

# The Retrospective Evaluation Of Endocrine Manifestations In Chinese Patients With Wilson's Disease

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## Research Article

**Keywords:** Wilson's disease, menstruation, abortion, sex hormones

**Posted Date:** February 14th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1326118/v1>

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# Abstract

**Purpose:** The endocrine manifestations of Wilson's disease (WD) tended to be ignored, especially as initial clinical aspects. Currently there was a paucity of studies for endocrine involvement in WD patients. We aim to explore the explicit impact of WD on the endocrine system, to reduce the misdiagnosis.

**Methods:** A retrospective study was performed in 37 female patients with WD. They were recruited from the Second Affiliated Hospital of Zhejiang University School of Medicine from October 2018 to October 2020. Each patient was diagnosed with WD according to clinical evaluation and genetic test. Their menstrual, pregnancy and childbirth history, and sex hormone levels were collected and analyzed.

**Results:** The average age of menarche was  $13.7 \pm 2.0$  years. The proportion of delayed menarche was 37.8%. The patients with irregular menstruation after menarche accounted for 50%. Among 65 conceptions of 37 WD patients, the spontaneous abortion, induced abortion, preterm birth, and full-term delivery rate was 46.2%, 27.7%, 12.3% and 13.8% respectively. The abnormal hormone levels of the 35 cases mainly consisted of 14 cases (40%) with increased PRL, 10 cases with decreased P (28.6%), 8 cases (22.9%) with increased SHBG and 6 cases (17.1%) with increased T.

**Conclusion:** The endocrinologic manifestations among WD patients could be not uncommon. WD patients could manifest as irregular menstruation, recurrent abortion, and even infertility. These minor aspects as a presenting feature of WD are prone to be neglected. Therefore, WD should be encountered in the differential diagnosis of endocrine system dysfunction.

## Introduction

Wilson's disease (WD) is an autosomal recessive genetic disease of copper metabolism dysfunction. The global prevalence of WD is estimated to be 1 in 10,000~30,000<sup>1-3</sup>. Its causative gene, *ATP7B*, encodes the copper-transporting ATPase, which mainly functions in the synthesis of ceruloplasmin and excretion of copper. *ATP7B* dysfunction may lead to excessive copper depositions in different organs, causing complicated clinical heterogeneities. Clinical expressions of WD patients are variable, including typical hepatic, neurological or ophthalmological aspects<sup>4</sup>, and atypical extrahepatic manifestations, such as osteoarthritis<sup>5</sup> and renal abnormalities<sup>6</sup>. WD diagnosis is relatively easy to be established in the affected individual with the former manifestations. Nevertheless, the diagnostic challenge which the patient had non-specific symptoms might lead to some confusions with other diseases. The delayed diagnosis and irreversible complications development ultimately render treatment unsuccessful<sup>7</sup>.

The endocrinologic presentations of WD tended to be ignored because single cases were mainly reported currently. Moreover, several observational studies were published only involving pregnancy and childbirth<sup>8</sup>. The endocrine disturbances of WD may include menstrual disorders, recurrent miscarriage, infertility, growth restriction, and parathyroid failure<sup>8,9</sup>. The affected patients with this non-specific could

be given for correct diagnosis after many years, only when typical symptoms including liver function or neurological symptoms presented.

The aim of this retrospective study was to observe the state of menstruation, pregnancy, and sex hormone levels in Chinese WD cohort, and confirm the absence of endocrinal abnormalities. Analysis of these symptoms could screen WD with high diagnostic accuracy to avoid the delayed treatment.

## Methods

### Patients

This retrospective study included female patients treated at the Department of Neurology in Second Affiliated Hospital of Zhejiang University from October 2018 to October 2020. The clinical diagnosis of WD was confirmed according to the Leipzig criteria<sup>10</sup> and Chinese guidelines for diagnosis and treatment of Wilson's disease 2021<sup>11</sup>. The biallelic pathogenic variants within *ATP7B* were confirmed in all patients. Other diseases, including premature ovarian failure, ovarian tumors, pituitary diseases, metabolic syndrome, and severe decompensated liver cirrhosis, were excluded among the affected individual. This study was approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University. After obtaining the informed consent of the patient or their legal guardian, they would be evaluated and analyzed.

### Clinical picture collection

We collected menstrual, pregnancy and childbirth history and sex hormone levels among WD patients. We judged the period of hormone examination (follicle, ovulation or luteal phase) via knowing the last menstrual period and menstrual regularity, then evaluated whether the data were normal or not. The sex hormone, including follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), progesterone (P), testosterone (T), and sex hormone binding globulin (SHBG) were analyzed. We ruled out pituitary adenoma, hypothalamic tumor, and chronic renal failure among WD patients.

### Statistical analysis

Normally distributed measurement data were expressed as mean  $\pm$  standard deviation, and quantitative data were depicted as frequency or rate (%).

