Medication Exposure During Pregnancy And The Risk Of Orofacial Clefts: A Scoping Review

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Abstract. Orofacial clefts (OFCs), including cleft lip with or without cleft palate (CL/P) and isolated cleft palate (CP), are among the most common congenital malformations worldwide, affecting approximately 1 in 500 to 550 live births. Such malformations occur due to a failure in the fusion of the embryonic facial processes, a process that generally occurs between the 4th and 12th weeks of gestation. OFCs have a substantial impact on quality of life and can cause lifelong issues, including feeding problems, speech abnormalities, hearing loss, dental abnormalities, and psychosocial challenges; therefore, there is a need for studies to explore possible solutions to these issues. There are studies examining the use of medications in the periconceptional period; however, the findings from these studies are largely inconsistent. This review strives to find answers to possible contributing factors to increased risks of OFCs by evaluating the association of maternal medication use during pregnancy and increased risk of OFCs. In conducting this review, we searched the PubMed and Dimensions databases for published literature relevant to the study's focus. We further selected the studies included in our review based on the inclusion criteria we had developed before the study. We included a total of five studies in this review — three case-control studies and one cohort study — most of which were conducted by researchers in European countries and the USA. The five articles included in this study featured research data from congenital disability registries, hospital medical records, and information obtained through interviews with mothers. The medications evaluated in the studies included in this review include corticosteroids administered via various routes, antiepileptics (such as lamotrigine), and bronchodilators commonly used in the treatment of asthma. The exposure period considered in the studies was mainly four weeks before pregnancy and the end of the first

trimester. Ultimately, the findings from this study showed that there is an association between medication use during pregnancy and the incidence of orofacial clefts in newborns. However, this association is dependent on the types or classes of medications. There are varying results from epidemiologic studies on the association between the maternal use of corticosteroids and the risk of orofacial clefts. However, administration during pregnancy should be with caution. However, antiepileptic drugs were found to be associated with an increased incidence of orofacial clefts, and maternal bronchodilators used in asthma management were linked to an increased risk of cleft lip only and cleft lip with cleft palate.

Keywords: Antiepileptic; Bronchodilators; Corticosteroids; Orofacial clefts; pregnant women

INTRODUCTION

Orofacial clefts (OFCs), including cleft lip with or without cleft (CL/P) and isolated cleft palate (CP), are among the most common congenital malformations in the world [1]. They are present in approximately 1 of 500-550 live births. Such malformations occur due to a failure in the fusion of the embryonic facial processes, a process that generally occurs between the 4th and 12th weeks of gestation [2, 3]. The prevalence of OFCs is known to differ by geographical area, race/ethnicity, education, and income [4]. Higher rates are reported in Asian and Latin American communities compared to those of African or European descent [4]. Approximately 1 in 1,050 US births involve cleft lip and palate, and 1 in 1,600 involve cleft palate only [5].

In addition, OFCs have a substantial impact on quality of life and can cause lifelong issues, including feeding problems, speech abnormalities, hearing loss, dental abnormalities, and psychosocial challenges [6]. These disorders often require a multidisciplinary approach involving a combined treatment plan that includes surgery, orthodontics, speech-language therapy, and psychological support [7, 8]. OFCs, therefore, present both emotional and psychological struggles for affected individuals and their relatives and are associated with added costs for healthcare systems worldwide [9, 10]. There is a need for ongoing research to unravel the aetiological factors and modifiable risk factors associated with OFCs, given their global implications for health, to inform preventive activities and influence public health initiatives.

OFCs are associated with various etiologic factors, including the interplay between genetic susceptibility and environmental factors [11, 12]. Numerous genetic mutations and syndromic associations, such as Van der Woude syndrome and 22q11.2 deletion syndrome, have been linked to OFCs [13, 14]. However, there are non-genetic risk factors, maternal smoking and alcohol consumption during pregnancy, poorly managed diabetes, lack of folic acid supplementation, obesity, and older maternal age are some of the most thoroughly documented environmental factors [15–20].

