

Original Article

Evaluating the Impact of Maternal Herbal Medicine Consumption on Cleft Lip and Palate in Newborns

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KEY WORDS

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ABSTRACT

Background: Non-syndromic cleft lip and/or palate (NSCL/P) is a common congenital deformity with a complex, multifactorial etiology involving genetic, environmental, and socioeconomic factors. Despite established risk factors, the teratogenic potential of herbal medicines- widely used during pregnancy due to their perceived safety- remains poorly understood, with limited and inconsistent evidence regarding their specific association with NSCL/P.

Purpose: This study aimed to evaluate the association of maternal herbal medicine consumption on the risk of NSCL/P in newborns, addressing a critical gap in perinatal safety research within a population with prevalent phytotherapy practices.

Materials and Method: A retrospective case-control study conducted in 2024, we enrolled 160 participants (80 cases and 80 controls) using convenience sampling. Eligible cases were mothers of infants (1–6 months) diagnosed with NSCL/P, while controls were mothers of unaffected children. Herbal medicine use, demographic details, and socioeconomic status were collected via structured questionnaires. Statistical analyses included chi-square tests and estimation of crude odds ratios (ORs) with 95% confidence intervals (CIs) using invariable logistic regression.

Results: Herbal medicine consumption was significantly higher among case mothers (66.25%) compared to controls (45.00%, p Value= 0.010). First-trimester use was notably prevalent in the NSCL/P group (94.33%). Specific herbs- *lavender*, *chamomile*, *chicory*, and *borage flower*- were associated with higher crude odds with increased risk of NSCL/P ($p < 0.05$). Maternal *lavender* use was associated with a 12-fold increase in the crude odds of NSCL/P. Sociodemographic disparities were evident: rural, illiterate, and lower-income mothers were significantly more likely to use herbal remedies. No significant associations were observed with mint, thyme, or alcohol/teratogenic medication use.

Conclusion: Maternal use of certain herbal medicines during pregnancy- particularly in the first trimester- may be associated with higher crude odds of NSCL/P in offspring. These findings underscore the need for heightened awareness, improved prenatal counseling, and stricter regulatory guidance regarding herbal product use during pregnancy, especially in low-resource and culturally herbal-dependent settings.

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Introduction

Non-syndromic cleft lip and/or palate (NSCL/P) is one

of the most common congenital deformities, occurring in approximately 1 out of every 700 births globally [1].

These malformations result from incomplete fusion of the facial structures during the fourth to twelfth weeks of pregnancy [2-3]. The condition can lead to various complications, including feeding challenges, speech disorders, hearing loss, dental and orthodontic issues, and psychological and social developmental disorders [4].

The etiology of NSCL/P is multifactorial, involving both genetic and environmental factors, with significant roles played by genes such as *MSX1* and *PAX9* [5]. Environmental risk factors for NSCL/P are mother's smoking, drinking alcohol, drinking too much caffeine, not getting enough nutrition, exposure to heavy metals, and taking certain medicines [6-7]. New research also shows that conditions like diabetes in mothers may increase the risks of NSCL/P [8]. Beyond genetic and environmental factors, socioeconomic and demographic factors also play a significant role in NSCL/P pathogenesis. Socioeconomic disparities, particularly low socioeconomic status, have been associated with an increased risk of NSCL/P, likely mediated through nutritional deficiencies (e.g., folate, zinc) and limited access to prenatal care [9-11]. Consanguinity is another significant risk factor, as it amplifies the inheritance of recessive genetic variants linked to craniofacial development. Advanced maternal age (>35 years) and young maternal age (<20 years) have also been correlated with a higher incidence of NSCL/P, possibly due to altered reproductive physiology or increased susceptibility to environmental insults [9, 12]. These risk factors collectively contribute to the disruption of neural crest cell migration and fusion of the facial processes, indicating the complex interplay of genetic predisposition and environmental factors in NSCL/P etiology [13-14].

Herbal medicines are frequently used by pregnant women to alleviate nausea, vomiting, and other pregnancy-related symptoms. Perceived as natural and safe, these remedies are often self-administered without medical supervision [7, 15]. However, bioactive compounds in herbs (e.g., alkaloids, terpenoids) can cross the placental barrier, potentially interfering with fetal development [16].

Several medicinal plants have been documented to have teratogenic effects, meaning they can cause developmental malformations or toxicity to the fetus when used during pregnancy. Medicinal plants like *aloe vera*, *rue*, *boldo*, *peppermint*, *chamomile*, *wormwood*, *black*

cohosh, and *castor oil* are among the medicinal plants recognized for their teratogenic effects and potential to induce abortion. Their use during pregnancy is contraindicated due to the risk of fetal malformations [17-20]. Despite the widespread use of herbal medicines among pregnant women, there is still a lack of comprehensive knowledge about their effects on cleft pathogenesis. Studies conducted so far have reported inconsistent findings, highlighting the need for further investigation [7, 21].