## Results

### Patient characteristics

The cohort included 37 female patients, aged 12~50 (mean 27.4) years. The age of onset ranged from 3 to 49 years old, and the average was  $17.0 \pm 11.4$  years. The onset presentations of WD were hepatic in 16, neurologic in 17, and 4 asymptomatic. There were 3 cases carrying homozygous p.R778L mutations,

1 with homozygous p.Y532C and p.V1216M mutations, 19 cases with compound heterozygous mutations containing p.R778L, and the remaining 13 cases with other compound heterozygous mutations (Table 1).

Table 1  
Patient characteristics of 37 female WD patients

Case(n)	
Age, y	37
Range	12~50
Mean ± SD	27.4 ± 9.8
Age at onset, y	37
Range	3~49
Mean ± SD	17.0±11.4
Disease duration, y	37
Range	0.58~27
Mean ± SD	10.4±8.3
Onset form	
Hepatic	16
Neurologic	17
Asymptomatic	4
Genotype	
Homo-R778L	3
Homo-Y532C	1
Homo-V1216M	1
Hete-R778L+other	19
Other compound	13
SD, standard deviation	

## Analysis of menstrual cycle and pregnancy

Among 37 female patients, the average age of menarche was  $13.7 \pm 2.0$  years, and the proportion of delayed menarche, whose menarche age  $\geq 14$  years<sup>12</sup>, was 37.8% (14/37). After menarche, 18 patients were found to have menstrual irregularities (48.65%). A total of 65 conceptions were recorded in 37 untreated patients. The proportions of spontaneous abortion, induced abortion, preterm birth and full-term delivery were 46.2% (30/65), 27.7% (18/65), 12.3% (8/65), and 13.8% (9/65) respectively (Table 2).

Table 2  
Analysis of menstrual cycle and conceptions

<b>Average age of menarche (years)</b>	<b>13.7 ± 2.0</b>
Rate of delayed menarche	37.8% (14/37)
Rate of irregular menstruation	48.65% (18/37)
Rate of spontaneous abortion	46.2% (30/65)
Rate of induced abortion	27.7% (18/65)
Rate of preterm birth	12.3% (8/65)
Rate of full-term delivery	13.8% (9/65)

## The detection of sex hormone levels in 35 patients

Of 37 WD patients, we analyzed the hormone levels of 35 cases, whereas the remaining 2 cases were excluded because of incomplete data. Consequently, we found 14 WD patients with increased PRL, 10 with decreased P, 8 with increased SHBG, and 6 with increased T (Table 3). Of 14 WD patients with hyperprolactinemia, 2 simultaneously manifested as polycystic ovary syndrome, and 9 as liver cirrhosis. Among 10 patients with hypoprogesterone, 1 simultaneously had polycystic ovary syndrome, and 5 with liver cirrhosis. Among 8 patients with elevated SHBG, 4 had uterus and ovaries dysfunction, manifesting as polycystic ovary, ovarian cystic mass, and uterine fibroids. Of 6 patients with hypertestosterone, 2 with abnormalities of the uterine ovary, manifested as polycystic ovary and uterine fibroids, and 5 with liver cirrhosis.

Table 3  
Abnormal sex hormone levels and comorbidities in 35 patients

	<b>FSH</b>	<b>LH</b>	<b>PRL</b>	<b>E2</b>	<b>P</b>	<b>T</b>	<b>SHBG</b>
High	1/35	4/35	14/35	3/35	2/35	6/35	8/35
Low	4/35	4/35	0	3/35	10/35	0	1/35

FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; E2, estradiol; P, progesterone; T, testosterone; SHBG, sex hormone binding globulin

# Recurrent abortions before WD diagnosis

The 47-year-old patient turned for aid to the neurologist because of 4-month extremity tremor and abnormal walking posture. The patient underwent involuntary body shaking, stiff walking posture and slurred speech after a miscarriage. The cranial MRI showed symmetrical high T2 signals in bilateral globus pallidus, putamen and substantia nigra. The K-F ring was positive. The heterogenous p.L1188F and p.G1149E mutations were identified.

She had the first menstrual cycles aged 16 years with BMI of 30.5. Among 14 pregnancies, the patient underwent 11 spontaneous abortions and 3 preterm births. Specifically, she had a 32-week premature delivery aged 19 years. However, the baby died after one day with unknown reason. Afterward, she repeatedly suffered from 11 spontaneous abortions between 8 and 16 weeks of pregnancy. She gave birth to 32-week infant aged 35 and 41 respectively. There is no clear diagnosis and treatment for abnormal pregnancy. When aged 31, she was found to have liver cirrhosis and received splenectomy.

