Wilson's Disease and Pregnancy

SEE ARTICLE ON PAGE 364

In a study appearing in this issue of HEPATOLOGY Brewer et al. present data on the results 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.[1] 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.[2] Additional data were published by us[3] and by Walshe.[4] 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[5-35] 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,[2] 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.[5-35] (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 homozygote for mannosidosis,[9] 1 was born with oral clefts,[32] and 1 infant, whose mother suffered from toxemia, died in utero.[8] 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.[36]

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.[21] (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 of Women	Number of Pregnancies	Normal Neonates	Defects
Wilson's Disease Center	43	71	69	2 therapeutic abortions
Case Reports[5-33]	32	41	38	1 mannosidosis,[9] 1 cleft lip and palate, 2 transient cutis laxa[14,15]
Walshe	35	40	36	1 premature, 2 therapeutic abortions, 1 miscarriage
Westermark	1	1	1	
Total	111	153	144	

From the National Center for the Study of Wilson's Disease, New York, NY.
Received December 6, 1999; accepted December 8, 1999.
Address reprint requests to: Irmin Sternlieb, M.D., Wilson's Disease Center, 432 W. 58th St., Suite 614, New York, NY 10019. E-mail: irmin@ix.netcom.com; fax: 858-558-0315.

0270-9139/00/3102-0040$3.00/0

TABLE 2. Results of Pregnancies in Women Taking Trientine

	Number of Women	Number of Pregnancies	Normal Neonates	Defects
Wilson's Disease Center	4	6	6	
Case Reports[34,35]	2	2	2	
Walshe	11	14	11	1 miscarriage, 1 therapeutic abortion, 1 isochromosome x
Total	17	22	19	

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 a well-tolerated, effective regimen.

IRMIN STERNLIEB, M.D.
National Center for the Study of Wilson's Disease
New York, NY

