

Pregnancy Outcome Following Gestational Exposure to Echinacea

A Prospective Controlled Study

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Background: Echinacea products are among the most popular phytomedicines on the North American market. Since at least half of all pregnancies are unplanned, many women inadvertently use echinacea in their first trimester. Presently, there is a paucity of information regarding the gestational safety of this herb. The primary objective of this study was to evaluate the safety of echinacea in pregnancy when used for upper respiratory tract ailments.

Patients and Methods: The study group consisted of women who were prospectively followed up after contacting the Motherisk Program regarding the gestational use of echinacea. This cohort was disease-matched to women exposed to nonteratogenic agents by maternal age, alcohol, and cigarette use. Rates of major and minor malformations between the groups were compared.

Results: A total of 206 women were enrolled in the study group after using echinacea products during preg-

nancy; 112 women used the herb in the first trimester. There were a total of 195 live births, including 3 sets of twins, 13 spontaneous abortions, and 1 therapeutic abortion. Six major malformations were reported, including 1 chromosomal abnormality, and 4 of these malformations occurred with echinacea exposure in the first trimester. In the control group, there were 206 women with 198 live births, 7 spontaneous abortions, and 1 therapeutic abortion. Seven major malformations were reported. There were no statistical differences between the study and control groups for any of the end points analyzed.

Conclusions: This first prospective study suggests that gestational use of echinacea during organogenesis is not associated with an increased risk for major malformations.

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THE USE of herbal medicines in the United States increased by 385% between 1990 and 1997,¹ with market sales estimated at \$3.4 billion.² Echinacea products are among the most popular phytomedicines in North America, representing almost 10% of the herbal market in the United States in 1995.³ Three members of the genus *Echinacea* are used medicinally: *Echinacea angustifolia* DC (narrow-leaved purple coneflower), *Echinacea purpurea* (L) Moench (common purple coneflower), and *Echinacea pallida* (Nutt) (pale purple coneflower).⁴ While echinacea has been used historically for a number of indications, including skin and arthritic conditions, it is primarily used today for the prevention and treatment of upper respiratory tract infections.^{5,6}

While echinacea is being used by millions in North America, results of controlled trials have been conflicting.⁶⁻⁹ Questions of trial design, variable routes of administration, and the selection of products in which echinacea is the only ingredient prevent this phytomedicine from be-

ing suggested for any one indication.⁶ Evidence from in vivo and in vitro studies demonstrates that extracts of echinacea increase the function of certain elements of the cell-mediated immune system.¹⁰⁻¹²

Adverse effects following oral administration appear to be rare, limited to taste abbreviations and transient numbness of the tongue.^{13,14} Mild allergic symptoms may be experienced by individuals with allergies to the sunflower (*Asteraceae*) family.⁵ A number of authoritative texts caution against the use of echinacea products in progressive conditions such as tuberculosis, human immunodeficiency virus infection, and multiple sclerosis.^{14,15} While the Commission E monographs suggest that *E pallida* has no effect on pregnancy,¹⁵ the safety of this herb in pregnancy is yet to be established. Given the popularity of this herb and the fact that at least half of all pregnancies are unplanned,¹⁶ it is important to establish the fetal safety of these products.

The primary objective of this prospective study was to determine the fetal safety following gestational use of echi-

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PATIENTS AND METHODS

The study group consisted of women who contacted the Motherisk Program, a teratogen information service at the Hospital for Sick Children in Toronto, Ontario, regarding the gestational exposure to echinacea between 1996 and 1998. During the initial counseling, intake forms were completed to record details of pregnancy and exposure. Women who had used echinacea during pregnancy were prospectively followed up, with standardized forms completed to collect details on demographics, medical and obstetrical histories, concurrent drug use, and pregnancy outcome.

This study group was matched to a control group by disease (upper respiratory tract ailments), maternal age (± 2 years), alcohol use, and cigarette use. The control group consisted of pregnant women who had contacted the Motherisk Program regarding the safety of echinacea for an upper respiratory tract ailment but subsequently did not use it or used a nonteratogenic antibiotic instead.