## Discussion

Menarche is an important clue for female puberty onset and also serve as a milestone in the process of female sexual development. The age at menarche (AAM) could reflect the time of female development and maturity. It correlates with reproductive health problems and social psychological<sup>13,14</sup>. In 2005, the average AAM in China was 12.76 years old, and that of Zhejiang province was 12.6, and there is a tendency to advance year by year<sup>15,16</sup>. The proportion of irregular menstruation in the same epidemiological survey was 16.41~22.61%<sup>17</sup>. In our cohort, menarche was significantly delayed, and the proportion of irregular menstruation was significantly increased compared to the general population. We found that WD was associated with delayed menarche and irregular menstruation. The menarche and menstrual cycle are dependent on sex hormone homeostasis. In the general population, spontaneous abortion rates ranged from 10–20%<sup>18</sup>. Notably in our cohort, spontaneous abortion rates were significantly high as 46.2%. The finding showed that WD could be closely related to abnormal conception. Among 37 WD patients, PRL, P and SHBG were the most affected, followed by T, FSH and LH. These metabolic disorders could be involved in irregular menstruation and abnormal delivery.

There were few studies on menstruation, sex hormones and pregnancy in WD patients. In 1991, the woman experienced 7 unexplained recurrent miscarriages from 21 to 26 years old<sup>19</sup>. Tarnacka et al. investigated the miscarriage, premature delivery, and stillbirth in 46 women with WD via questionnaires, and found that the proportion of spontaneous abortions between the treatment group and non-treatment group was 26.6% and 26% respectively, higher than the baseline proportion in Polish<sup>20</sup>. Sinha et al. also found that the spontaneous abortion rate was significantly higher with 40.7%<sup>21</sup>. The retrospective multi-center study in Germany found that the presence of cirrhosis at initial diagnosis of WD was not associated with a significant increase in spontaneous abortion compared with non-cirrhosis patients<sup>22</sup>.

Therefore, combined with our cases accompanying abnormal pregnancy, when recurrent miscarriage and premature delivery could not be explained by gynecological related diseases, WD screening could be necessary.

At present, the causes of abnormal sex hormone, pregnancy and delivery in WD remained elusive. Arieh et al. analyzed hormone levels in 4 WD patients with obvious menstrual abnormalities, and concluded that the menstrual and ovulation dysfunction could be caused by the aromatase activity due to copper deposition<sup>23</sup>. Moreover, the previous studies demonstrated that copper was prone to accumulate in the maternal side of the placenta among WD patients, thereby leading to placental abruption, irregular menstruation, and even infertility<sup>24,25</sup>. Excessive copper deposition in the uterus could also result in repeated abortion in the early trimester. Moreover, there were reports on the successful pregnancy and childbirth after copper-exhaustion treatment. Additionally, deposited copper could affect the function of the hypothalamic-pituitary-ovarian (HPO) axis, and lead to delayed menarche, irregular menstruation, repeated miscarriage, and even infertility. However, other causative factors such as liver involvement, endocrinal disorders and anemia may be also responsible for the cause. Cirrhosis may lead to decreased estrogen inactivation ability and increased estrogen level. Moreover, anemia due to splenomegaly could also induce the pregnancy difficulties and menstrual disorder<sup>26</sup>.

In sum, we systematically described the sex hormone levels, menstrual history, pregnancy and childbirth history among 37 Chinese WD patients. We found that the ratio of delayed menarche, abnormal menstrual cycle, recurrent miscarriage, and premature delivery in WD patients was high, followed by abnormal sex hormone levels. These abnormalities could be related to the copper deposition in the gonad and liver cirrhosis. However, the specific mechanism still remained unknown. Combined the previous studies and our experience, we concluded that the reproductive system involvement in WD could be not rare, especially in untreated WD patients. The finding emphasized that early WD diagnosis is of vital importance due to its curability. The timely and individualized treatment might reverse the reproductive abnormalities. We need to realize that amenorrhea and recurrent abortions could precede the onset of typical manifestations in WD patients. Therefore, the affected patients should be evaluated for WD, especially accompanied by liver cirrhosis with unknown etiology.

## **Declarations**

### **Data availability**

The data that support the findings of this study are available on request from the corresponding author.

### **Author contributions**

All authors contributed to the study conception and design. Material preparation and data collection were performed by Mei-Yan Zhang, Zi-Wei Zheng and Zhi-Feng Shi. Analysis was performed by Meng-Hui Xu, Rou-Min Wang, and Wan-Qing Xu. The first draft of the manuscript was written by Mei-Yan Zhang with critical appraisal from Yi Dong and Zhi-Ying Wu. All authors read and approved the final manuscript.

## Funding information

This work was supported by the grant (81701126) to Dr. Yi Dong from the National Natural Science Foundation of China.

## Compliance with ethical standards

## Conflict of interest

The authors declare no competing interests.

## Ethical

The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

## Consent to participate

Informed consent was obtained from all participants in this study.

## Consent to publish

Informed consent was obtained from all participants for the publication of the results of this study.

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