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Pregnancy outcomes after prenatal exposure to echinacea: the Norwegian Mother and Child Cohort Study

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Abstract
Introduction Previous studies have shown that echinacea is among the most widely used herbal medicines during pregnancy in Western countries. Despite its frequent use, we know little about the safety of this herbal medicine during pregnancy. The primary aim of this study was to study the consequences of the use of echinacea on malformations and common adverse pregnancy outcomes. Secondly, we aimed to characterize women using this herb in pregnancy.
Method This study is based on the Norwegian Mother and Child Cohort Study (MoBa) and included 68,522 women and their children. Information was retrieved from three self-administered questionnaires completed by the women in pregnancy weeks 17 and 30 and 6 months after birth. Information on pregnancy outcomes was retrieved from the Medical Birth Registry of Norway. Generalized estimating equations analyses were performed to assess the association between exposure to echinacea and pregnancy outcomes. Pearson's chi-square test was used to assess factors related to use of echinacea in pregnancy.
Results Among 68,522 women, 363 (0.5 %) reported the use of echinacea during pregnancy. These women were characterized by high age and delivery before 2002 and were to a less extent smoking in pregnancy. The use of echinacea was not associated with an increased risk of malformations or adverse pregnancy outcomes.
Conclusion This study revealed no increased risk of malformations or adverse pregnancy outcomes after the use of echinacea in pregnancy. Studies on the safety of commonly used herbal medications are important to identify herbals that should be avoided in pregnancy.

Keywords Echinacea · Pregnancy · Herbal medicine · MoBa

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Introduction

Echinacea sp. is a group of wildflowers native to North America and was in traditional use by the Native North Americans for various purposes [1, 2]. Today, three species of the genus *Echinacea*, *Echinacea purpurea*, *E. angustifolia*, and *E. pallida*, referred to as *Echinacea* spp., are used in a large variety of echinacea products in Europe and North America for preventing and treating the common cold, flu, and upper respiratory tract infections [1, 2]. Different parts of the plants are used; "radix" and "herba" and commercial preparations may contain one or more plant parts from one or more of the three species [3]. In addition, different methods of extraction are used by various manufacturers, resulting in a large variety of preparations that are difficult to compare with respect to both effect and safety [3]. A Cochrane review from 2014 [3] that included over 4600 patients enrolled in 24 randomized controlled trials comparing mono-preparations of echinacea with placebo found suggestive evidence that the use of echinacea products may be associated with a small reduction in cold incidence. In treatment trials, there

was no association between the use of echinacea products and the shorter duration of colds.

Several studies show that echinacea is commonly used during pregnancy ranging from 2.6 % in North America, to 4.3 % in the United Kingdom, and to 8.3 % in Norway [4–6]. Though no negative case reports are identified [7], the documentation on safety of echinacea use during pregnancy is sparse, as only one safety evaluation study is found [8]. This was a cohort study including 206 pregnant echinacea-exposed women, of whom 112 had used echinacea during the first trimester. Reassuringly, this study did not detect any significant differences between the exposed group and the control group with respect to any of the end points analyzed: pregnancy outcome (live birth, spontaneous abortion, therapeutic abortion), delivery method, maternal weight gain, gestational age, birth weight, fetal distress, or major malformations. However, due to the study sample size, this study could only exclude a 3.5 times increase in the baseline risk of major malformations (80 % statistical power).

Whereas some sources [8–12] consider the use of echinacea as compatible with pregnancy, the European Medicines Agency concludes that safety during pregnancy has not been established [13]. They therefore state that in the absence of sufficient data, use during pregnancy is not recommended. So far, documentation of efficacy against, for example, the common cold and safety in pregnancy is insufficient to permit a risk-benefit assessment of echinacea use [7]. Providing safety data is therefore of great importance to aid women and healthcare providers in making knowledge-based decisions and to avoid unnecessary anxiety. The primary aim of this study was therefore to study the consequences of the use of echinacea on malformations and common adverse pregnancy outcomes including preterm birth, low birth weight, and small for gestational age. Secondly, we aimed to characterize women using this herb in pregnancy.