This knowledge deficit is especially pertinent in societies, where phytotherapy maintains strong historical and cultural foundations. Cultural beliefs and a lack of awareness about potential teratogenic effects may heighten exposure risks. Given the widespread use of herbal medicine among Iranian pregnant women (like *Zingiber officinale*, *Mentha spicata*, *Matricaria chamomilla*, *Echium amoenum*, *Crocus sativus*) and the potential teratogenic risks, this study might provide critical insights into the association between maternal herbal consumption and NSCL/P, addressing a significant gap in perinatal safety research.

Materials and Method

This study was approved by the institutional Ethics Committee (approval code: IR.SUMS.DENTAL. REC. 1403.040), we recruited two groups: cases (mothers of children aged 1-6 months with NSCL/P attending a cleft clinic at a tertiary care center in 2024) and controls (mothers of unaffected children visiting other departments). We excluded subjects with confounding factors, including addictive behaviors (smoking ≥ 5 cigarettes/day, alcohol ≥ 1 drink/week, or illicit drug use), genetic syndromes, maternal infection (*rubella*), folic acid deficiency, or family history of NSCL/P.

Using convenience sampling, we calculated a minimum required sample size of 160 participants (80 per group) based on G*Power analysis (crude odds ratio [OR]= 2.1, power= 95%, $\alpha=0.05$) [22]. Trained researchers collected data using a structured questionnaire, which gathered: (1) demographic data (age, residence, socioeconomic status, education); and (2) detailed herbal exposure history during pregnancy (specific herbs, trimester, preparation methods, frequency, how many kinds of distinct herbal species consumed per mother).

To reduce differential recall between case and contr-

ol mothers, data collection was standardized across groups. All participants completed the same structured questionnaire with identical wording and item order, administered by trained interviewers using a predefined script. Interviews were conducted in the same hospital setting and within the same postpartum window (infants aged 1–6 months) to harmonize the recall period. Questions were phrased neutrally to avoid leading participants toward perceived risky exposures. A predefined list of commonly used Iranian herbal remedies and common preparation routes was used to facilitate consistent exposure ascertainment. Inter-rater reliability was assessed in pilot testing ($\kappa = 0.82$).

The structured questionnaire included a pre-defined pictorial list of common Iranian herbal remedies (*lavender*, *chamomile*, *chicory*, *borage*, *thyme*, *mint*, *flixweed*, *Citrus aurantium*, *four-seed mixture*) with photographs to aid recall. Mothers selected 'yes/no' for each herb and specified trimester/ frequency. Questionnaire completion time was 10 ± 2 minutes.

The frequency of herbal medicine consumption was estimated based on an adaptation from Rocha *et al.* [23], utilizing a six-point scale including (1) less than one cup/month, (2) one to three cups/month, (3) two to four cups/week, (4) one cup/day, (5) two to three cups/day, and (6) more than three cups/day. Based on these responses, herbal consumption was subsequently aggregated into three distinct categories including 'light consumers' (less than 1 cup/month to 1–3 cups/month), 'medium consumers' (2–4 cups/week to 1 cup/day), and 'heavy consumers' (more than one cup per day).

Categorical variables were summarized as frequencies and percentages and compared between groups using the chi-square test or Fisher's exact test, as appropriate. Crude ORs with 95% CIs were estimated using univariable logistic regression to assess the association between maternal herbal medicine use and NSCL/P. No multivariable logistic regression analysis was performed; therefore, all reported ORs should be interpreted as crude, unadjusted estimates. Given the multiple comparisons across herbal species, Bonferroni correction was applied ($\alpha = 0.05/7 = 0.0071$). A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using GraphPad Prism version 9.

Results

Demographic data were evaluated in both the case (n=

80) and control (n=80) groups. (Table 1) Maternal age distribution showed no significant association with the use of herbal medicine ($p = 0.79$), with consumption rates of 61.53% (<25 years), 53.53% (26–35 years), and 60.00% (>35 years). However, we observed prominent geographical and socioeconomic disparities regarding the use of herbal medicine as follows.

Regarding residence, rural mothers exhibited significantly higher consumption rates (79.31%) versus urban mothers (42.15%, $p < 0.0001$).

Considering education, a strong inverse relationship emerged, with illiterate mothers showing 88.88% usage compared to 35.84% among academically educated mothers ($p = 0.001$).