With the outcome of pregnancy being the primary focus of this study, the rates of major malformations were compared between the study and control groups. A major malformation was defined as any anomaly that has an adverse effect on either the function or the social acceptability of the child.¹⁷ Rates of minor malformations, miscarriages, and neonatal complications were also compared. With patient consent, documentation was requested from the child's primary physician to confirm pregnancy outcome information. This protocol was approved by the hospital's research ethics board.

An additional questionnaire recorded the patient's perception of risk after gestational exposure to echinacea, efficacy as reported by the patient, and recommendations made by the patient's health care provider.

The rates of malformations between the groups were compared using the Fisher exact test. Statistical analysis of pregnancy outcomes and neonatal complications were compared using the χ^2 and Mann-Whitney rank sum tests whenever appropriate.

nacea products. A secondary objective was to characterize patterns of use of this herb in Canada.

RESULTS

A total of 206 women were enrolled and prospectively followed up after gestational use of echinacea. In the study group, 112 women (54%) used echinacea in the first trimester, with 17 (8%) exposed in all 3 trimesters. There were 195 live births, including 3 sets of twins; 13 spontaneous abortions; and 1 therapeutic abortion. The disease-matched control group consisted of 206 women with 198 live births, 7 spontaneous abortions, and 1 therapeutic abortion. No statistical difference was seen between the 2 groups in terms of pregnancy outcome, delivery method, maternal weight gain, gestational age, birth weight, or fetal distress (**Table 1**).

Rates of malformations between the study and control groups were also not statistically significantly dif-

Table 1. Characteristics of Pregnancies in the Study and Control Groups

| Characteristics | No. (%) [*] | | P |
|---------------------------------------|-----------------------------|-------------------------|-------------------|
| | Echinacea Group (n = 206) | Control Group (n = 206) | |
| Outcome | | | |
| Live birth | 195/206 (94.7) [†] | 198/206 (96.1) | .40 [‡] |
| Spontaneous abortion | 13/206 (6.3) | 7/206 (3.4) | |
| Therapeutic abortion | 1/206 (0.5) | 1/206 (0.5) | |
| Delivery method | | | |
| Vaginal | 162/195 (83.1) | 161/198 (81.3) | .74 [‡] |
| Cesarean delivery | 33/195 (16.9) | 37/198 (18.7) | |
| Maternal weight gain, kg [§] | 15.2 \pm 5.1 | 14.4 \pm 5.4 | .12 |
| Gestational age, wk [§] | 39.2 \pm 2.0 | 39.2 \pm 2.7 | .58 |
| Birth weight, g [§] | 3466.4 \pm 641.4 | 3451.9 \pm 579.7 | .89 |
| Fetal distress | 46/195 (23.6) | 41/194 (21.1) | .64 |
| Major malformations | 4/98 (4.1) | 7/198 (3.5) | .76 [#] |

^{*}Unless otherwise indicated.

[†]Includes 3 sets of twins.

[‡] χ^2 Test.

[§]Values are mean \pm SD.

^{||}Mann-Whitney test.

[#]Fisher exact test.

Table 2. Major Malformations

| Major Malformations | |
|-----------------------------------------------------|-------------------------------------------------|
| Echinacea Group (n = 195) | Control Group (n = 198) |
| Left inguinal hernia (surgical repair) [*] | Ventricular septal defect |
| Bilateral hydronephrosis [*] | Hip dysplasia |
| Syndactyllyl (2nd and 3rd toes) [*] | Cranial synostosis |
| Duplicate renal pelvis (left kidney) [*] | Hypospadias (surgery required) |
| Laryngotracheomalacia | Clubbed feet |
| Trisomy 18 syndrome | Down syndrome/ ventricular septal defect (2) |

^{*}Malformations reported following first-trimester exposure to echinacea.

ferent (Table 1). There were 6 major malformations including 1 chromosomal abnormality, and 6 minor malformations in the echinacea-exposed group. With first-trimester use of the herb, 4 major and 2 minor malformations were reported. In the control group, 7 major and 7 minor malformations occurred (**Table 2**).