On the other hand, the use of medication by mothers during pregnancy is also a modifiable risk factor. Numerous investigations have revealed connections between specific pharmaceutical agents, such as anticonvulsants (e.g., phenytoin, valproic acid) [21, 22] and isotretinoin [23]. Nonetheless, these relationships remain inconsistent and challenging to interpret due to confounding variables and methodological limitations. The diverse range of medications used by pregnant women, coupled with insufficient data regarding dosage, timing, and duration of exposure, adds complexity to the risk assessment process; this highlights the necessity for ongoing investigation to clarify these intricate connections and pinpoint high-risk pharmacological exposures.

The administration of medications throughout pregnancy is prevalent and often essential from a clinical perspective. Research indicates that more than 80% of pregnant women utilise at least one prescription or over-the-counter (OTC) medication throughout their pregnancy [24, 25]. Many of these women need pharmacologic interventions for chronic conditions such as epilepsy, hypertension, depression, or diabetes, in addition to addressing pregnancy-related symptoms like nausea, pain, and insomnia [26]. Although some drugs are safe, others are known teratogens, and a large proportion remain unclassified due to the

lack of data from clinical trials, which usually exclude pregnant women on ethical grounds.

The thalidomide disaster that occurred in the 1960s with thousands of teratogenic congenital disabilities represented a profound change in evaluating teratogenic risk during pregnancy [27]. There has been a significant change in attitudes towards drug treatment during pregnancy by healthcare providers and women as a result of the thalidomide disaster and subsequent public awareness campaigns following the disaster [28]. However, evidence-based recommendations exist for few drugs, hence the need for ongoing investigation of adverse effects on fetal development for many medicines. Therefore, clinicians should tread carefully in prescribing medications for pregnant women and those trying to convince, balancing the health benefits-risk ratios for mothers and growing foetuses. Physicians need to have knowledge of the effects of different drugs on the development of the foetus, particularly on craniofacial morphogenesis and take it as a responsibility to educate women on safety measures in the use of medication during prenatal counselling.

There are studies relating to the use of medications in the periconceptional period , but findings from such studies are largely inconsistent [29]. Numerous observational studies have indicated potential associations between specific drugs and the risk of OFC; however, the results vary significantly across different populations and research methodologies. For example, valproic acid and isotretinoin are known to have teratogenic effects, which include an increased risk of craniofacial malformations [30]. However, other medications, such as corticosteroids, antibiotics, and certain antiepileptic drugs, show varied evidence based on the timing of exposure and the health conditions of the mother [31].

Furthermore, a significant portion of current investigations depend on retrospective methodologies and self-reported medication usage. There are limited studies on medications that carry an increased risk of over-the-counter (OTC) and other unauthorised (OFC) use. A scoping review is particularly well-suited for mapping this field of study. The objective of this scoping review is to systematically map the evidence of maternal medication exposure and the risk of OFCs. The specific aim is to determine the drugs or drug classes associated with increased incidence of OFCs.

Ultimately, the implications of this review for the subject area are of great relevance to clinical practice, public health policy, and future research. The review can inform the regulatory framework for drug labelling, foster pharmacovigilance programs and help shape public health programs to optimise drug safety.

METHOD

An expert panel of medical doctors and clinical pharmacists initially formed the foundation of this scoping review. Together, they developed the research questions, established the inclusion and exclusion criteria, and assessed the overall study quality. The following sections present the protocol they used to conduct the study.

The *research question* was structured using the PICO framework, and it is as follows: What medications, when used during pregnancy, are associated with an increased risk of orofacial clefts in newborns?

A comprehensive search of the available literature was conducted using both PubMed and Dimensions databases. During the search, we utilised a combination of MeSH keywords related to orofacial clefts, pregnancy, and medication use. To refine the search, Boolean operators (AND and OR) were utilised. The research team filtered the search results based on the eligibility criteria.

