Brief Report

Use of Atypical Antipsychotics During Pregnancy and the Risk of Neural Tube Defects in Infants

Gideon Koren, M.D., F.A.C.M.T., F.R.C.P.C.
Tony Cohn, M.B., Ch.B.
David Chitayat, M.D., F.R.C.P.C.
Bhushan Kapur, Ph.D.
Gary Remington, M.D., Ph.D.
Diane Myles Reid, M.Sc.
Robert B. Zipursky, M.D., F.R.C.P.C.

Objective: Folate deficiency in early pregnancy and maternal adiposity, independent of folate intake, lead to a greater risk of neural tube defects in infants. Atypical antipsychotics cause various degrees of weight gain. The authors assessed folate status and obesity among patients with schizophrenia receiving atypical antipsychotics.

Method: A sample of 70 inpatients and outpatients (21 of them women) who were taking antipsychotics was randomly selected. Body weight, body mass index, daily folate intake, and folate serum concentrations were determined.

Results: The majority of the patients were overweight. Only eight of 37 patients had folate intake above 400 µg/day, the level shown to be protective against neural tube defects. Mean serum folate was significantly lower than in a general hospital group of 810 patients.

Conclusions: Women with schizophrenia who take atypical antipsychotics have a higher risk of neural tube defects in their infants because of the associated low intake of folate and obesity.

(Am J Psychiatry 2002; 159:136–137)

The atypical antipsychotic drugs have emerged as effective medications for the treatment of schizophrenia, and their use has been steadily increasing (1, 2). One of their prominent adverse effects is various degrees of weight gain (3–5). Adiposity in pregnancy has been shown to increase the risk of neural tube defects in infants (6–8), and this risk has been only partially accounted for by the known risk of low levels of folic acid (6). We undertook a study to evaluate the folate status of patients with schizophrenia who were receiving atypical antipsychotics.

Method

Inpatients and outpatients were randomly recruited from three sites: an academic acute care specialty psychiatric facility and two provincial psychiatric hospitals. All of the patients had been taking a single atypical antipsychotic medication for at least 3 months. Daily folate intake was calculated with a standardized, computer-based software package: Foodsmart (Sasquatch Software Corporation, Vancouver, B.C., Canada). Dietary information was collected by use of 24-hour recall and a subsequent 2-day food diary to determine the mean daily folate intake of a subsample of 37 subjects. The patients were carefully instructed in the use of the food diary and coached through this process. Serum folate levels were measured by using radioimmunoassay procedures. Their body mass index was calculated by using weight (kg)/height $(m)^2$.

Demographic characteristics of the schizophrenic patients were correlated with serum folate levels by least square regression analysis, as was the correlation between folate intake and the resultant folate serum concentration. The mean serum folate level of the schizophrenia patients was compared to that of a general hospital sample of 818 patients by use of Student's t test. The patients in that sample were selected randomly from a group of patients in whom folate measurement was performed and who had normal values for hemoglobin and normal corpuscular volumes. Rates of obesity (body mass index >27 kg/m^2) were compared with standard rates for the general population (9) by using chi-square analysis.

Results

Our study sample consisted of 70 psychiatric patients (21 women) with a mean body weight of 84.2 kg (SD=21, range=52–167, median=79.2). Their mean age was 39.5 years (SD=11.5, range=20.0–73.5). A total of 38% of the male patients and 63% of the female patients were obese (body mass index >27 kg/m^2). These rates were significantly greater than the published rates of 25% of men and 20% of women found in Statistics Canada's National Population Health Survey Overview 1994–95 of 20,000 Canadians (9) (men: χ^2=4.2, df=1, p<0.05; women: χ^2=20.3, df=1, p<0.001). A total of 65 (93%) of the 70 patients had been taking a single antipsychotic for more than 3 months. The antipsychotics received were risperidone (N=18), olanzapine (N=17), clozapine (N=11), quetiapine (N=3), and typical antipsychotics (N=21). The mean treatment duration was 38 months (range=2–276, median=21). The women's body mass index (median=28.8 kg/m^2) was similar to the men's body mass index (median=25.5 kg/m^2) (Mann-Whitney U, df=68, p=0.70). Serum folate levels correlated significantly with folate intake (r=0.51, p=0.001). In contrast, there was no correlation between body mass index and serum folate level, and there were no differences in serum or dietary folate levels among patients taking different atypical antipsychotics.

Mean folate intake was 278 µg/day (SD=194, range=39–1174, median=249) among the 37 patients in the folate subsample. Only eight of 37 patients who had their folate

levels measured had folate intake above 400 μg/day, the dose shown to be protective against neural tube defects in infants. The mean serum folate level was 23.2 nmol/liter (SD=12, range=5.7–58.4, median=20.7), significantly lower than in a general hospital population (mean=35.8 nmol/liter, SD=30) (Student's t=3.5, df=886, p=0.0005). Male and female psychiatric patients both also tended to have lower levels of serum folate than the general population.