Concerning economic status, consumption decreased with improving economic status (Poor: 84.61%, Average: 52.41%, Good: 41.17%, $p = 0.04$).

No significant differences were observed for alcohol (NSCL/P: 8.75% vs. controls: 6.25%, $p = 0.76$) or teratogenic medications known for craniofacial risks, including aminopterin (cranial dysostosis at ≥ 10 mg doses), high-dose aspirin (> 325 mg/day, cardiac/neural defects), phenytoin (fetal hydantoin syndrome at 300–400 mg/day), isotretinoin (> 0.5 mg/kg/day, central nervous system/heart malformations), and thalidomide (phocomelia at 50–200 mg/day). Prevalence was low and comparable (NSCL/P: 6.25% vs. controls: 5.00%, $p > 0.99$) [24–26].

Mothers of NSCL/P cases reported significantly higher herbal use (66.25% vs 45.00%; $\chi^2 = 6.45$, $p = 0.011$, crude OR=2.7, 95% CI 1.3–5.6). First-trimester exposure was particularly elevated (94% vs 81%, $p =$

Table 1: Demographic predictors of herbal medicine use during pregnancy

Characteristic	Subgroup	Users (%)	Non-users (%)	p Value
Age (years)	<25	61.5	38.5	0.792
	26–35	53.5	46.5	
	>35	60.0	40.0	
Residence	Urban	42.2	57.8	<0.001
	Rural	79.3	20.7	
Education	Illiterate	88.9	11.1	0.001
	Elementary	60.0	40.0	
	Below Diploma	79.2	20.8	
	Diploma	58.8	41.2	
Economic Status	Academic	35.8	64.2	0.046
	Poor	84.6	15.4	
	Average	52.4	47.6	
	Good	41.2	58.8	

Data are presented as numbers and percentages. The chi-square test was used for comparisons

0.045). The mean number of distinct herbal species consumed frequency was also higher in the NSCL/P group (1.65 ± 1.60 vs. 0.87 ± 1.19 ; $*p = 0.0007$).

Herbal teas accounted for 62.26% of preparations in the NSCL/P group versus 27.77% in controls, although the overall distribution of methods (raw, tinctures, teas) did not differ significantly ($*p = 0.054$) (Table 2).

The first trimester was the peak period for the use of herbal medicine in both groups, with significantly higher exposure in the NSCL/P group (94.33% vs. 80.55%). There was no significant difference between case and control groups regarding herbal medicine use during second and third trimesters ($*p = 0.105$).

The analysis of herbal medicine consumption during pregnancy revealed some differences between mothers of newborns with NSCL/P and controls. While *thyme* (16.25% NSCL/P vs. 12.50% control; $*p = 0.653$) and *mint* (35.00% NSCL/P vs. 38.75% control; $*p = 0.743$) showed comparable prevalence, *chicory* (33.75% NSCL/P vs. 12.50% control; $*p = 0.002$) and *lavender* (23.75% NSCL/P vs. 2.50% control; $*p < 0.001$) were significantly associated with NSCL/P.

Similarly, *chamomile* (20.00% NSCL/P vs. 2.50% control; $*p = 0.001$) and *borage flower* (13.75% NSCL/P vs. 2.50% control; $*p = 0.017$) were more frequently used by mothers in the NSCL/P group.

Chicory ($p = 0.002$), lavender ($p = 0.001$), and chamomile ($p = 0.001$) remained significant after Bonferroni correction ($\alpha = 0.0071$), while *borage flower* ($p = 0.017$) became non-significant.

In contrast, *Citrus aurantium* (7.50% NSCL/P vs.

3.75% control; $*p = 0.495$), *flaxweed* (11.25% NSCL/P vs. 10.00% control; $*p > 0.999$), and *four seeds* (5.00% NSCL/P vs. 3.75% control; $*p > 0.999$) exhibited no significant differences between groups (Table 3).

The reported pattern of herbal medicine exposure differed according to the specific product. Oral consumption, mainly in the form of teas, infusions, and decoctions, was the most common route of administration. Based on the quantitative consumption-frequency categories, most herbal products were classified within the light-to-medium range among exposed case mothers, whereas mint showed the highest reported consumption category. The first trimester was the predominant exposure window for all listed products (Table 4).

Among exposed mothers, the predominant route of administration, consumption category, and main trimester of use were comparable between the case and control groups for the herbal products assessed; therefore, these variables are presented as shared exposure characteristics in Table 4.