Compiled Search terms for databases that do not use Mesh terms (Dimension) are as below:

(("Orofacial Clefts" OR "Cleft lip/palate") AND ("Pregnancy" OR "gravid" OR "trimester" OR "antenatal")) AND ("Medication Use" OR "Medication" OR "Medication Exposure" OR "Drug" OR "Drug Exposure" OR "Drug Use" OR "Valproic acid" OR "Antibiotics" OR "Phenytoin" OR "Lamotrigine" OR "Antidepressants" OR "Anticonvulsants" OR "NSAIDs" OR "Steroids" OR "Corticosteroids" OR "Ibuprofen" OR "Opioids" OR "Diclofenac" OR "Paracetamol" OR "Analgesics")

Compiled Search term for databases that use Mesh terms (PubMed) is as follows: ((("Orofacial Clefts"[Mesh] OR "Cleft Lip"[Mesh] OR "Cleft Palate"[Mesh]) OR (("cleft lip" OR "cleft palate" OR "orofacial clefts") AND (title/abstract/keywords))) AND (("Pregnancy"[Mesh] OR "Pregnancy Trimesters"[Mesh] OR "Prenatal Care"[Mesh]) OR (("pregnancy" OR "gravid" OR "trimester" OR "antenatal") AND (ti-

tle/abstract/keywords)))) AND ((("Drug Therapy"[Mesh] OR "Pharmacology"[Mesh] OR "Medication Adherence"[Mesh]) OR (("medication use" OR "medication" OR "medication exposure" OR "drug" OR "drug exposure" OR "drug use") AND (title/abstract/keywords))) OR (("Valproic Acid"[Mesh] OR "Antibiotics"[Mesh] OR "Phenytoin"[Mesh] OR "Lamotrigine"[Mesh] OR "Antidepressants"[Mesh] OR "Anticonvulsants"[Mesh] OR "NSAIDs"[Mesh] OR "Steroids"[Mesh] OR "Corticosteroids"[Mesh] OR "Ibuprofen"[Mesh] OR "Opioids"[Mesh] OR "Diclofenac"[Mesh] OR "Paracetamol"[Mesh] OR "Analgesics"[Mesh]) OR (("valproic acid" OR "antibiotics" OR "phenytoin" OR "lamotrigine" OR "antidepressants" OR "anticonvulsants" OR "NSAIDs" OR "steroids" OR "corticosteroids" OR "ibuprofen" OR "opioids" OR "diclofenac" OR "paracetamol" OR "analgesics") AND (title/abstract/keywords))))

The review encompassed primary studies that adhered to the following criteria:

Population: Pregnant mothers of all ages.

Exposure: All medications consumed during pregnancy, which include prescription drugs, over-the-counter medications, and dietary supplements.

Outcome: The occurrence of orofacial clefts (including cleft lip, cleft palate, or both).

Study Design: Observational studies, including cohort and case-control designs, as well as interventional studies such as randomised controlled trials (RCTs).

Language: English.

Timeframe: Publications from the year 2000 onward.

Exclusion criteria. All non-human studies and those utilising non-primary data, including animal studies and in vitro studies, will be omitted. Books and/or book chapters, dissertations, thesis, case studies, systematic reviews/literature reviews, meta-analyses, reports, qualitative studies

Insufficient Outcome Data: Research that fails to include orofacial clefts as an outcome.

Inadequate Data: Studies lacking sufficient data (such as missing risk estimates or 95% confidence intervals).

Study Selection. Initially, two independent reviewers evaluated the titles and abstracts of all identified studies according to the established inclusion and exclusion criteria. The reviewers addressed their differences by consulting a third reviewer. The research team thoroughly examined the full-text articles to verify their eligibility. Disagreements concerning study inclusion were addressed and resolved through consensus or with the assistance of a third reviewer. The process for selecting studies is depicted through a PRISMA-ScR flow diagram.

