OS report

Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	Risk association of orofacial cleft and Corticosteroids exposure during pregnancy: a meta-analysis (GC_OC)
Report version and date	1.0, 15 Jul 2020
IMPACT study number	20638
Study type / Study phase	OS - Retrospective; OS - Data Analysis external; OS - Secondary use of data; OS - Other observational type; Post Authorization Commitment Study; Post Authorization Safety Study; Non-interventional Trial; Meta-analysis PASS: x YES
EU PAS register number	EUPAS26922
Active substance	Diflucortolone valerate (BAY 866146); Corticosteroids
Product reference	Not applicable
Procedure number	N/A
Comparator / Reference therapy	Unexposed control
Study Initiator and Funder	Bayer AG
Research question and objectives	Corticosteroid-containing dermatological preparations have been available in the market for more than six decades, however most evidence regarding the use of these medications during pregnancy are based on animal studies with systemic formulations. These studies showed a possible increased risk of orofacial clefts (OFCs) among new-borns of mothers who were treated with corticosteroids during the first trimester of pregnancy. Post-marketing publications, however, have shown contradictory results.

	The primary objective of this study was to evaluate if the exposure of corticosteroids during the first trimester of pregnancy is associated with the development of OFCs. Subgroup analyses for route of administration and types of OFC were performed as secondary objectives.
Country of study	N/A
Author	PPD PPD PPD PPD PPD PPD Key Study Member: PPD PPD Other Study Team Members: PPD PPD PPD

Marketing authorization holder

Marketing authorization holder(s)	BAYER AG Muellerstrasse 178 13353 Berlin Germany
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1. Abstract

Acronym/Title	Risk association of orofacial cleft and Corticosteroids exposure during pregnancy: a meta-analysis (GC_OC)
Report version and date **Author**	1.0, 15 Jul 2020 PPD PPD PPD PPD PPD PPD PPD PPD
IMPACT study number	20638
Keywords	Orofacial cleft, Corticosteroids, Meta-analysis, Literature review
Rationale and background	Corticosteroid-containing dermatological preparations have been available in the market for more than six decades, however most evidence regarding the use of these medications during pregnancy are based on animal studies with systemic formulations. These studies showed a possible increased risk of orofacial clefts (OFCs) among newborns of mothers who were treated with corticosteroids during the first trimester of pregnancy. Post-marketing publications, however, have shown contradictory results. In the scope of a regulatory procedure for Nerisona (diflucortolone valerate), the French Health Authority observed that no cases of cleft lip associated with Nerisona had been reported on the French PV database. Therefore, due to the lack of conclusive information, the French Health Authority requested Bayer to conduct a meta-analysis encompassing all studies about the risk of OFCs in neonates of women treated with corticosteroids during the first trimester of pregnancy.
Research question and objectives	The primary objective of this study was to evaluate if the use of corticosteroids during the first trimester of pregnancy is associated with the development of OFCs. Subgroup analyses for route of administration and types of OFC were performed as secondary objectives.

Study design	A meta-analysis of published literature was conducted with 19 shortlisted observational studies with 12 case-control (CCS) and seven cohort studies (CS) (from 18 publications) identified through a Systematic Literature Review (SLR) which was conducted using keywords and MeSH terms on Embase and Medline via Ovid®. Articles published up to 25 June 2018 were reviewed. Based on the publications identified in the SLR, the risk association of OFC and corticosteroids exposure during the first trimester of pregnancy was assessed by the odds ratio (OR) with corresponding 95% confidence interval (CI). Data analysis • Direct treatment comparison: Use of any corticosteroid irrespective of route of administration vs. no use of corticosteroids. • Model: Fixed-effect model was used. It was assumed that the underlying effect size for each route of administration is the same across the studies, and that differences in observed effects were due to random error or sampling error within studies. The observed effects mainly depend on sample size, and weighted average could give more precise estimation of the overall effect. However, any deviation from this assumption has been discussed and quantified. • Measure of relative effect: Dichotomous outcomes were assessed by OR. • Inverse variance method was used to assess the association between treatment and observed OFC occurrence. • Publication bias: Reporting or publication bias was assessed by using funnel plot (symmetry or asymmetry) and confirmed by Egger's test (in case of asymmetry of funnel plot). Further, any outliers in effect size were determined by Galbraith plot. • Sub-group analyses were performed per route of administration (topical, dermatological, systemic, inhalational, nasal, oral [buccal, local application], unspecified use and any route) and types of OFC. • Data was analysed by meta package in R software version 3.5.1. • Outcome results were presented as OR (mean, 95% CI).

