Reproductive Toxicology 69 (2017) 99–105

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

The relationship between maternal corticosteroid use and orofacial clefts-a meta-analysis

Wen-lin Xiao[a,b,*], Xiao-ya Liu[a,b], Yan-shan Liu[a,b], Dai-zun Zhang[a,b], Ling-fa Xue[a,b]

[a] Department of Stomatology, The Affiliated Hospital of Qingdao University, Qingdao 266003, China
[b] The Key Laboratory of Oral Clinical Medicine of Shandong Province, The Affiliated Hospital of Qingdao University, Qingdao 266003, China

ARTICLE INFO

Article history:
Received 13 March 2016
Received in revised form
23 December 2016
Accepted 7 February 2017
Available online 13 February 2017

Keywords:
Orofacial clefts
Corticosteroids
Meta-analysis

ABSTRACT

The aim was to evaluate the relationship between maternal corticosteroid use during first trimester of pregnancy and risk of orofacial clefts (OC). The overall findings showed a certain association between maternal corticosteroid use and occurrence of OC, compared with non-users (OR = 1.16 [95% CI: 1.01–1.33]). When study type was considered this association was significant only for case-control studies (OR = 1.22 [95% CI: 1.02–1.47]), and not for cohort studies (OR = 1.09 [95% CI: 0.88–1.34]) when there are many confounders (dose, route of application, disease etc.) and biases (re-call, loss-to follow-up etc.) that still need to be considered. A subgroup analysis based on the type of OC gave an overall OR of 1.41 (95% CI: 1.14–1.74) in the case-control studies for cleft lip with or without palate (CL/P) and 1.09 (95% CI: 0.80–1.48) for cleft palate only (CPO), when comparing maternal corticosteroid users with non-users. However, for cohort studies, the overall OR for CL/P is 1.06 (95% CI: 0.82–1.37) and 1.20 (95% CI: 0.83–1.75) for CPO. The absolute risk of facial cleft after prenatal exposure to corticosteroids, if any, is small.

1. Introduction

Orofacial clefts are one of the most common congenital malformations in the oral and maxillofacial area, with a global birth prevalence of about 0.1–0.2% [1]. The Non-syndromic cleft lip with or without cleft palate (NCL/P) deformities seriously affect the patient's facial appearance, chewing, and psychological and physiological function. These malformations can be isolated or associated with other congenital defects and isolated clefts have, in most cases, a multifactorial pathogenesis. Studies have shown that inherited and environmental factors are responsible for these malformations [2]. A variety of maternal factors could contribute to the occurrence of orofacial clefts during pregnancy, including the use of alcohol, tobacco, retinoic acid, etc. [3–5]. Studies of relevant environmental factors have also reported an association between maternal corticosteroid exposure during the first trimester and fetal clefts [6,7].

Corticosteroids represent a class of steroid hormones, similar to the cortisol secreted by the adrenal cortex, which have anti-inflammatory and immunosuppressive effects. There are many other diseases that occur during pregnancy that may require corticosteroids such as systemic lupus erythematosus, rheumatoid arthritis, or urticaria. They are administered by 2 methods: systemically by oral, inhaled or intravenous dosing; and by topical application. Women who discontinue needed treatment during pregnancy may experience poor symptom control or disease exacerbation. However, continued application of hormone could induce side effects in the infant such as orofacial clefts. An experimental model in mice showed that application of glucocorticoid hormones during pregnancy can lead to cleft palate [8–10], and some epidemiological studies have also found that maternal application of glucocorticoids in early pregnancy was associated with an up to 3–6 fold increased incidence of orofacial clefts [10–12,15]. Edwards et al. [12] conducted a case-control study which indicated that maternal topical application of glucocorticoids in the first trimester clearly correlated with orofacial clefts; however, some studies have not found such an association [6,7,11,13]. To date, the implication of glucocorticoid use in human teratogenicity has been controversial, and in particular it remains unknown whether there is a link between maternal corticosteroid exposure and fetal orofacial clefts. Therefore, we conducted a meta-analysis to collect evidence-based, relevant research regarding maternal corticosteroid exposure and fetal orofacial clefts, in order to provide a scientific basis for a recommendation that may avoid its occurrence.

