The Safety of St. John's Wort (*Hypericum perforatum*) During Breastfeeding

Amy Lee, M.Sc.; Ravinder Minhas, B.Sc.;
Noriko Matsuda, M.Sc.; Michael Lam, B.Sc.; and Shinya Ito, M.D.

Background: We examined the safety of St. John's wort to nursing mothers and their infants.

Method: A prospective, observational, cohort study was conducted. Thirty-three breastfeeding women receiving St. John's wort (Group 1) who contacted our teratogen/toxicant counseling service regarding the safety of St. John's wort during breastfeeding were followed up between May 1999 and April 2001. These women were compared with 101 disease-matched (Group 2) and 33 age- and parity-matched nondisease controls (Group 3). Information collected included maternal and neonatal demographics, breastfeeding duration, use of St. John's wort, maternal and infant adverse events, infant weight over the first year of life, and whether or not the mother experienced a decrease in lactation.

Results: There were no statistically significant differences found in maternal or infant demographics or maternal adverse events. Whereas only 1 infant each in Groups 2 and 3 was reported to be colicky, there were 2 cases of "colic," 2 of "drowsiness," and 1 of "lethargy" in Group 1 ($p < .01$; Group 1 vs. Group 2, $p < .01$; Group 1 vs. Group 3, $p = .20$). Although 3 of these women in Group 1 consulted their doctor, specific medical treatment was not required. No significant difference was observed in the frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life.

Conclusion: These results provide a framework for the management of breastfeeding women receiving St. John's wort.

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Received Sept. 13, 2002; accepted Feb. 14, 2003. From the Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Departments of Pediatrics and Pharmacology, University of Toronto, Toronto, Ontario, Canada.

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Corresponding author and reprints: Shinya Ito, M.D., Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario Canada M5G 1X8 (e-mail: ito@sickkids.on.ca).

Approximately 10% to 15% of all women suffer from depression in the postpartum.[1] Therefore, it is not uncommon for women to require antidepressants in the period following childbirth. The safety of antidepressants has been addressed by case reports and series, with the general consensus that the risk-benefit assessment be made on a case-specific basis.[2,3] Recently, extracts from the plant St. John's wort (*Hypericum perforatum*) have been gaining in popularity as a natural antidepressant. This may be due in part to the common misconception by patients and health care providers that herbal products, being "natural," are safer than synthetic pharmaceuticals. Patients may also turn toward St. John's wort because it is easily accessible as an over-the-counter product.

St. John's wort has been reported to adversely affect the quality and quantity of milk when consumed in "large enough" amounts by cattle.[4] A recent study by Franklin et al.[5] found a decrease in plasma prolactin after a 2700-mg single dose of St. John's wort in healthy male volunteers. If St. John's wort has the potential to decrease prolactin levels, this could potentially affect milk production.

In a study by Klier et al.,[6] hypericin and hyperforin, which are active constituents of St. John's wort, were measured in the breast milk of a woman receiving 300 mg of St. John's wort 3 times a day. Both hypericin and hyperforin were excreted in minimal levels. Levels were undetected in infant plasma. The only published case of infant exposure to St. John's wort through pregnancy and breastfeeding reported an infant exposed to a maternal dose of 900 mg/day from 24 weeks' gestation to the day before delivery. St. John's wort was recommenced on day 20 postpartum at a dose of 300 mg/day. On days 4 and 33 of life, behavioral assessment of the infant was within normal parameters.[7]

To date, there is no systematic study that examines the safety of St. John's wort during breastfeeding. This study aims to identify possible adverse effects on the breastfeeding mother and infant due to maternal St. John's wort use.

METHOD

Study Setting and Subjects

The Motherisk Program, Toronto, Ontario, Canada, is a teratogen/toxicant counseling service. Women with con-

cerns about fetal/infant exposure to maternal medications/infections/chemicals during pregnancy or lactation contact the program seeking information on the safety of the agent. Between May 1999 and April 2001, we contacted and administered a standard follow-up questionnaire to all women who consulted the program regarding the safety of St. John's wort during breastfeeding. Of these, 33 women took St. John's wort and breastfed (Group 1). One hundred one of those followed up did not take St. John's wort and were enrolled as disease-matched controls (Group 2). Thirty three age- and parity-matched women were selected as a second control group (Group 3).