Materials and method

Study population and data collection

The data used in this study were provided by the Norwegian Mother and Child Cohort Study (MoBa) and the Medical Birth Registry of Norway (MBRN). MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [14]. Pregnant women in Norway were recruited through a postal invitation in connection with a routine ultrasound examination offered to all pregnant women around pregnancy week 17. The cohort now includes 114,500 children and 95,200 mothers recruited from all over Norway from 1999 to 2008, with a participation rate of 40.6 % of all invited women. The current study used version 4 of the MoBa quality-assured data files made available for research in 2009. This file includes 72,934 women who delivered between 1999 and 2006.

The MBRN is based on compulsory notification to the register of all live births, stillbirths, and late abortions, including information on pregnancy, delivery, and neonatal health [15]. The MoBa cohort was linked to the MBRN via the women's personal identification number. Participation in the current study included women who had a record in MBRN and had answered three self-administered MoBa questionnaires. The first (Q1) and third (Q3) questionnaires were completed during pregnancy weeks 13–17 and 30, respectively, and the fourth (Q4) was completed when the child was 6 months old [14]. From the original MoBa cohort, the response rate was 95 % for Q1, 92 % for Q3, and 87 % for Q4 [14]. A flowchart with exclusion criteria to achieve the final study population is outlined in Fig. 1.

Exposure variable

Information on echinacea use was retrieved from the three MoBa questionnaires. In each questionnaire, the women were first asked disease-oriented questions where they were asked to report the use of all medicinal products in relation to use against a list of specified complaints including cold, flu, and upper respiratory illness. For each indication the women were asked to give complete names and exposure windows of the products in free-text entry fields. The women could specify when the complaint was experienced and when the products were used; in Q1: 6 months before pregnancy, gestational weeks 0–4, 5–8, 9–12, and 13+ (until completion of the first questionnaire); in Q3: gestational weeks 13–16, 17–20, 21–24, 25–28, and 29+ (until completion of the third questionnaire); and in Q4: last part of pregnancy, 0–3 months after birth and 4–6 months after birth. Secondly, the questionnaires included an open-ended question about the use of all vitamins and dietary supplements, including alternative/herbal remedies, where the women were asked to give the complete names of the products. In these cases it was not possible to specify the timing of use or indication.

The authors reviewed all herbal products in the three questionnaires for echinacea as an ingredient. Exposure was classified as use during pregnancy (total), use during early pregnancy (in Q1, covering the period between conception up to pregnancy week 17), and use during late pregnancy (in Q3 and Q4, covering the period after pregnancy week 17 up to delivery).

Outcome variables

Information on outcome variables was retrieved from the MBRN. We investigated all malformations as defined by the MBRN [16]. The MBRN follows the European Surveillance of Congenital Anomalies (EUROCAT) classification system of congenital anomalies using the International Statistical

