the gold standard of diagnosis is laparoscopy [15]. Nowadays, 3D ultrasound is increasingly used in clinical practice. It enables the determination of the type of congenital uterine defect with high probability.

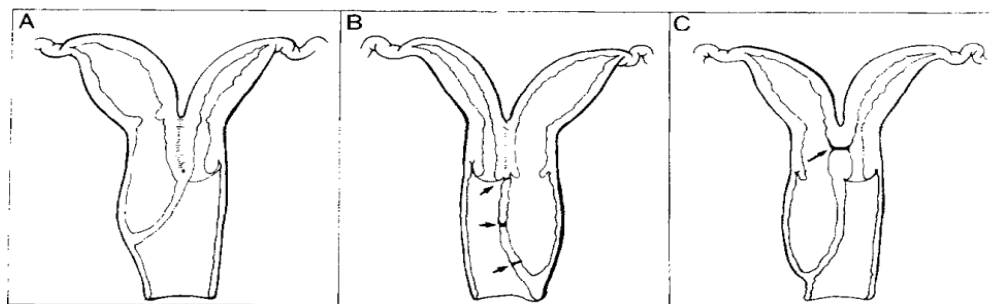
There are multiple classification systems for Müllerian anomalies but there is no consensus on which system is more appropriate. The American Society for Reproductive Medicine (ARSM; formerly known as the American Fertility Society [AFS]) published a classification system in 1988, which has endured over time and is the most used system in the included articles [16]. In 2013, the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) also reached a consensus on the classification of congenital abnormalities of the female genital organs.



According to ESHRE - ESGE, HWW syndrome is classified into groups: U3 or U2 (bicorporeal or septate uterus)/C2, C1 (double, or septate cervix)/V2 (longitudinal obstructing vaginal septum) [3]. In accordance with the ASRM 1988 classification, this syndrome belongs to group III, IV or V. However, this classification only focuses mainly on uterine congenital anomalies without mentioning vaginal-cervical abnormalities. Therefore, abnormalities related to the vagina, cervix, fallopian tubes, and urinary system must be detected and resolved separately. In 2021, based

on the 1988 classification, ASRM has applied a new and more comprehensive classification that includes abnormalities related to the uterus, cervix, and vagina similar to the ESHRE - ESGE system.

Currently, the classification of HWW syndrome according to Rock and Jones in 1980 is widely used. This classification includes 3 groups: *Group 1*: Complete vaginal obstruction with a hematocolpos; *Group 2*: Incomplete vaginal obstruction without a hematocolpos; *Group 3*: Complete vaginal obstruction with a laterally communicating double uterus [17].



**Figure 3.** Illustration of a double uterus, complete or incomplete vaginal obstruction, and ipsilateral renal agenesis. A: Complete vaginal obstruction. B: Incomplete vaginal obstruction. C: Complete vaginal obstruction with a laterally communicating double uterus [17].

In 2015, Chinese gynecology and obstetrics specialists headed by Peking Union Medical College Hospital divided HWWs into 2 types [18], as follows:

Classification 1, completely obstructed hemivagina:

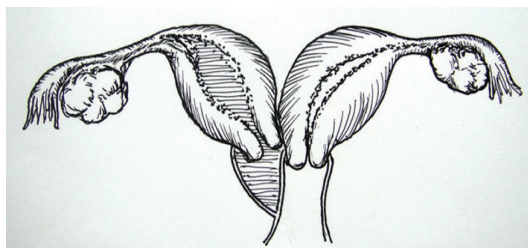
+ Classification 1.1, with blind hemivagina

+ Classification 1.2, cervicovaginal atresia without communicating uteri

Classification 2, incompletely obstructed hemivagina:

+ Classification 2.1, partial reabsorption of the vaginal septum

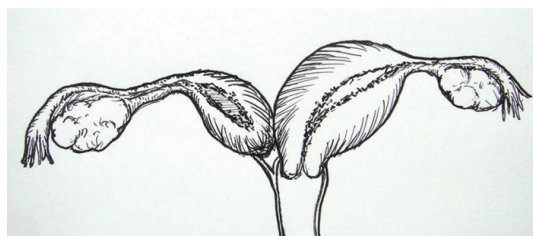
+ Classification 2.2, with communicating uteri



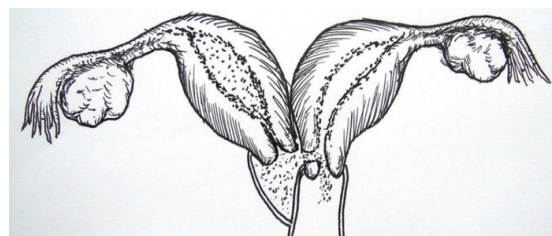
**Figure 4.** Classification 1.1, with blind hemivagina



**Figure 5.** Classification 2.1, partial reabsorption of the vaginal septum



**Figure 6.** Classification 1.2, cervicovaginal atresia, without communicating uteri.



**Figure 7.** Classification 2.2, incompletely obstructed hemivagina with communicating uteri [18].

By the case presented here, there are 2 separate uteruses, 2 cervixes, along with ipsilateral obstructed hemivagina with fistula, so it is classified in group B according to the classification of Rock and Jones (1980) and classification 2.1 of the Chinese gynecology and obstetrics specialists.

The standard treatment of the obstructed hemivagina is the surgical excision of the vaginal septum. The excision should be wide to avoid stenosis and the subsequent recurrence of hematocolpos and symptoms. Surgery should be planned before menses as a large distended hematocolpos is easy to visualize and palpate, which aids in resection [18]. The hemostasis of the excision margins should be interrupted and not continuous, to avoid stenosis. In cases of stenosis and the recurrence of symptoms, re-excision is recommended [19]. Treatment for patients with Classification 1.2 differs from the treatment of patients with other classifications. Cervical agenesis is difficult to correct surgically. After being diagnosed with renal agenesis or renal malformation by imaging studies, laparoscopic or the transabdominal resection of the atresic uterus is suggested [18]. Timely and successful surgical treatment will help improve life significantly.

The prognosis of HWWS is good with early diagnosis and early treatment, except for patients with Classification 1.2 [18]. The fertility of women with HWW syndrome was good. According to a 2013 study of 70 treated HWW syndrome cases, 35 women in total were married and sexually active. There were 52 pregnancies among 28 (84.8%) of the 33 women who wished to conceive; there were 20 living infants (9 vaginal and 10 cesarean deliveries at term, and 1 preterm vaginal delivery) at the end of the follow-up period. Fifteen women conceived and delivered their first infants at term before undergoing treatment for obstructed hemivagina. Pregnancy occurred in the uterus ipsilateral to the hemivaginal septum in 19 (36.5%) cases, and in the uterus contralateral to the hemivaginal septum in 33 (63.5%) cases. Eight women experienced separate pregnancies in each of the bilateral uteri [20].

#### 4. CONCLUSION

Herlyn - Werner - Wunderlich syndrome is a rare congenital abnormality. The main symptom is progressively pelvic pain and is related to menstruation. Ultrasound is the initial means of diagnosis, while MRI plays an important role in diagnosing genital tract defects. Early diagnosis and treatment provide a good prognosis for patients.

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