Capsule and/or tablet formulations of this phytomedicine were used by 114 (58%) of the 198 respondents, while 76 (38%) of the respondents used varied tinctures. The dosage of capsules and/or tablets used varied from 250 to 1000 mg/d. Tincture dose varied from a minimum of 5 to 10 to a maximum of 30 drops per day. The percentage of alcohol content of echinacea tinctures may vary, but in our cohort, it was between 25% and 45%. Duration of use also varied but was normally continuous for 5 to 7 days. The different brands used covered 2 species of echinacea, *E angustifolia* and *E purpurea*. Only 1 woman in the cohort reported using *E pallida*. The respondents rated their perception of risk after gestational use of echinacea as low (95%), medium (3%), and high (2%). Most participants (81%) reported that echinacea improved the symptoms of their upper respiratory tract ailment.

Use of echinacea by the study group was often at the suggestion of a friend or relative (70%). One hun-

Table 3. Patterns of Echinacea Use

| | No. (%) |
|---------------------------------------------------------|------------|
| Echinacea use suggested by | |
| Friend/relative | 129 (69.7) |
| Reading/advertisements | 31 (16.8) |
| Complementary health care provider | 11 (5.9) |
| Pharmacist | 6 (3.2) |
| Midwife | 6 (3.2) |
| Physician | 2 (1.1) |
| Recommendation of health care provider regarding safety | |
| Safe | 58 (48.3) |
| Consult Motherisk Program | 38 (31.7) |
| Unsure of safety | 14 (11.7) |
| Advised against use | 10 (8.3) |

dred twenty study group respondents (60%) consulted a health care provider regarding gestational use, with 48% of the health care providers suggesting that the herb was safe (**Table 3**). Alternate over-the-counter remedies were recommended to 15% of the respondents.

COMMENT

Millions of people in North America regularly consume phytomedicines, many using these products in pregnancy under the potentially false assumption that "natural" is synonymous with "safe." To the authors' knowledge, this is the first prospective study to examine fetal safety after gestational use of a phytomedicine, specifically, echinacea. After controlling for different maternal characteristics, including maternal disease, the rates of major malformations between the study and control groups were not statistically different. Moreover, the observed malformations did not follow any specific clustering.

Although several formulations of echinacea are available, capsules, tablets, and tinctures were the most popular. Women in this cohort generally used the herb for short periods and were often unaware that the standard dosage is 1 g of dried herb or 1 to 2 mL of tincture 3 times a day.¹⁴ This indicates that the over-the-counter industry as a whole may lack proper guidelines. In this cohort, the alcohol content of the echinacea tinctures varied between 25% and 45%. At a maximum dosage of 30 drops daily, this is equivalent to approximately 1 mL (1/8 tsp) of alcohol daily. This minuscule amount of alcohol over a 5- to 7-day period is highly unlikely to have an effect on the outcome of pregnancy. No brand appeared to be the preferred choice, and 2 popular North American species, *E angustifolia* and *E purpurea*, were used. Although chemical constituents do differ between the species, no one chemical constituent or group of constituents appears to be responsible for the medicinal properties.⁶ The 3 species of echinacea are often considered clinically interchangeable.¹⁸

Prescription and over-the-counter pharmaceuticals are usually used with caution in pregnancy. In contrast, many women in the study group used echinacea during organogenesis and with the knowledge of being pregnant; they perceived the risk to be low. Some of the health care providers consulted also felt that gestational use of echinacea was unlikely to be a concern, with almost half of them suggest-

ing that the product is safer, even though studies are not available. Without proper evidence-based information, health care providers are often left with the difficult task of estimating the reproductive risks of such remedies.

While a number of clinical trials have been conducted, definitive evidence regarding the efficacy of this medicinal herb is still lacking.⁸ In this cohort, self-reported efficacy of echinacea for upper respiratory tract ailments was over 80%. This study was not designed to address efficacy, but with the placebo effect documented between 30% and 40%,¹⁹ the high reported rate of efficacy may be important.

This study, limited by its sample size and the lack of standardization of dosages, had 80% power to detect a 3.5-fold increase in the rate of major malformations with $\alpha = .05$ and a 95% confidence interval. This first prospective study suggests that gestational use of echinacea during organogenesis is not associated with a detectable increased risk for major malformations.

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