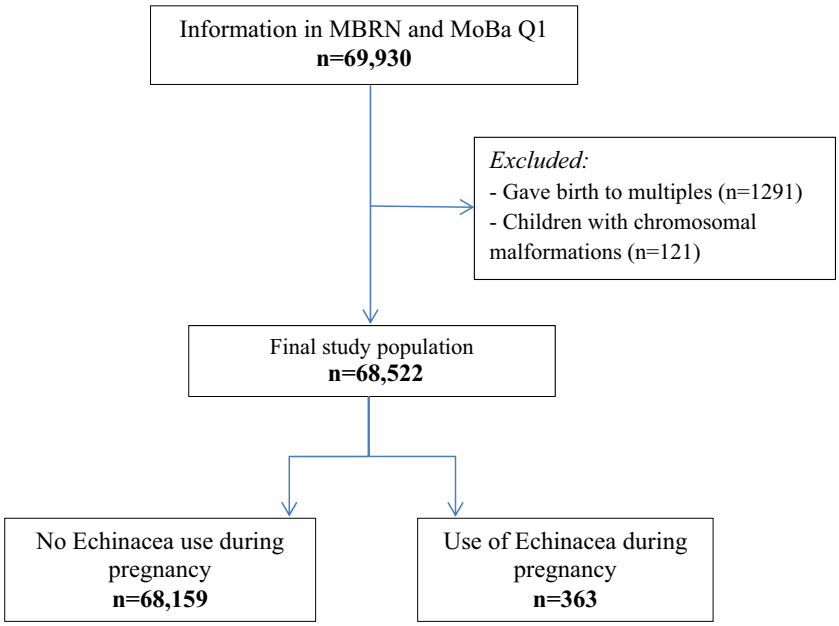

Fig. 1 Flowchart of final study population

Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [17]. Malformations were classified as follows: all malformations, defined as any birth defect registered in the MBRN as all ICD-10 Q-codes plus P83.5; major malformations, defined by the MBRN as malformations considered to be life threatening or to have serious medical or functional consequences in accordance with the EUROCAT definition; and cardiovascular malformations, defined as any malformation classified with the ICD-10 codes Q20–26 [17]. A patent ductus arteriosus (ICD-10 code Q25.0) in premature infants was not considered a cardiovascular malformation.

Other outcome variables included were preterm birth (<37 weeks gestational age), low birth weight (<2500 g), and small for gestational age (under the 10th percentile). The outcomes were not mutually exclusive.

Other variables

The following potential confounders were explored in relation to echinacea use and the different outcome variables: maternal age, parity, education, marital status, pre-pregnancy body mass index (BMI), smoking at the end of pregnancy, any folic acid use, year of delivery, sick leave, and previous miscarriages/stillbirths. The categorization of the potentially confounding variables is presented in Appendix 1.

Statistical analyses

Descriptive statistics was utilized as appropriate. The Pearson's χ^2 test was used to compare the maternal characteristics in users of echinacea and non-users of echinacea. A p value of <0.05 was considered statistically significant.

Associations were explored via the generalized estimating equations (GEE) [18]. The GEE was used to take into account that a woman might appear several times. Data are presented as crude and adjusted odds ratios (cOR and aOR, respectively) with 95 % confidence intervals (CI). The variables listed in Appendix 1 were considered potential confounders. Statistically or clinically significant variables were explored for each pregnancy outcome. The selection of variables to be included in the potential confounder sets was based on theoretically potential influences, as well as the results from exploratory data analysis. Maternal age, parity, pre-pregnancy BMI, folic acid use, smoking, education, previous miscarriages/stillbirths, and year of delivery were considered possible confounders and adjusted for. In addition, low birth weight was adjusted for by length of gestation. All statistical analyses were performed with the Statistical Package for the Social Sciences, SPSS, for Windows version 20.

Results

The study population consisted of 68,522 pregnancies; among these 68,198 (99.5 %) resulted in a live birth, 219 (0.3 %) resulted in a stillbirth, and 104 (0.2 %) resulted in a neonatal death. Any malformation occurred in 3,201 (4.7 %) of the pregnancies. The mean birth weight and the median gestational age among live-born infants was 3605 g and 40 weeks, respectively.

The cost common indications for the use of echinacea are shown in Table 1.

Maternal characteristics of users and non-users of echinacea are shown in Appendix 1. There were 363 (0.5 %) women who reported the use of echinacea during pregnancy. A total of 206 (0.3 %) and 183 (0.3 %) women had used echinacea

Table 1 Most common indications for use of echinacea, $n = 363$

Indications	*n* (%)
Cold/flu	145 (39.9)
Upper respiratory infections[a]	22 (6.1)
Lower respiratory infections[b]	2 (0.6)
Other infections[c]	4 (1.1)
No indication given[d]	196 (53.9)
Total women[e]	363 (100.0)

[a] Includes sinusitis, otitis, tonsillitis, and cough

[b] Includes bronchitis and pneumonia

[c] Includes vaginal infections and oral herpes infections

[d] Echinacea use reported in the open-ended question where there was no space for the timing of use or indication

[e] Total numbers of indications exceed 363 as some women used echinacea for several indications

during early and late pregnancy, respectively. Users and non-users of echinacea differed significantly in age, smoking status, and year of delivery.