Discussion

The findings of this study reveal important insights about the relationship between the use of herbal medicine during pregnancy and the risk of incidence of NSCL/P in newborns. Our analysis demonstrates that mothers who used herbal medicines during pregnancy (66% in cases vs 45% in controls) had significantly higher rates of infants born with NSCL/P. This association was powerful for first-trimester use (94% exposure in cases vs 81% in controls), suggesting these herbal products may have potential teratogenic effects on fetal development [27-29].

Table 2: Herbal medicine consumption patterns in NSCL/P vs control groups

Variable	NSCL/P Group (n=80)	Control Group (n=80)	p Value
Any herbal use	66.25%	45.00%	0.011
How many kind of distinct herbal species (mean $\pm$ SD)	1.65 ± 1.60	0.87 ± 1.19	0.001
Preparation Method			0.055
- Raw	35.8%	50.0%	
- Tinctures	45.3%	44.4%	
- Teas	62.3%	27.8%	
Timing of Use			0.105
- 1st Trimester	94.3%	80.6%	
- 2nd Trimester	3.8%	16.7%	
- 3rd Trimester	1.9%	2.8%	

Non-syndromic cleft lip and/or palate (NSCL/P); standard deviation (SD)

Table 3: Association between maternal herbal medicine consumption and NSCL/P: prevalence and crude odds ratios

Herbal Medicine	NSCL/P Group (%)	Control Group (%)	Crude OR (95% CI)	p Value
Chicory	33.75	12.50	3.6 (1.6-8.2)	0.002
Lavender	23.75	2.50	12.1 (2.7-54.7)	<0.001
Chamomile	20.00	2.50	9.8 (2.2-44.2)	0.001
Borage Flower	13.75	2.50	6.2 (1.3-29.1)	0.017
Thyme	16.25	12.50	1.4 (0.6-3.3)	0.653
Mint	35.00	38.75	0.9 (0.5-1.6)	0.743

Non-syndromic cleft lip and/or palate (NSCL/P); odds ratio (OR); confidence interval (CI). Bonferroni-adjusted significance threshold was set at $\alpha = 0.0071$

Table 4: Characteristics of maternal herbal medicine exposure during pregnancy

Herbal product	Cases exposed n (%)	Controls exposed n (%)	Predominant route in both groups	Consumption Category in both groups	Main Trimester in both groups
Chicory	27 (33.75)	10 (12.50)	Oral	Medium	1st
Lavender	19 (23.75)	2 (2.50)	Oral	Medium	1st
Chamomile	16 (20.00)	2 (2.50)	Oral	Light	1st
Borage flower	11 (13.75)	2 (2.50)	Oral	Light	1st
Thyme	13 (16.25)	10 (12.50)	Oral	Medium	1st
Mint	28 (35.00)	31 (38.75)	Oral	Heavy	1st

Consumption categories were derived from the quantitative six-point consumption frequency scale adapted from Rocha *et al.* [23] Light consumers were defined as those consuming less than one cup/month to one to three cups/month; medium consumers as those consuming two to four cups/week to one cup/day; and heavy consumers as those consuming more than one cup/day. The category shown represents the predominant consumption category reported among exposed case mothers for each herbal product. Predominant route, consumption category, and main trimester were identical between exposed case and control mothers for each herbal product; therefore, these exposure characteristics are presented as shared characteristics for both groups

The marked predominance of herbal supplement use in the first trimester (94.33% in NSCL/P cases and 80.55% in controls), followed by a sharp decline in subsequent trimesters (3.8% and 1.9% in second/third trimesters for cases), aligns with established patterns of herbal medicine consumption during pregnancy. Pregnant women commonly initiate these remedies early to manage prevalent first-trimester symptoms such as nausea, vomiting, and fatigue, often perceiving them as safe natural alternatives self-prescribed or recommended by family. This temporal pattern may indeed reflect growing awareness of potential fetal risks post-pregnancy confirmation, prompting discontinuation upon prenatal counseling, as evidenced by higher education and urban residence correlating with reduced overall use in our cohort [30-32].

After Bonferroni correction for multiple comparisons (7 herbs), *chicory*, *lavender*, and *chamomile* retained significant associations with NSCL/P ($p < 0.007$), confirming their independent risk rather than type I error.

Current evidence regarding herbal safety in pregnancy remains inconclusive. Our results substantiate safety concerns regarding particular herbal medicines, demonstrating significantly greater usage among case mothers for *chamomile* (20% case group vs 3% control group), *lavender* (24% case group vs 3% control group), *chicory* (34% case group vs 13% control group), and *borage flower* (14% case group vs 3% control group). In contrast no significant differences were observed for *mint* (35% case group vs 39% control group) or *thyme* (16% case group vs 13% control group) [22, 33-35].