* Corresponding author at: Department of Stomatology, The Affiliated Hospital of Qingdao University, Qingdao, 266003, China.
E-mail address: wenlinxiao@sina.com (W.-l. Xiao).

http://dx.doi.org/10.1016/j.reprotox.2017.02.006
0890-6238/

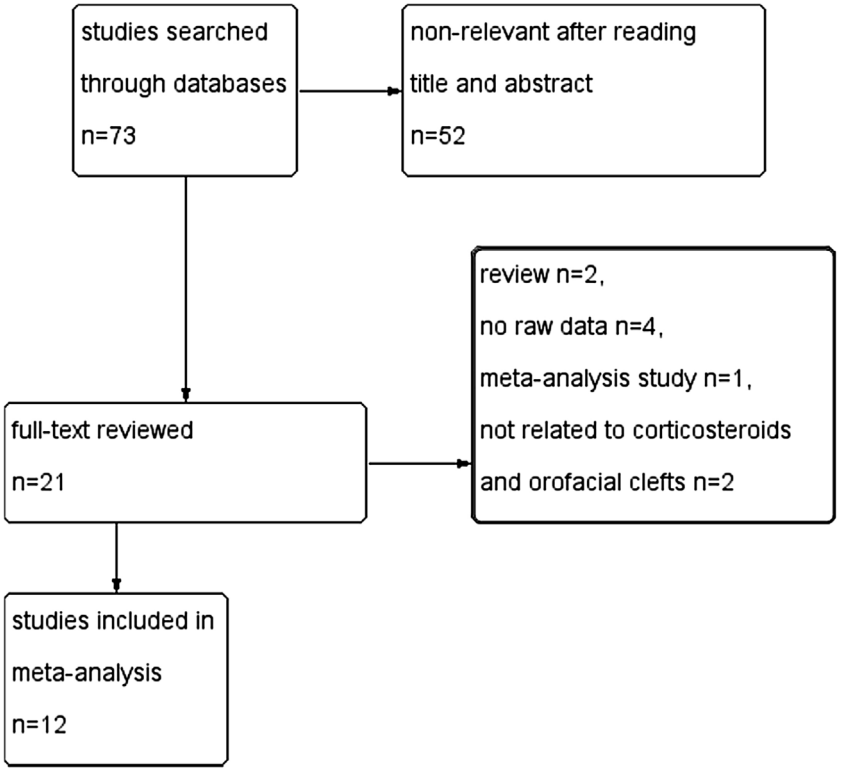

Fig. 1. Flow diagram for study selection.

2. Methods

2.1. Search strategy

Systematic electronic searches of PubMed, Embase, Google Scholar, Ovid, Springer, Elsevier, Chinese National Knowledge Infrastructure, and the Chinese Biomedical Database, up to January 2016 were performed to identify published epidemiological studies on maternal exposure to corticosteroids and fetal orofacial clefts. All searches were performed by 2 independent researchers using the following key words: cleft lip and cleft palate; orofacial clefts; cleft lip with or without palate; glucocorticoid; pregnancy; adrenal cortical hormone; and corticosteroids. If there were any uncertainties regarding eligibility; a third reviewer was consulted.

2.2. Selection of studies

Strict inclusion and exclusion criteria were determined. We focused on the association between maternal corticosteroid use during the first trimester of pregnancy and fetal orofacial clefts. Study duration, sample size, and study language were not limited. Furthermore, identified literature also complied with the following criteria: (1) good baseline comparability in each study; (2) the studies had to contain sufficient raw data; (3) the full text of the study was available. Exclusion criteria were as follows: (1) reviews or letters to the editor; (2) animal experiments; (3) case reports; (4) studies without a control group; (5) studies that included other congenital malformations and it was not possible to separate out the data regarding orofacial clefts.

2.3. Data extraction

Study characteristics were extracted by two reviewers in a standardized form that included the author, duration, country, type of study, number of cases and controls, administration and the methodological quality assessment of the included studies.

Table 1
Basic characteristic of included studies in the Meta-analysis

Author	Year	Country	Study design	N1/T1	N2/T2	Administration	NOS	Study time
Edwards MJ[12]	2003	Australia	Case-control	9/48	57/58	topical	7	1990–2000
Carmichael SL[13]	2007	US	Case-control	39/1769	4071/4143	Any way	8	1997–2002
Skuladottir H[14]	2014	Norway	Case-control	24/573	744/763	Any way	7	1996–2001
Rodríguez-Pinilla E[15]	1998	Spain	Case-control	5/1184	1172/1173	Systemic	6	1976–1995
Garne E[16]	2015	Europe	Case-control	35/3794	43475/43824	inhaled	8	1995–2010
Skuladottir[17]	2014	US	Case-control	48/2372	5785/5922	Any way	6	2003–2009
Carmichael SL[18]	1999	US	Case-control	9/489	731/734	Not available	7	1987–1989
Chi CC[19]	2011	UK	Cohort study	11/53	26450/32589	topical	7	2000– 2006
Hviid A[20]	2011	Denmark	Cohort study	84/1232	779515/831404	Any way	8	1996–2008
Bay Bjørn AM[21]	2014	Denmark	Cohort study	1/146	80805/82027	Any way	6	1999–2009
Chi CC[22]	2013	UK	Cohort study	1/8	7205/7955	topical	7	1989–2006
Gur C[23]	2004	Israel	Cohort study	0/311	790/790	Systemic	6	1988–2001

N1: exposed pregnancies in first trimester T1:orofacial clefts.
N2: unexposed pregnancies in first trimester T2: non-orofacial clefts.