No increased risk of malformations was detected among the women who had used echinacea during early pregnancy (Table 2). There was a prevalence of 1.5 % of major malformations among the women who had used echinacea compared with 2.6 % among the non-exposed. The three cases of major malformations that were detected among the users of echinacea were hypospadias, cleft lip, and hypoplastic left heart syndrome (Appendix 2). Users of echinacea were not found to have any increased risk of preterm birth, low birth weight, or small for gestational age (Table 3).

Discussion

To our knowledge, this study is the largest study identified to investigate the safety of echinacea in pregnancy and the results are reassuring: the use of echinacea during pregnancy seems not to increase the possibility for malformations or negative pregnancy outcomes such as preterm birth, low birth weight, or small for gestational age. This also adds valuable knowledge that strengthens our confidence in the findings of the safety evaluation study by Gallo et al. [8] and the recent review by Holst et al. [7]. These findings are important for clinical practice, as they provide healthcare professionals with more evidence for use on the risk-benefit scale when evaluations of current, past, or future echinacea use are discussed with pregnant patients.

Some caregivers might interpret the lack of documentation on safety as the existence of a risk, but in fact it means that we just do not have the information. The expectant woman's anxiety that follows the undeliberate use of any potential teratogen during pregnancy might be eased, as we are able to provide more evidence of safety. In the case of pharmaceuticals such as antiepileptics, it is "easy" to recommend use during pregnancy, although the medications are not exempt from risks to the fetus, as the benefits are overwhelming. This is hardly the case for herbal remedies (at least in the industrialized world); therefore, any healthcare professional should be reluctant to recommend use during pregnancy unless the evidence is comprehensive. Still, because of the long-term traditional use of echinacea against, for example, the common cold, pregnant women will continue using this herb in the future. Also, some women believe herbal products are safer than pharmaceuticals because they are "natural."

Women using echinacea in this study are older and more often non-smokers at the end of pregnancy. Attempts have been made to map the general "herbal medication user," but studies show diverse results [5, 19–23], although high maternal age and education seems somewhat of a consistent characteristic.

Only 0.5 % of the study population reported the use of echinacea in pregnancy, which is a lower estimate than the 3.1–36.5 % reported in previous international studies [4, 5, 24–28]. Comparing studies on the use of herbal medicines in Norway, the share of echinacea use among herbal medicine use in general has gone down over the past years; from 22.9 % in 2001 [6] to 18.9 % in 2005 [20] and finally to 6.7 % in 2009 [21]. A recent master thesis study (2014) collecting data on herbal use during pregnancy found that none of the 117 interviewed women had used echinacea during pregnancy [29]. The declining use in pregnancy might be explained by a general decline in echinacea

Table 2 Association between malformations and exposure to echinacea during early pregnancy

Outcome	Total (%)	Echinacea use ($n = 206$) *N* (%)	No echinacea use ($n = 68{,}159$) *N* (%)	Crude OR (95 % CI)	Adjusted OR[b] (95 % CI)
All malformations[a]	3201 (4.7)	11 (5.3)	3190 (4.7)	1.2 (0.6–2.1)	1.1 (0.6–2.1)
Major malformations[a]	1777 (2.6)	3 (1.5)	1774 (2.6)	0.6 (0.2–1.7)	0.6 (0.2–1.8)
Cardiac malformations[a]	605 (0.9)	1 (0.5)	604 (0.9)	0.5 (0.1–3.9)	0.6 (0.1–4.3)

OR resulting from GEE analyses

CI confidence interval, *OR* odds ratio,

[a] Malformations were defined according to the definitions of the MBRN and EUROCAT [16, 17]

[b] Adjusted for maternal age, parity, pre-pregnancy BMI, level of education, maternal smoking, folic acid use, previous miscarriages or stillbirths, and year of delivery

Table 3 Associations between prenatal exposure to echinacea and pregnancy outcomes

