

Pregnancy outcome of recurrent spontaneous abortion in Wilson's disease after decoppering therapy

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Summary

Purpose of Investigation: To report pregnancy outcome after decoppering therapy in patients with recurrent spontaneous abortion (RSA) and Wilson's disease (WD). **Materials and Methods:** In a retrospective study, 12 WD patients who suffered from RSA were treated with dimercaptosuccinic acid and zinc gluconate. The average daily dose of dimercaptosuccinic acid and zinc gluconate was 1.00 and 1.68 grams, respectively. Dimercaptosuccinic acid was discontinued, while zinc gluconate was continued during pregnancy. The primary clinical outcomes were the pregnancy outcome after decoppering therapy and the mean age at diagnosis. **Results:** Six patients conceived at least once after treatment. Five of them had successful pregnancies with seven healthy live births. Mean age at diagnosis was significantly lower in patients who delivered healthy babies than in those who failed to conceive. **Conclusions:** Decoppering therapy is efficacious in reversing the pregnancy outcome of RSA in patients with WD, especially in the women who are diagnosed at young age. Age at diagnosis is an important risk factor that affects the pregnancy outcome in these patients.

Key words: Pregnancy outcome; Recurrent spontaneous abortion; Wilson's disease; Decoppering therapy.

Introduction

Wilson's disease (WD) is a disorder of copper metabolism with a prevalence of 1:7,026 predicted by a recent genetic study [1]. Copper accumulates and causes toxicity primarily in the liver and brain [2, 3]. In essence, WD also leads to toxicity in reproductive system [4-10], which are usually neglected by neurologic doctors. Klee, J. G. and Schagen van Leeuwen, J.H., respectively reported one case of recurrent spontaneous abortion (RSA) in WD patients [4, 8]. However, the pregnancy outcome in a series of patients with RSA and WD after treatment is not known until now.

The authors report 12 cases of RSA in patients with WD after treatment with decoppering therapy, describing the response to therapy and pregnancy outcome.

Materials and Methods

The study was conducted in compliance with the Declaration of Helsinki and Ethics Committees on Human Research of Anhui Provincial Hospital Affiliated to the Anhui Medical University and The First Affiliated Hospital of Anhui University of Traditional Chinese Medicine. The research project received the approval of Ethics Committees on Human Research of Anhui Provincial Hospital affiliated to the Anhui Medical University. The permit number is 2013030112 and the trial registration num-

ber is ChiCTR-ERC-17010522.

The authors retrospectively analyzed the medical records of the previous year, from which they found 109 cases of RSA patients, and then began their research. A large group (n=109) of female patients of reproductive age (18-45 years) with confirmed WD is being followed from the Encephalopathy Center of the 1st Affiliated Hospital of Anhui University of Chinese Medicine range from January 2016 to January 2017. Fifty-eight of them conceived at least once, one of them delivered one baby after treatment and 13 of them suffered from two or more previous spontaneous abortions (RSA) [11] before standard treatment. One of the 13 patients was ruled out because she used contraception after diagnosed with WD. Twelve patients who were involved in the study received the treatment with dimercaptosuccinic acid and zinc gluconate for at least ten months. The average daily dose of dimercaptosuccinic acid and zinc gluconate was 1.00 and 1.68 grams, respectively. Dimercaptosuccinic acid was discontinued, while zinc gluconate was continued during pregnancy. Diagnosis of WD was established by clinical features, laboratory evidence of low serum ceruloplasmin, increased 24-hour urinary copper excretion, and the presence of Kayser-Fleischer (KF) rings by slit lamp examination [12]. A flow diagram of the selection process is shown in Figure 1.

Statistical analyses were performed using SPSS version 23.0. Comparisons of quantitative data were performed with independent two-sample *t*-test and chi-square test, and were considered significant when the *p*-value was less than 0.05.