Discussion

The newer atypical antipsychotic agents have not been shown to be teratogenic in animal studies or in preliminary human reports (10, 11). However, they cause various degrees of weight gain, which has been shown to increase the risk for neural tube defects in the infants of adipose women (6, 7). This effect is largely independent of low folate status (6), which is a well-established risk factor for neural tube defects in infants. Of importance, we have shown low folate intake in the majority of these patients, which results in low serum concentrations of folate. In addition, there is strong evidence for a greater prevalence of diabetes in schizophrenic patients and patients treated with certain atypical antipsychotics (12–14).

It is evident that the female patients in our study were substantially more likely to have a body mass index above 27 kg/m^2 than the men. This may further increase the risk of neural tube defects in the infants of these women. The poor intake of folate may relate to dietary choices secondary to schizophrenia, to an atypical antipsychotic regimen, or to some effect of the medications on metabolism. Fung et al. (15) recently showed that in healthy individuals, a higher intake of fat was associated with lower plasma folate levels. Our results suggest that the majority of these female patients are overweight and have low folic acid intake and low resultant serum concentrations, which puts their infants at high risk for neural tube defects.

Although the method we used for estimation of dietary folate has not been validated for use in schizophrenia patients, these patients were analyzed in a clinical setting that focused on weight gain, and they were motivated to give an accurate dietary account. In addition, the patients were carefully coached through the collection of food records. Future studies should address the relationship of weight gain and folate levels over time.

It is conceivable to supplement these women with high doses of folate (e.g., 4 mg/day), which is recommended in other high-risk populations (e.g., those with previous infants with neural tube defects, those with diabetes, and those taking antiepileptics). Because many pregnancies in women with schizophrenia are unplanned, it is likely that pregnancy may be first detected beyond the first postconceptional month, after the neural tube defect has formed. Hence, it makes clinical sense to perform diagnostic tests to rule out neural tube defects among the fetuses of these patients, including using detailed level-2 ultrasounds and maternal alpha-fetoproteins test. Patients with schizophrenia, their families, and caregivers need to be aware and educated about these risks, their prevention, and detection.

Received March 7, 2001; revisions received June 4 and June 29, 2001; accepted July 5, 2001. From the Motherisk Program, The Hospital for Sick Children; the Center for Addiction and Mental Health, Toronto; Mount Sinai Hospital, Toronto; the Department of Clinical Pathology, Sunnybrook and Women's College Health Science Centre, University of Toronto, Toronto; and the Canadian Institutes for Health Research, Ottawa, Ont., Canada. Address reprint requests to Dr. Koren, Division of Clinical Pharmacology/Toxicology, The Hospital for Sick Children, 555 University Ave., Toronto, Ont. M5G 1X8, Canada; gkoren@sickkids.on.ca (e-mail).

Supported in part by Janssen Ortho, Toronto. Dr. Koren is a Senior Scientist with the Canadian Institutes for Health Research.

References

1. Mossman D, Lehrer DS: Conventional and atypical antipsychotics and the evolving standard of care. Psychiatr Serv 2000; 51: 1528–1535
2. Kapur S, Remington G: Atypical antipsychotics: patients value the lower incidence of extrapyramidal side effects. Br Med J 2000; 321:1360–1361
3. Blackburn GL: Weight gain and antipsychotic medication. J Clin Psychiatry 2000; 61(suppl 8):36–42
4. Green AI, Patel JK, Goisman RM, Allison DB, Blackburn G: Weight gain from novel antipsychotic drugs: need for action. Gen Hosp Psychiatry 2000; 22:224–235
5. Taylor DM, McAskill R: Atypical antipsychotics and weight gain—a systematic review. Acta Psychiatr Scand 2000; 101: 416–432
6. Werler MM, Louik C, Shapiro S, Mitchell AA: Pre-pregnancy weight in relation to risk of neural tube defects. JAMA 1996; 275:1089–1092
7. Shaw GM, Velie EM, Schaffer D: Risk of neural tube defect-affected pregnancies among obese women. JAMA 1996; 275: 1093–1096
8. Shaw GM, Todoroff K, Finnell RH, Lammer EJ: Spina bifida phenotypes in infants or fetuses of obese mothers. Teratology 2000; 61:376–381
9. National Population Health Survey Overview 1994–95. Ottawa, Ont, Statistics Canada, 1995, pp 1–17
10. Goldstein DJ, Carbin LA, Fung MC: Olanzapine-exposed pregnancies and lactation; early experience. J Clin Psychopharmacol 2000; 20:399–403
11. Stones SC, Sommi RW, Rasken PA, Anya I, Vaughn J: Clozapine use in two full-term pregnancies. J Clin Psychiatry 1997; 58: 364–365
12. Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL: Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996; 37:68–73
13. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A: Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000; 26:903–912
14. Henderson DC, Cagliero E, Gray C, Nasrallah RS, Hayden DL, Schoenfeld DA, Goff DC: Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000; 157:975–981
15. Fung TT, Rimm EB, Spiegelman D, Fifai N, Tafler GH, Willett WC, Hu FB: Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001; 73:61–67