Outcome	Total *N* (%)	Echinacea use (*n* = 363) *N* (%)	No echinacea use (*n* = 68,159) *N* (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)
Preterm birth[a]	3535 (5.2)	19 (5.3)	3516 (5.2)	1.0 (0.6–1.6)	1.0 (0.6–1.7)[d]
Small for gestational age[b]	4281 (6.2)	24 (6.6)	4257 (6.2)	1.1 (0.7–1.6)	1.0 (0.7–1.6)[d]
Low birth weight[c]	2182 (3.2)	12 (3.3)	2170 (3.2)	1.0 (0.6–1.8)	1.1 (0.5–2.1)[e]

OR resulting from GEE analyses

CI confidence interval, *OR* odds ratio

[a] Includes infants born at a gestational age of <37 weeks

[b] Includes infants with a birth weight below the 10th percentile at the attained gestational age

[c] Includes infants with a birth weight of <2500 g

[d] Adjusted for maternal age, parity, pre-pregnancy BMI, folic acid use, smoking, education, previous miscarriages/stillbirths, and year of delivery

[e] Adjusted for maternal age, parity, pre-pregnancy BMI, folic acid use, smoking, education, previous miscarriages/stillbirths, length of gestation and year of delivery

use. Different herbal medicinal products are probably "popular" at different times, affected by commercial advertising and general health trends in society.

Strengths and limitations

The main strength of the study is the large sample size of the cohort. The risk of recall bias was minimized as a consequence of the prospective nature of data collection in MoBa. The prospective design also diminishes the risk of differential misclassification of the exposure with subsequent limited risk of biased measures of associations. Additionally, the vast variety of information on health-related, sociodemographic, and lifestyle factors enabled controlling for important potentially confounding factors in the multivariate models. MBRN provides medically confirmed records, as all information is prospectively collected by healthcare professionals during prenatal care and at birth. In addition, MBRN is unlikely to suffer from selection bias given its population-based characteristic.

A limitation of MoBa is the low response rate (40.6 % of all women invited), with a possible self-selection of the healthiest women to the study. Among those who accepted to participate, however, the response rate was high [14]. On the other hand, in comparing the MoBa population with the total Norwegian birthing population in relation to potential selection bias, the measures of the associations tested are valid, despite the fact that prevalence estimates cannot necessarily be generalized in MoBa [30]. Another limitation of the study is that MoBa is based upon self-reporting. Therefore, information on the use of echinacea may not be complete. Furthermore, a dose and administration form was not available, and the majority of women did not specify the pregnancy week of echinacea use. Lastly, though it is the largest study identified to investigate the safety of echinacea, there were few cases with malformations and adverse pregnancy outcomes; hence, we could only exclude a doubling of malformations in general and only exclude a fourfold increased risk of cardiac defects. Thus, study power for these outcomes was low.

Conclusion

In conclusion, this study revealed no increased risk of malformations or any of the following pregnancy outcomes: preterm delivery, low birth weight, or small for gestational age, among women exposed to echinacea. Even though there is no clear scientific evidence to support the use of echinacea in, for example, the treatment of cold, pregnant women will probably continue to use this herb because of the traditional use. The findings of this study are therefore reassuring and will assist women and their healthcare providers when discussing treatment options during pregnancy and the benefit-risk ratio of the echinacea.

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Authors' contributions HN, LH, and KH drafted the study protocol. All authors participated in the design and analytical plan of the study. KH performed the statistical analyses and drafted the manuscript. All authors (KH, GCH, LH, HN) contributed to the interpretation of the results and to the final manuscript. All authors (KH, GCH, LH, HN) read and approved the final manuscript.

Compliance with ethical standards Informed written consent was obtained from each participant. MoBa has been approved by the Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate.

Conflicts of interest The authors declare that they have no conflicts of interest.