Quality Assessment. The assessment of bias risk and methodological quality for the included studies was conducted using the Checklist for Assessing the Quality of Quantitative Studies [32]. The research team chose this evaluation tool for its completeness and inclusion of all criteria deemed pertinent in assessing quantitative studies. They assigned a score to each item using the following criteria: 2 for 'Yes,' 1 for 'Partial yes,' and 0 for 'No.'

The literature considered did not involve any intervention or treatment, as it consisted of observational studies. They primarily consist of cohort studies and case-control studies. Consequently, we did not assign scores for questions V, VI, and VII of the evaluation tool, as they are intended for interventional studies. The researchers assessed the risk of bias in these studies based on 11 specific items. A low score signifies a considerable risk of bias, whereas a high score denotes a minimal risk of bias. The lowest bias score recorded was 0, while the highest score was 22.

Data Extraction. The extraction of data was conducted using a standardised form. Essential data fields comprised: 1) Details of the study include the author, year of publication, country of origin, research design, and sample size. 2) Characteristics of participants include maternal age, gestational age, and medication exposure.

Details of exposure: Class of medication, individual drugs, dosage amounts, duration of treatment, and timing of administration.

Outcome measures: Classification OFCs.

Statistical measures include odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), accompanied by 95% confidence intervals.

RESULTS AND DISCUSSION

Literature selection. We retrieved 613 articles (449 from PubMed and 164 from Dimensions). The research team filtered out 421 articles based

on the study's eligibility criteria and removed nine duplicates. They then reviewed the titles and abstracts of the remaining 183 articles and excluded 163 that did not meet the inclusion criteria. Of the 20 remaining articles, they were unable to retrieve four full texts. The team further evaluated the 16 retrieved articles and, after a full-text review, excluded 11 that did not meet the inclusion criteria. The remaining five articles were included in the study [31, 33–36]. The literature selection process of this study is depicted using the PRISMA flow diagram, as shown in Figure 1 below.
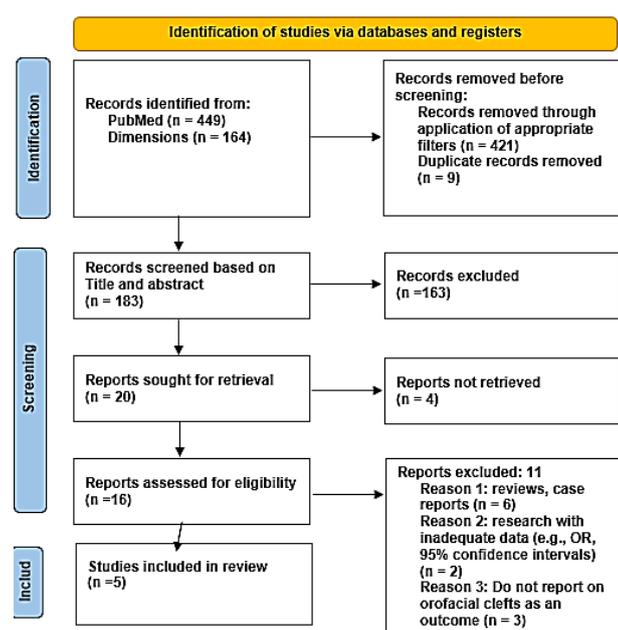
Figure 1 – PRISMA flow diagram

Study characteristics. The studies included in this review were three case-control studies [34–36], one cohort study [33], and one study that combined both case-control and cohort study designs [31]. In total, the studies included in this review were primarily conducted in European countries (including Denmark and Norway) and the USA, and the bias risk score for these studies ranged from 20 to 22. The five articles included in this study featured research data from congenital disability registries, hospital medical records, and information obtained through interviews with mothers. The time range of the studies span from 1995 to 2008. The medications evaluated in the studies included in this review include corticosteroids administered via various routes, antiepileptics (such as lamotrigine), and bronchodilators, including beta-agonists, anticholinergics, and methylxanthines (such as theophylline),

which are commonly used to treat asthma. The exposure period considered in the studies was mainly four weeks before pregnancy and ended in the first trimester.