REFERENCES

1. Brewer GJ, Johnson VD, Dick RD, Fink JK, Kluin KJ. Treatment of Wilson's disease with zinc. XVII: Treatment during pregnancy. HEPATOLOGY 2000;31:364-370.
2. Scheinberg IH, Sternlieb I. Pregnancy in penicillamine-treated patients with Wilson's disease. N Engl J Med 1975;293:1300-1302.
3. Scheinberg IH, Sternlieb I. Wilson's disease. Vol. 23. Major Problems in Internal Medicine. Philadelphia: Saunders 1984:156-162.
4. Walshe JM. Pregnancy in Wilson's disease. Quart J Med 1977;46:73-83.
5. Stähler E, Stähler F, Sturm G. Gravidität bei Wilsonscher Kupferstoffwechselstörung. Geburtsh Frauenheilk 1972;32:590-593.
6. Toulouse R, Poirier PY, de Villartay A, Kerisit J. Maladie de Wilson et grossesse. J Gynecol Obstet Biol Repr 1974;3:1057-1062.
7. Mareček Z, Graf M. Pregnancy and parturition in Wilson's disease. Sbornik Lek 1975;77:45-50.
8. Gollan IL, Hussein S, Hoffbrand AV, Sherlock S. Red cell aplasia following prolonged D-penicillamine therapy. J Clin Pathol 1976;29:135-139.
9. Arbisser LI, Scott CI Jr, Howell BR. Mannosidosis and maternal penicillamine therapy. Lancet 1976;I:312-313.
10. Tsuzuki E, Scaff M, Roitman I, Neme B, Canelas HM. Degeneracao hepatolenticular e gravidez. Rev Hosp Clin Fac Med (São Paolo) 1976;31:35-38.
11. Toaff R, Toaff ME, Peyser MR, Streifler M. Hepatolenticular degeneration (Wilson's disease) and pregnancy. A review and report of a case. Obstet Gynecol Surv 1977;32:497-507.
12. Fukuda, K, Ishii A, Matsue Y, Funaki K, Hoshiai H, Maeda S. Pregnancy and delivery in penicillamine treated patients with Wilson's disease. Tohoku J Exp Med 1977;123:279-285.
13. Master CH, Dawkins RL, Zilko PJ, Simpson JA, Leedman RJ, Lindstrom J. Penicillamine-associated myasthenia gravis, antiacetylcholine receptor and antistriational antibodies. Am J Med 1977;63:689-694.
14. Linares A, Zarranz JJ, Rodriguez-Alarcon J, Diaz-Perez JL. Reversible cutis laxa due to maternal penicillamine treatment. Lancet 1979;II:43.
15. Harpey J-P, Jaudon M-C, Clavel J-P, Galli A, Darbois Y. Cutis laxa and low serum zinc after antenatal exposure to penicillamine. Lancet 1983;II:858.
16. Biller J, Swiontoniowski M, Brazis PW. Successful pregnancy in Wilson's disease: a case report and review of the literature. Eur Neurol 1985;24:306-309.
17. Morimoto I, Ninomiya H, Komatsu K, Satho M. Pregnancy and penicillamine treatment in a patient with Wilson's disease. Jpn J Med 1986;25:59-62.
18. Bunke H, Cario W-R, Schneider M. Abweichungen in der Zusammensetzung der Muttermilch bei Morbus Wilson. Kinderärztl Prax 1989;57:89-92.
19. Dupont P, Irion O, Beguin F. Pregnancy in a patient with treated Wilson's disease: a case report. Am J Obstet Gynecol 1990;163:1527-1528.
20. Chin RKH. Pregnancy and Wilson's disease. Am J Obstet Gynecol 1991;165:488-489.
21. Shimono N, Ishihashi H, Ikematsu H, Kudo J, Shirahama M, Inaba S, Maeda K, et al. Fulminant hepatic failure during perinatal period in a pregnant woman with Wilson's disease. Gastroenterol Jpn 1991;26:69-73.
22. Soong YK, Huang HY, Huang CC, Chu NS. Successful pregnancy after D-penicillamine therapy in a patient with Wilson's disease. J Formosa Med Assoc 1991;90:693-696.
23. Avramovic D, Gligorovic S, Jovanovic-Tajfl S, Kastratovic B. Wilson's disease and pregnancy. Srp Arh Celok Lek 1992;120:306-308.
24. Stvrtinova V, Balazovjech I, Hlinstakova S, Hlinstak K, Sasko A. Wilson's disease and pregnancy. Vnitr Lek 1992;38:276-280.
25. Pilishegyi J, Lacza T, Kazy Z, Czeizel E. Successful pregnancy in a patient with treated Wilson's disease after genetic counseling. Orv Hetil 1993;134:1813-1816.
26. Pierzchala W, Zamlynski J, Rzempoluch J. Pregnancy and delivery and the diagnosis of Wilson's disease. Pol Tyg Lek 1994;49:200-201.
27. Hartard C, Kunze K. Pregnancy in a patient with Wilson's disease treated with D-penicillamine and zinc sulfate. Eur Neurol 1994;34:337-340.
28. Nunns D, Hawthrone B, Goulding P, Maresh M. Wilson's disease in pregnancy. Eur J Obstet Gynecol Reprod Biol 1995;62:141-143.
29. Berghella V, Steele D, Spector T, Cambi F, Johnson A. Successful pregnancy in a neurologically impaired woman with Wilson's disease. Am J Obstet Gynecol 1997;176:712-714.
30. Miranda M, Villagar R. Embarazo y enfermedad de Wilson: inocuidad del uso de penicilamina. Rev Med Chil 1997;125:497-498.
31. Messner U, Gunter HH, Niesert S. Wilson disease and pregnancy. Review of the literature and case report. Z Geburtshilfe Neonatol 1998;202:77-79.
32. Martinez-Frias ML, Rodriguez-Pinilla E, Bermejo E, Blanco M. Prenatal exposure to penicillamine and oral clefts: case report. Am J Med Genet 1998;76:274-275.
33. Mustafa MS, Shamina AH. Five successful deliveries following 9 consecutive spontaneous abortions in a patient with Wilson's disease. Aust N Z J Obstet Gynaecol 1998;38:312-314.
34. Devesa R, Alvarez A, de las Heras G, de Miguel JR. Wilson's disease treated with trientine during pregnancy. J Pediat Gastroenterol Nutr 1995;20:102-103.
35. Desbriere R, Roquelaurae B, Sarles J, Boubli L. Grossesse chez une patiente traitée par trientine dihydrochloride pour maladie de Wilson. Presse Méd 1998;27:806.
36. Kaushanksy A, Frydman M, Kaufman H, Homburg R. Endocrine studies of the ovulatory disturbances in Wilson's disease. Fertil Steril 1987;47:270-273.