Wilson's Disease and Pregnancy

In a study appearing in this issue of Hepatology Brewer et al. present data on the outcomes of pregnancies in 19 women treated with zinc acetate during 26 pregnancies, which resulted in 24 normal infants, 1 with a heart defect, and 1 microcephalic. Based on these results the authors conclude that "zinc is the optimal choice for the pregnant Wilson's disease patients," although no data on outcomes of pregnancies in women with Wilson's disease treated with other agents are given.

Twenty-five years ago we reported on the outcomes of 29 pregnancies in 18 women treated with penicillamine giving birth to 29 normal infants. Additional data were published by us and by Walshe. Clearly, pregnancy in women with Wilson's disease is safe and successful when treatment with a chelating drug is continued uninterruptedly. Since then, numerous reports regarding the outcomes of pregnancies in patients with Wilson's disease confirm this statement (Table 1).

Some of the therapeutic agents, namely dimercaprol, penicillamine, and trientine, chelate excess tissue copper, which is excreted via the urine. Zinc, in contrast, acts by inducing the synthesis of metallothionein, which sequesters copper in enterocytes and in hepatocytes. Unfortunately, no rigorously controlled, statistically valid study comparing the outcomes of various regimens has been performed and in all probability never will be. Penicillamine is the most widely used drug, frequently producing dramatic beneficial effects that enable many severely ill patients to return to normal, productive lives. Its long-term tolerance is demonstrated by patients who have remained asymptomatic by continuing to take their daily doses of penicillamine uninterruptedly for over 30 years! Trientine appears to be similarly effective based, however, on a more limited experience (Table 2).

In the absence of controlled studies, we have pooled data concerning the results of pregnancy in women with Wilson's disease receiving penicillamine or trientine: (1) Data of the National Center for the Study of Wilson's Disease showed 26 women treated during 44 pregnancies in addition to the previously published cases; for totals of 43 women treated with penicillamine during 71 pregnancies, and 4 women treated with trientine who delivered 6 normal babies. (2) Case reports from Medline showed 32 women treated with penicillamine and 2 with trientine during 43 pregnancies. (3) A personal communication from Dr. John M. Walshe, Cambridge, UK, showed 34 women treated with penicillamine and 14 with trientine. (4) A personal communication from Dr. Kerstin Westermark, Uppsala, Sweden, showed 1 woman treated with penicillamine.

There were 153 infants born to 111 women with 164 pregnancies. There were two therapeutic abortions (one for portal hypertension with esophageal varices and the second for spina bifida detected on prenatal screening), 2 miscarriages, and 3 premature babies. There was 1 bearer of a chromosomal defect, 1 infant was a homozgyote for mannosidosis, and 1 infant, whose mother suffered from toxemia, died in utero. One of the normal-appearing infants was found later to have Wilson's disease being fortuitously treated prophylactically during gestation.

It is not uncommon for symptomatic women with Wilson's disease to suffer amenorrhea, oligomenorrhea, irregular menses, and multiple miscarriages. These disturbances are the nonspecific consequences of hepatic dysfunction causing reversible hormonal changes. In addition, fertility in the untreated patient with Wilson's disease is also affected by diffusion of non–ceruloplasmin-bound copper from plasma into tissues, a process that may affect the ovarian follicular aromatase activity.

Review of the penicillamine and trientine data showed the following results: (1) Mothers and infants tolerate pregnancy safely, providing that compliance with the prescribed regimen is maintained. We have used a daily dose of 0.75 to 1 g of either penicillamine or trientine in patients whose Wilson's disease was well controlled during the first 2 trimesters of the pregnancy and reduced the dose to 0.5 g/d during the last trimester. (2) Interruption of therapy carries a high risk of hemolytic episodes with hepatic insufficiency and fatality for the mother. (3) Concerns regarding possible teratogenic effects of either penicillamine or trientine are not supported by data obtained in patients with Wilson's disease because of the lower dose required compared with that used in patients with cystinuria. The excess tissue copper in the mother may

| Table 1. Results of Pregnancies in Women Taking Penicillamine |
|------------------|------------------|------------------|------------------|
|                  | Number           | Number           | Normal           | Defects             |
|                  | of Women         | of Pregnancies   | Neonates         |                    |
| Wilson's Disease |                  |                  |                  |                    |
| Total            | 1                | 1                | 1                |                    |
| Case Reports     |                  |                  |                  |                    |
| Walshe           | 35               | 40               | 36               | 1 premature, 2     |
|                  |                  |                  |                  | therapeutic abortions|
| Westermark       | 1                | 1                | 1                | 1                   |
| Total            | 111              | 153              | 144              |                     |
TABLE 2. Results of Pregnancies in Women Taking Trientine

<table>
<thead>
<tr>
<th>Wilson's Disease Center</th>
<th>Number of Women</th>
<th>Number of Pregnancies</th>
<th>Normal Neonates</th>
<th>Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Reports^34,35</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>1 miscarriage, 1 therapeutic abortion, 1 iso-chromosome x</td>
</tr>
<tr>
<td>Walshe</td>
<td>11</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>22</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

be protective. (4) No ill effects on the babies have been reported by nursing mothers taking penicillamine even though concentrations of zinc and copper were found to be reduced in the mother's milk in one study.\(^{18}\)

It is evident that the outcome of pregnancy in women with Wilson's disease is determined by compliance with the prescribed regimen or deviation from it, rather than the choice of medication. The available data do not support the claim that zinc is "optimal" or that patients should be advised to change their current treatment. The available data do not support the use of trientine as a substitute for penicillamine in patients with Wilson's disease.

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REFERENCES