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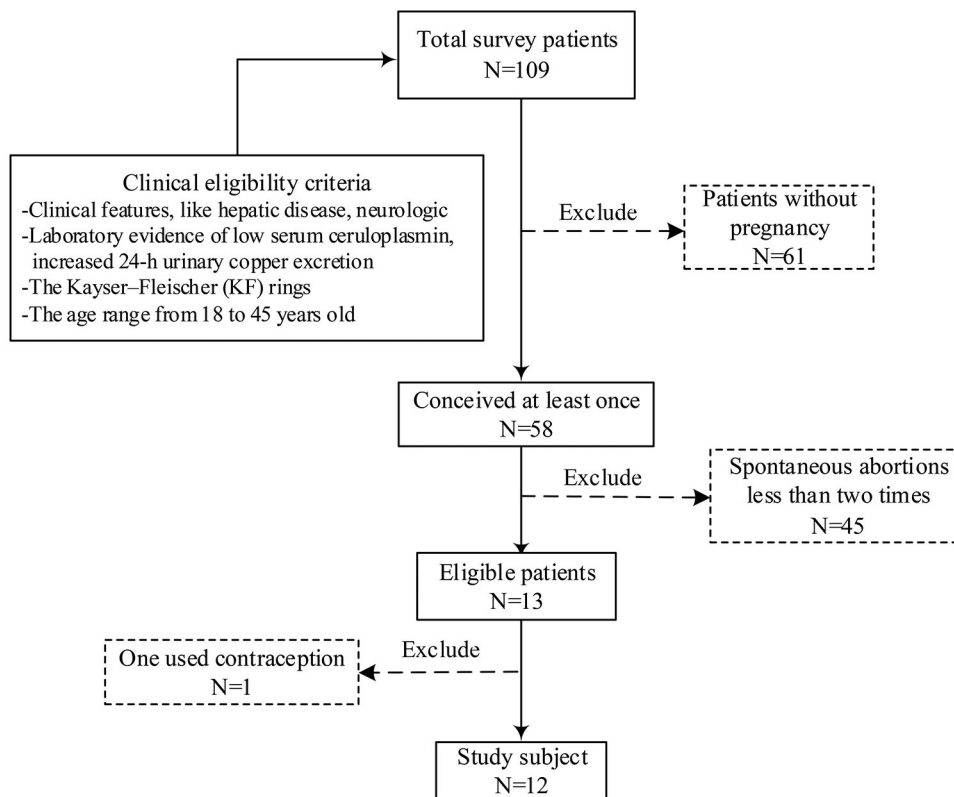


Figure 1. — Flow diagram for study subject selection.

Results

Among the 58 patients who conceived at least once, the mean age of menarche (onset of menstruation) was 14.60 ± 1.77 (normal range for Chinese girls: 12.43–14.70 [13, 14]) years. The mean age of menarche in this study group of 12 patients was 14.42 ± 1.08 years. Irregular menstruation (41.7%) was the common clinical feature including oligomenorrhea (33.3%), menostaxis (16.7%), and secondary amenorrhea (8.3%). Nine patients were presymptomatic at the time of their first pregnancy and three already had neurologic involvement. Eventually, all the patients had neurological features and, in addition, ten had hepatic involvement, serological tests as well as by ultrasonography.

Mean serum ceruloplasmin of the 12 patients who were on treatment was 0.084 ± 0.008 g/L (normal range: < 0.1 g/L) and was reduced in all. The mean 24-hour urinary copper excretion was 1065.40 ± 677.05 $\mu\text{g}/24$ hours (normal range: < 100 $\mu\text{g}/24$ hours) and was increased in all. KF rings were found in the cornea by slit lamp examination in all of the patients.

Table 1 provides basic clinical, obstetrical characteristics, and the pregnancy outcome on the 12 women. There were six patients (cases 1–6) conceived at least once besides six patients (cases 7–12) failed to conceive after treat-

ment. They had 11 pregnancies with spontaneous abortions occurring on four occasions (4/11). Five of them (cases 1–5) had successful pregnancies with seven live births (7/11). One of them successively delivered three babies after treatment. All the newborn infants were healthy. The mean age at diagnosis was 23.60 ± 4.45 years-old in the five patients who delivered healthy babies, and the mean age at diagnosis was 34.33 ± 7.84 years in the other six patients who failed to conceive after treatment. Mean age at diagnosis was significantly lower in patients who delivered healthy babies than in those who failed to conceive ($p < 0.05$). All the patients who diagnosed before 25-years-old, 4/6 patients who diagnosed before 30-years-old, and 5/9 patients were diagnosed before 35-years-old successfully gave birth to healthy babies. While all of patients who diagnosed > 35 -years-old failed to conceive.

Among the five patients who initially presented with neurologic disorders, four delivered healthy babies. However, among the other seven patients initially presenting with hepatic manifestations, only one had a health baby. The rate of patients who delivered healthy babies in the former was significantly higher than the latter ($p < 0.05$). The mean age at diagnosis in patients initially presented with neurologic disorders was lower than in those initially presented with hepatic manifestations ($25.20 \pm$

Table 1. — *Clinical characteristics and pregnancy outcome.*

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12
Present age (years)	25	27	33	45	41	40	39	30	31	42	45	44
Type of initial presentation	N	N	N	N	H	H	H	H	H	N	H	H
Age at diagnosis (years)	19	22	23	23	31	34	26	27	29	39	43	42
Duration of decoppering therapy at first childbirth (years)	4.3	2.4	4.5	5.2	7.1	NA	NA	NA	NA	NA	NA	NA
Number of spontaneous abortions before decoppering therapy	2	4	3	2	2	4	2	2	2	2	5	5
Number of pregnancies after decoppering therapy	2	4	2	1	1	1	0	0	0	0	0	0
Number of spontaneous abortions after decoppering therapy	1	1	1	0	0	1	0	0	0	0	0	0
Number of live births	1	3	1	1	1	0	0	0	0	0	0	0
Condition of child at birth	Good	Good	Good	Good	Good	NA	NA	NA	NA	NA	NA	NA

N = neurological presentation; H = hepatic presentation; NA = not applicable.