Data Collection

During the follow-up interview, information regarding the following characteristics was confirmed or newly collected: maternal age, marital status, education, family income, obstetrical history, and medications used. Infant information included gestational age at delivery, birth weight, age and weight at time of follow-up, health problems, and name of health care provider. Breastfeeding information included duration of breastfeeding and age at introduction of formula, and maternal and/or infant problems related to breastfeeding. Subjects were also asked whether they experienced any decrease in milk production and whether there were concerns with the infant's weight gain. In order to ensure that the infant was receiving adequate milk intake, information on the infant's weight gain for the first year of life was also obtained from the infant's physician. Informed verbal consent was obtained from all patients, and the study was approved by the institution's research ethics board.

Data Analysis

The 3 groups were compared using analysis of variance and chi-square analyses for parametric data. The Kruskal-Wallis test was used to compare nonparametric data between the 3 groups. All infant weights were corrected for gestational age, and gender-specific weight-for-age percentiles, expressed as z scores, were calculated. The mean z score for each child was calculated and used in the comparison of the 3 groups. A p value of $< .05$ was considered significant.

Table 1. Demographic Characteristics of Mother/Infant Pairs Exposed to St. John's Wort (Group 1), Disease-Matched Control Pairs Not Exposed to St. John's Wort (Group 2), and Age- and Parity-Matched Control Pairs (Group 3)

Characteristic	Group 1 (N = 33)	Group 2 (N = 101)	Group 3 (N = 33)	p Value
Maternal age, mean ± SD, y	32.6 ± 5.2	33.0 ± 5.1	33.0 ± 5.5	.88
Parity, N (%)				
1	9 (27.3)	35 (34.7)	9 (27.3)	.80
2	15 (45.5)	46 (45.5)	15 (45.5)	
≥ 3	9 (27.3)	20 (19.8)	9 (27.3)	
Education level, N (%)				
≤ Secondary	5 (15.2)	21 (20.8)	5 (15.2)	.66
Post-secondary	28 (84.8)	80 (79.2)	28 (84.8)	
Marital status, N (%)				
Single	2 (6.1)	6 (5.9)	4 (12.1)	.59
Married	30 (90.9)	94 (93.1)	29 (87.9)	
Other	1 (3.0)	1 (1.0)	0 (0)	
Family income, N (%)	N = 32	N = 90	N = 30	
< $20,000	5 (15.6)	2 (2.2)	3 (10.0)	.06
$20,000–$39,999	8 (25.0)	21 (23.3)	3 (10.0)	
$40,000–$59,999	6 (18.8)	28 (31.1)	8 (26.7)	
$60,000–$79,999	7 (21.9)	19 (21.1)	4 (13.3)	
≥ $80,000	6 (18.8)	20 (22.2)	12 (40.0)	
Reason for St. John's wort inquiry, N (%)	N = 33	N = 93		
Depression	27 (81.2)	75 (80.6)	…	
Anxiety	5 (15.2)	9 (9.7)	…	.37
Other	1 (3.0)	9 (9.7)	…	
Gestational age at delivery, mean ± SD, wk	N = 33	N = 101	N = 33	
	39.6 ± 1.5	39.7 ± 1.7	39.7 ± 1.7	.44
Birth weight of infant, mean ± SD, kg	3.6 ± 0.6	3.6 ± 0.5	3.6 ± 0.5	.85
Breastfeeding duration, mean ± SD, mo	N = 17	N = 57	N = 21	
	12.1 ± 9.9	10.8 ± 5.7	10.8 ± 5.6	.64
Age formula introduced, mean ± SD, mo	N = 16	N = 50	N = 21	
	4.3 ± 3.4	5.6 ± 3.6	6.3 ± 3.9	.30

RESULTS

Women in Groups 1, 2, and 3 were followed up when their infants were 15.9 ± 9.7, 16.8 ± 9.1, and 15.1 ± 7.8 months old, respectively (p = .66). There were no significant differences between the 3 groups in terms of maternal and infant demographics or infant feeding methods (Table 1).

There was no significant difference between Groups 1 and 2 for the indications given for wanting to use St. John's wort. However, more women in Group 1 were also receiving a prescription antidepressant when compared with Group 2 (14/33 [42.4%] vs. 18/101 [17.8%], $p < .01$).

The dose of St. John's wort used by the women in Group 1 was 704.9 ± 463.6 mg/day (range, 225–2150 mg/day), for a duration of 1.5 ± 1.7 months, commencing at 4.2 ± 3.6 months (median = 4.0 months; range, 0–11 months) postpartum. Three of the women in Group 1 commenced St. John's wort therapy during pregnancy. The mean duration of infant St. John's wort exposure through breastfeeding was 2.1 ± 3.5 months.