Appendix 1

Characteristics of study participants according to echinacea use ($n = 68,522$)

Maternal characteristics	Total No. (%) 68,522 (100.0)	No echinacea use during pregnancy No. (%) 68,159 (99.5)	Use of echinacea during pregnancy No. (%) 363 (0.5)
Age (years)*			
≤24	8,034 (11.7)	8,001 (11.7)	33 (9.1)
25–29	23,050 (33.6)	22,945 (33.7)	105 (28.9)
30–34	26,157 (38.2)	26,013 (38.2)	144 (39.7)
≥35	11,281 (16.5)	11,200 (16.4)	81 (22.3)
Parity			
0 previous live births	29,778 (43.5)	29,612 (43.4)	166 (45.7)
≥1	38,738 (56.5)	38,541 (56.5)	197 (54.3)
Education[a]			
Primary	6,123 (8.9)	6,095 (8.9)	28 (7.7)
Secondary	20,519 (29.9)	20,413 (29.9)	106 (29.2)
Tertiary—short	27,204 (39.7)	27,061 (39.7)	143 (39.4)
Tertiary—long	13,112 (19.1)	13,039 (19.1)	73 (20.1)
Marital status			
Married/cohabitating	65,765 (96.0)	65,416 (95.8)	349 (96.1)
Other	2,427 (3.5)	2,415 (3.5)	12 (3.3)
Pre-pregnancy BMI[b]			
Underweight	2,055 (3.0)	2,041 (3.0)	14 (3.9)
Normal weight	43,058 (62.8)	42,816 (62.8)	242 (66.7)
Overweight	14,736 (21.5)	14,669 (21.5)	67 (18.5)
Obese	6,538 (9.5)	6,507 (9.5)	31 (8.5)
Smoking at the end of pregnancy*			
No	53,198 (77.6)	52,908 (77.6)	290 (79.9)
Sometimes	472 (0.7)	470 (0.7)	2 (0.6)
Daily	3,524 (5.1)	3,515 (5.2)	9 (2.5)
Missing	11,328 (16.5)	11,266 (16.5)	62 (17.1)
Any folic acid use[c]			
No	32,098 (46.8)	31,944 (46.9)	154 (42.4)
Yes, before or during	21,735 (31.7)	21,612 (31.7)	123 (33.9)
Yes, before and during	14,689 (21.4)	14,603 (21.4)	86 (23.7)
Year of delivery*			
1999–2002	13,640 (19.9)	13,512 (19.8)	128 (35.3)
2003–2006	54,882 (80.1)	54,647 (80.2)	235 (64.7)
Sick leave	43,300 (63.2)	43,087 (63.2)	213 (58.7)
Previous miscarriages/stillbirths	14,975 (21.9)	14,911 (21.9)	64 (17.6)

Numbers may not add up to 68,522 due to missing values. Missing values under 4 % are not presented in the table

BMI body mass index

*$p < 0.05$, Pearson's chi-square test, "no use of echinacea" vs. "use of echinacea"

[a] Primary: <10 years of education (the Norwegian compulsory primary + secondary school); secondary: 10–12 years (high school/upper secondary or vocational school); tertiary—short: college education; tertiary—long: university education

[b] BMI: underweight: <18.5 kg/m^2 ; normal weight: 18.5–24.9 kg/m^2 ; overweight: 25.0–29.9 kg/m^2 ; obese ≥30 kg/m^2

[c] Folic acid use is reported from 4 weeks prior to pregnancy to week 8 of gestation

Appendix 2

Description of the three pregnancies resulting in major malformations after exposure of echinacea during early pregnancy

No.	Sex	Birth defect	Pregnancy outcome	Gestational age (weeks)	Birth weight (g) Length (cm)	Apgar score 5 min	Maternal age (years)	Maternal use of folic acid and smoking during pregnancy
1	F	Cleft lip	Live birth	40	3570 53	9	32	No folic acid use; no smoking
2	M	Hypoplastic left heart syndrome	Live birth, died within 7 days after birth	36	2850 46	9	31	No folic acid use; smoking information missing
3	M	Hypospadias	Live birth	29	920 35	6	32	Folic acid use during pregnancy; no smoking

Early pregnancy is defined as use of echinacea reported in Q1 (covering the period from conception up to week 17)

F female, *M* male

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