7.89 vs. 33.14 ± 6.91 years), but the difference was not statistically significant because of the small sample size ($p > 0.05$).

Discussion

WD is the commonest monogenetic neurologic disorder that is found all over the world [1]. It mainly leads to neurological disturbances and hepatic damage. Reproductive disorders, such as irregular menstruation, miscarriages, and infertility are also common but usually are ignored in clinic. It was reported that decoppering therapies improved the pregnancy outcome in patients with WD [15, 16], but the pregnancy outcome in a series of patients with WD and RSA is not known until now. Here, the authors firstly report the pregnancy outcome in WD patients with RSA after treatment with dimercaptosuccinic acid and zinc gluconate.

The authors found the rate of RSA in fertile women with WD is 22.4 % (13/58), which is about 7-20 times as high as noticed in fertile women (1-3%) [17-20], indicating that WD is associated with RSA in these women. The exact mechanism of miscarriage is unclear but it is believed that excess copper deposition in uterus hampers implantation of fetus. The mechanism has been assumed to be similar to that of copper-containing intrauterine contraceptive devices [21]. Scheinberg *et al.* [22] proposed that such a high miscarriage rate is likely due to excess free intrauterine copper derived from the non-ceruloplasmin bound copper in female WD patients. In addition, other factors such as chronic liver disease, anemia and endocrinal disorders, may also contribute to the cause.

WD not only leads to spontaneous abortion, but also can lead to significant morbidity and can be potentially fatal if not treated promptly [23]. So once the diagnosis has been made, medical therapy must be life-long [24]. Patients with WD may have a regular life expectancy when their neurologic and hepatic manifestations improved with the regular life-long decoppering treatment [25, 26]. Permanent organ damage can be effectively prevented if early decoppering treatment is initiated [27]. When hepatic and neurologic signs improve, the pregnancy outcome of RSA

patients will be effectively reversed. It is also recognized that treatment of WD should be continued during pregnancy, with the exception of the presence of severe liver disease [28]. Patients who have withheld or discontinued treatment during pregnancy have experienced serious complications, including death [25]. Thus, the present continued treatment with zinc gluconate during pregnancy in this study group.

After treatment, 83.8% (5/6) of the pregnant patients successfully give birth to babies, which showed that decoppering therapy is highly efficacious in reversing the pregnancy outcome of WD induced RSA. Meanwhile, it seems that zinc gluconate has no obvious side effect on embryos, since all the newborn infants were healthy. Unfortunately, there were six patients in this study group that failed to conceive. Their age at diagnosis should be partially responsible for their pregnancy outcome. Three of them diagnosed with WD at the age of more than 38-years-old. Age-related diminished ovarian function is probably a primary cause for their failure to conceive. The other three younger patients are still attempting to become pregnant.

The type of initial presentation of WD appears to be a factor affecting the pregnancy outcome after treatment. The present authors observed that the patients initially presenting with neurologic manifestations had a better pregnancy outcome than those who initially presented with hepatic disorders. The exact cause is unknown. It may be because the hepatic manifestations of WD are insidious and multiple, which makes the diagnosis very complicated and delayed, which was supported by the higher age at diagnosis in patients initially presenting with hepatic disorders in this data. In addition, hepatic manifestations are due to the accumulation of copper in the liver, which is near the pelvis and uterus.

A limitation was that the data had a small sample of individuals covered under the Encephalopathy Center of the 1st Affiliated Hospital of Anhui University of Chinese Medicine. A comprehensive set of information should be included in a database that contains an administrative data which can be used to expand the sample and conduct further research. However, this study employed clinical ob-

servation of WD patients with RSA after treatment with dimercaptosuccinic acid and zinc gluconate. The research findings may be reflective of treatment and outcomes for WD patients with RSA which can provide evidence for further clinical discussion.

Conclusion

In conclusion, this data showed that RSA was common in WD patients, especially in untreated women. Decoppering therapy is efficacious in reversing the pregnancy outcome of RSA in patients with WD, especially in the women who are diagnosed at young age. Age at diagnosis is an important factor that affects the pregnancy outcome in these patients. Teratogenicity was not seen in the present series with dimercaptosuccinic acid and zinc gluconate but further studies need to be carried out.

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