Several biological mechanisms could explain these concerning findings. Many of the herbal products identified as high-risk, including *lavender*, *chamomile*, and

borage flower, contain active compounds that can interfere with crucial developmental processes [27, 36]. For instance, certain herbs contain phytoestrogens that may disrupt normal hormone signaling during critical periods of facial development [29, 37]. *Lavender* (*Lavandula angustifolia*) contains phytoestrogens such as *linalool*, which may disrupt hormone signaling during the critical facial developmental window (weeks 4-12), interfering with neural crest cell migration and palatal fusion processes. *Chamomile* (*Matricaria chamomilla*) and *borage flower* (*Echium amoenum*) contain bioactive molecules like *apigenin* and *pyrrolizidine alkaloids* that may induce oxidative stress and impairment of cellular differentiation required for normal lip and palate formation [38-39]. Others contain alkaloids or other bioactive molecules that could potentially interfere with the complex cellular processes required for proper fusion of the lip and palate [40]. The first trimester appears to be a particularly vulnerable window, as this is when the face structures are forming and may be most sensitive to external influences [41]. The average number of distinct herbal species consumed was notably higher among case mothers (1.7 vs 0.9 in controls), suggesting possible cumulative teratogenic effects.

Our study revealed marked sociodemographic disparities in maternal herbal medicine use during pregnancy. Mothers in rural areas reported significantly higher usage rates than those in urban settings (79% vs. 42%; crude OR=2.7). Similarly, consumption was notably greater among women with lower educational attainment (89% in illiterate or less-educated versus 36% among those with higher education) and in lower socioeconomic status groups (85% vs. 41% in higher-income categories). These findings suggest that limited access

to formal healthcare, prenatal counseling, and cultural reliance on traditional remedies strongly influence herbal medicine use among pregnant women in disadvantaged populations. Such disparities likely contribute to increased risk of NSCL/P through factors including reduced availability of preventive care and nutritional supplementation, consistent with prior research linking low socioeconomic status to adverse pregnancy outcomes [42–44].

The use of herbal medicine in pregnancy has become increasingly widespread. Many pregnant women choose these products, thinking they are safer and more natural than regular medicines [45]. However, our study found some herbs were linked to more than 10 times higher risk for incidence of NSCL/P. These findings raise concern that some herbal products may not be safe during pregnancy.

Several limitations warrant consideration. First, the retrospective case-control design and reliance on maternal self-report may have introduced recall bias, including differential recall between mothers of affected and unaffected infants. To reduce this risk, both groups were assessed within the same postpartum interval using the same structured questionnaire, standardized interview script, predefined pictorial list, trained interviewers, and uniform data-collection procedures; nevertheless, recall bias cannot be excluded. Second, no multivariable-adjusted analysis was performed; therefore, the reported associations should be interpreted as rudimentary estimates that may be affected by confounding, including socioeconomic and educational differences between groups. Third, convenience sampling at a single tertiary care center, together with recruitment of controls from other hospital departments, may have introduced selection bias and limits the generalizability of the findings. Therefore, the results should be interpreted as exploratory and hypothesis-generating rather than causal. Larger prospective, multicenter studies using standardized quantitative exposure assessment and prespecified multivariable models are required to confirm these associations.

These results show that we need to make some critical changes. First, doctors and midwives should ask every pregnant woman if she is using any herbal medicines, just like they ask about regular medication. It is essential for them to specify which herbs may be dangerous for pregnant individuals. Second, we need to

improve public education, especially in rural areas, to change the wrong belief that all natural herbs are always safe to use during pregnancy. Shops that sell herbal products should have clear warning labels for pregnant women. Finally, scientists need to understand how these herbs might impact a growing infant. Following these measures will ensure the safety of both mothers and their infants.

This study highlights key areas that require further investigation. First, we need to determine which substances in these herbs might be dangerous during pregnancy. Additionally, research that tracks women from pregnancy through childbirth would provide more reliable evidence regarding potential risks. Emphasizing these significant concerns will aid in formulating safety standards that preserve maternal health.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conclusion

This study provides important insights into the association between maternal herbal medicine consumption during pregnancy and the risk of NSCL/P in newborns. The findings demonstrate that the overall use and number of herbal products consumed during pregnancy were significantly higher among mothers of children affected by NSCL/P compared to those of healthy infants. Notably, specific herbs- including *lavender*, *chicory*, *chamomile*, and *borage*- were identified as having significant associations with NSCL/P occurrence. In contrast, other commonly used herbs, such as *thyme* and *mint*, showed no such link.

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This study was approved by the Institutional Ethics Committee (approval code: IR.SUMS.DENTAL.REC. 1403.040)

Disclosures

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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