Narrative synthesis

Association Between Orofacial Clefts and Maternal Corticosteroids Administration. Three studies included in our review investigated the association between maternal corticosteroid use during pregnancy and the risk of developing Orofacial clefts in newborns [31, 33, 35]. These studies considered all corticosteroids administered, regardless of the route of administration. According to authors [33], there is no statistically significant increased risk of orofacial clefts associated with the use of corticosteroids. With prevalence odds ratio (OR) 1.05 (95% confidence interval [CI] 0.80–1.38] for cleft lip with or without cleft palate and prevalence OR 1.23 (95% CI 0.83–1.82) for cleft palate alone. However, odds ratios for the risk of orofacial clefts by the method of delivery (i.e., oral, inhalant, nasal spray, or dermatologic and other topicals) do not show significant heterogeneity.

On the other hand, authors [31] Annals of Epidemiology study, which is a combined case-control study (The Norway Cleft Study) and cohort study (The Norwegian Mother and Child Study or MoBa) conducted in Norway found an association between dermal corticosteroids administration with both CLP (adjusted OR (aOR) = 2.3, 95% confidence interval = 0.71, 7.7) and CPO (adjusted OR (aOR) = 3.4, 95% confidence interval = 0.87–13) in the case-control study. However, there was no evidence of this association in the cohort data (OR for CLP = 1.2; 0.50–2.8; OR for CPO = 1.0; 0.30–3.4). However, no associations were found with other types of corticosteroids.

Moreover, according to authors [35], a Birth Defects Research study, a centre case-control study carried out in ten states in USA (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), there was association of corticosteroids and cleft lip and palate with prevalence odds ratio (OR) 1.0 (95% CI, 0.7–1.4) and there was little evidence of associations between specific corticosteroid components or timing and clefts.

Association Between Orofacial Clefts and Maternal Antiepileptics (lamotrigine) Administration. One study included in our review investigated the as-

sociation between maternal use of two or more Antiepileptic drugs (AEDs) in the first trimester and the risk of developing orofacial clefts in newborns [33]. Categorically, this study, a case-matched control study, evaluated lamotrigine monotherapy exposure and lamotrigine combined with any antiepileptic drug (AED), excluding valproic acid. Findings from this study show that OC was significantly associated with AED exposure with adjusted odds ratio (ORadj): 1.34, 95%; CI 1.11–1.62 for all OC and adjusted odds ratio (ORadj): 1.97; CI: 1.54–2.52 for all cleft palates, with lower OR for isolated OC/cleft palate and increased ORs after excluding valproic acid. This study also reported nonsignificant associations for all OC (ORadj 1.31, 95% CI 0.73–2.33) and all cleft palate (ORadj 1.60, 95% CI 0.70–3.65) cases for lamotrigine monotherapy. However, the odds ratios (ORs) for isolated occlusal cleft palate were slightly higher but not statistically significant.

Association Between Orofacial Clefts and Maternal Bronchodilators Administration. One study included in our review examined the relationship between maternal use of bronchodilators and the risk of orofacial clefts in newborns. Authors [36] conducted a case-control study examining the use of bronchodilators alone and in combination with anti-inflammatory medications, including fluticasone, prednisone, beclomethasone, triamcinolone, cromolyn sodium, budesonide, montelukast, zafirlukast, methylprednisolone, flunisolide, and prednisolone. According to this study, albuterol is the most commonly used bronchodilator (88.7%), and there is an association between maternal bronchodilator use during the four-month periconceptional period and cleft lip only (CLO) (ORadj = 1.77, 95% CI: 1.08–2.88). However, for cleft palate only (CPO) (ORadj = 1.53, 95% CI: 0.99–2.37), the risk was increased but was not statistically significant. On the other hand, the study also reported no association between maternal bronchodilator use and the risk of cleft lip with cleft palate (Adjusted Odds Ratio = 0.78, 95% confidence interval: 0.46–1.31).