No maternal adverse events were reported in any group. In addition, there was no significant difference in the proportion of maternal reports of decreased milk volume among Groups 1, 2, and 3 (12.1%, 6.9%, and 6.1%, respectively; p = .58). Whereas only 1 infant each in Groups 2 and 3 was reported to be colicky, there were 2 cases of "colic," 2 of "drowsiness," and 1 of "lethargy" in Group 1 ($p < .01$; Group 1 vs. Group 2, $p < .01$; Group 1 vs. Group 3, p = .20). Although 3 of these women in Group 1 consulted their doctor, specific medical treatment

was not required. The daily dose of St. John's wort ingested by women reporting adverse events was not significantly different from that of women not reporting adverse events (median = 450 mg/day vs. 600 mg/day; p = .50). Two of the 5 infants in Group 1 were also exposed to antidepressants during breastfeeding. This proportion (40%) was not different from the overall proportion of antidepressant use in Group 1.

Weight data were obtained from physicians for 24, 21, and 41 infants in Groups 1, 2, and 3, respectively. There were no significant differences in the mean z scores between the 3 groups (0.6 ± 1.0, 0.6 ± 0.9, 0.6 ± 0.7, respectively; p = .97).

DISCUSSION

To our knowledge, this is the first cohort study to address the safety of St. John's wort exposure to the infant during breastfeeding. Contrary to the report by Muenscher in 1951,[4] the study was unable to detect a clear signal indicating lower milk production due to St. John's wort use. Granted that the retrospective nature of the study did not allow direct quantitative measurements of milk production, the absence of differences in infant weight gain between the groups suggests that even if milk production is affected, this did not have a clinical effect on infant weight and growth. The dose of St. John's wort observed to cause a decrease in serum prolactin concentrations in the study by Franklin et al.[5] was 3 times the standard total daily dose. Whether St. John's wort causes a decrease in serum prolactin levels at therapeutic doses awaits further studies.

A statistically significant higher rate of prescription antidepressant use was observed in Group 1 when compared with Group 2. This may be because women in Group 1 were more willing to take medication in the postpartum period (and therefore, also took St. John's wort) when compared with Group 2 (who did not take St. John's wort). Another explanation may be that their disease state was more severe than that of women in Group 2. Although there was no significant difference in the reported indications for St. John's wort use between Groups 1 and 2, the design of the current study did not allow disease severity to be measured.

A higher rate of reported infant adverse effects was observed in Group 1 when compared with the 2 control groups. Although in 3 of the study cases a physician was consulted, no medical intervention was required. That women in Group 1, who were receiving St. John's wort, may have been more anxious and more likely to perceive adverse events when compared with women in the control groups, who were not using the product, cannot be dismissed. However, these findings suggest that a more cautious approach should be used when dealing with St. John's wort or other herbal products that lack adequate studies.

This is the first cohort study to look at the safety of St. John's wort during breastfeeding. Contrary to the report by Muenscher in 1951,[4] this study was unable to detect a change in milk production due to St. John's wort use. Although 5 infants in Group 1 were reported to experience adverse events, it is not known whether these events are due to St. John's wort exposure through the breast milk. Also reassuring is the fact that none of these infants required medical attention.

REFERENCES

1. Oates MR. The treatment of psychiatric disorders in pregnancy and the puerperium. Clin Obstet Gynaecol 1986;13:385–395
2. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. Am J Psychiatry 1996;153:1132–1137
3. Burt VK, Suri R, Altshuler L, et al. The use of psychotropic medications during breast-feeding. Am J Psychiatry 2001;158:1001–1009
4. Muenscher W. Poisonous Plants of the United States. New York, NY: The Macmillan Company; 1951
5. Franklin M, Chi J, McGavin C, et al. Neuroendocrine evidence for dopaminergic actions of hypericum extract (LI 160) in healthy volunteers. Biol Psychiatry 1999;46:581–584
6. Klier CM, Schafer MR, Schmid-Siegel B, et al. St. John's wort (Hypericum perforatum): is it safe during breastfeeding? Pharmacopsychiatry 2002;35:29–30
7. Grush LR, Nierenberg A, Keefe B, et al. St John's wort during pregnancy [letter]. JAMA 1998;280:1566