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 number 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.
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 µg/24 hours (normal range: < 100 µg/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 treatment. 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 ±
neurologic signs improve, the pregnancy outcome of RSA
decoppering treatment is initiated [27]. When hepatic and
mental organ damage can be effectively prevented if early
regular life-long decoppering treatment [25, 26]. Perma-
nneurologic and hepatic manifestations improved with the
with WD may have a regular life expectancy when their
not treated promptly [23]. So once the diagnosis has been
lead to significant morbidity and can be potentially fatal if
expected copper in fetuses, which is
cause of RSA in these women. The exact
noticed in fertile women (1–3%) [17-20], indicating that
WD is 22.4 % (13/58), which is about 7-20 times as high as
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 mis-
carrriage rate is likely due to excess free intrauterine copper
derived from the non-ceruloplasmin bound copper in fe-
male 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]. Perma-
nent 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 preg-
nancy, with the exception of the presence of severe liver
disease [28]. Patients who have withheld or discontinued
treatment during pregnancy have experienced serious com-
lications, including death [25]. Thus, the present contin-
ued 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 de-
coppering 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. Un-
fortunately, there were six patients in this study group that
failed to conceive. Their age at diagnosis should be par-
tially 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 pre-
senting with neurologic manifestations had a better preg-
nancy 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 di-
agnosis in patients initially presenting with hepatic disor-
ders 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 in-
dividuals 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 fur-
ther research. However, this study employed clinical ob-

Discussion
WD is the commonest monogenetic neurologic disorder
that is found all over the world [1]. It mainly leads to neu-
rological 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.

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

| 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               | 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               |
| Number of spontaneous abortions before decoppering therapy | 2               | 4               | 3               | 2               | 2               | 4               | 2               | 2               | 2               | 5               | 5               |
| Number of pregnancies after decoppering therapy | 2               | 4               | 2               | 1               | 1               | 1               | 0               | 0               | 0               | 0               | 0               |
| Number of spontaneous abortions after decoppering therapy | 1               | 1               | 1               | 0               | 0               | 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.
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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References


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