Although medication use during pregnancy is of great benefit for the health of both mother and child, it is essential to critically review the medications of pregnant women and prospective mothers to avoid congenital malformations [37, 38], as most of the studies included in this review considered the exposure period from four weeks before conception to the first trimester. The re-

sults of this review provide an overview of studies conducted to evaluate various medications, including corticosteroids of different routes of administration, antiepileptics (such as lamotrigine), and bronchodilators (such as beta-agonists, anticholinergics, and methylxanthines, including theophylline), which are commonly used to treat asthma; this shows that medication use during pregnancy is for varying indications, not just the routine supplements prescribed to pregnant women [39], as the drug needs of pregnant women have to be met considering the health benefit-risk ratio to both pregnant women and the growing fetus [40].

Our results show there is an association between medication use during pregnancy and the occurrence of orofacial clefts in newborns. A combined case-control study (The Norway Cleft Study) and a cohort study (The Norwegian Mother and Child Study, or MoBa) were conducted in Norway [31]. This study found an association between dermal corticosteroid administration and both CLP and CPO in the case-control study; however, there is no evidence of this association in the cohort data; this suggests that epidemiologic studies on the association between corticosteroids and the risk of orofacial clefts have yielded varying results, as inconsistent findings have been reported.
While authors [33] found no statistically significant increased risk of orofacial clefts associated with the use of corticosteroids, authors [31, 41] and a study in Annals of Epidemiology found an association between maternal corticosteroid use during the first three months of pregnancy and the development of fetal cleft lip with or without palate.

However, for antiepileptic drugs, according to the authors [34] study included in our review, OC was significantly associated with AED exposure. This finding is consistent with authors [21], who evaluated 12 antiepileptic drugs in the FDA Adverse Event Reporting System and found that 10 out of the 12 antiepileptic drugs were associated with 156 cases of CL/P out of a total of 817 CL/P reports.

Nevertheless, the study by authors [36] included in our review investigated the association between maternal bronchodilator use in asthma management and the increased risk of orofacial clefts. It found an association between maternal bronchodilator use during the four-month periconceptional period and cleft lip only and cleft lip with cleft palate. However, for cleft pal-

ate, there was no statistically significant association despite an increased risk. It is worth noting that there are limited studies investigating the association between maternal use of bronchodilators during pregnancy and the increased risk of developing orofacial clefts in newborns. An in vivo study by authors [42] found that anti-asthmatics, including bronchodilators (Formoterol) and corticosteroids (Budesonide), have the potential to induce orofacial clefts.

This study has several limitations. Firstly, we included a limited number of literature in our review, as we only searched two databases and did not screen the reference lists from the included studies. Additionally, we omitted grey literature. The next point is that we included only articles published in the English language. As such, we may have omitted some articles within our scope that were published in languages other than English. Moreover, most of the studies included in this review only covered the exposure period from 1995 to 2008 and, as such, did not account for exposures beyond this period. Accordingly, in line with the inclusion criteria of this study, we only considered published articles from 2000

onwards; therefore, this study fails to evaluate studies published outside this timeframe. Nevertheless, the studies included in our review are primarily from European countries and the USA and did not account for studies from other countries worldwide.

CONCLUSIONS

The findings from this study showed that there is an association between medication use during pregnancy and the occurrence of orofacial clefts in newborns. However, this association is dependent on the type or class of medication. Epidemiologic studies have reported varying results on the association between maternal corticosteroid use and the risk of orofacial clefts, leading to inconsistent findings; therefore, clinicians should exercise caution when administering these drugs during pregnancy. In contrast, researchers have found that antiepileptic drugs increase the incidence of orofacial clefts, and maternal use of bronchodilators for asthma management is linked to a higher risk of cleft lip alone and cleft lip with cleft palate.

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