	Quality Assessment: Studies were ranked as high, medium, or low quality based on the risk of bias. Two reviewers independently extracted data and study characteristics from each citation, and any discrepancy between the reviewers was reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this stage, whereas unclear citations were included. The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) were employed for reporting of included studies. Newcastle-Ottawa scale (NOS) was used to assess and appraise the methodological quality of included studies.
Setting	Pregnant women exposed to any corticosteroid in the first trimester of pregnancy irrespective of route of administration and reporting incidence of OFCs in neonates, identified by SLR.
Subjects and study size, including dropouts	All subjects included in the studies identified by the SLR (More details in Section 9.2). In total, 18 publications (encompassing 19 studies) were selected for the meta-analysis with sample size for any route of administration ranging from 96,512 (23,216 from case-control and 73,296 from cohort) in exposed patients to 2,461,849 (691,315 from case-control and 1,770,534 from cohort) in unexposed patients.
Outcomes and data sources	Outcomes: • OFC: cleft lip and/or cleft palate Route of administration of corticosteroids: • All routes of administration identified in the publications, i.e., topical, dermatological systemic, inhalational, nasal, oral [buccal, local application] unspecified use, and any route of corticosteroids were analysed. All combined routes of administration were regarded as 'any route'. Data sources: • Embase and Medline via Ovid®, Cochrane database, Google Scholar were used for data collection. • All records retrieved from the literature searches were screened for relevance based on eligibility criteria (inclusion/exclusion). Relevant back

	references from the shortlisted studies were also reviewed.
Results	The results show that the use of corticosteroids in the first trimester of pregnancy is associated with higher risk to develop OFCs in comparison to non-use. The OR for the use of corticosteroid in all combined routes of administration (i.e. anyroute) and any type of OFC was 1.20 (95% CI, 1.05; 1.38) for CCS and 1.19 (95% CI, 1.01; 1.40) for CS and thus considered as significant outcomes. For dermatological route, the OR for any type of OFC was 2.72 (95% CI, 1.41; 5.22) for CCS and 1.36 (95% CI, 1.06; 1.74) for CS, and thus considered significant. For topical route, the OR for any type of OFC was 1.14 (95% CI, 0.66; 1.95) for CCS, and considerd non-significant. The meta-analysis was not feasible for nasal and oral routes due to lack of at least two comparable data sets that could have been analysed. All other subgroup analyses showed the same outcome but with different effect sizes. The increased risk was smaller with inhalation and topical routes, relatively higher with systemic corticosteroids, and the highest odds were observed with dermatological administration.
Discussion	The meta-analysis was conducted using the inverse variance method with the fixed effect model assumption. It was based on 12 CCS and 7 CS and deemed as robust. Based on their clinical / observational settings, the selected studies could be used for the meta-analysis with the scope of assessing the risk association. The statistical heterogeneity for CS was considered moderate to low, whereas for CCS the statistical heterogeneity was high. Apart from oral and nasal routes for which meta-analysis was not feasible, all other subgroup analyses showed the same outcome but with different effect sizes. The increase in risk was smallest with inhalation and topical routes, relatively higher with systemic corticosteroids, and the highest odds were observed with dermatological administration(See Section 10, Section 11.1 for more details). Lack of relevant information on potency and comorbidities in the published studies led to the inability to perform subgroup analysis for these variables. The included studies also lacked data evaluating the relationship of dosage and duration of medication use with teratogenic effects, which could have affected the results of the study. Furthermore,

	skin conditions and extent of dermatological application were not reported, which may have influenced the absorption of corticosteroids and potentially altered effect outcomes. Due to limited availability of relevant information in the studies included in this meta-analysis, a definite conclusion could not be established. However, the results show a potential association between the use of corticosteroids in the first trimester of pregnancy and increased risk of developing OFCs.
Marketing Authorization Holder(s)	BAYER AG Muellerstrasse 178 13353 Berlin Germany

2. List of abbreviations

CCS	Case-control study
CI	Confidence interval
CL	Cleft lip
CLP	Cleft lip with or without palate
CP	Cleft palate
CS	Cohort study
EMA	European Medicine Agency
GCS	Corticosteroids
GVP	Good Pharmacovigilance Practices
INN	International non-proprietary name
MAR	Meta-analysis report
MeSH	Medical Subject Headings
MoBa	The Norwegian mother and child cohort study
NA	Not applicable
NCS	Norway cleft study
NOS	Newcastle-Ottawa scale
OFC	Orofacial cleft
OR	Odds ratio
PASS	Post-authorization safety study
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
SAP	Statistical analytical plan
SLR	Systematic literature review

3. Responsible parties

3.1. Study Team (internal or external)

Role:	PPD
Name:	PPD
E-mail:	PPD
Role:	PPD
Name:	PPD
Role:	PPD
Name:	PPD
Role:	PPD
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Name:	PPD
Role:	PPD
Name:	PPD
Role:	PPD (Regulatory Affairs)
Name:	PPD

3.2. Other responsible parties

Additional information:	Contact details of the responsible parties are available upon request.

4. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (SLR)	12 June 2018	*< dd MMM yyyy >*	*[Text]*
End of data collection (SLR)	25 June 2018	*< dd MMM yyyy >*	*[Text]*
Registration in the EU PAS register	*< dd MMM yyyy >*	*< dd MMM yyyy >*	*[Text]*
Final report of study results (SLR)	9 July 2018	*< dd MMM yyyy >*	*[Text]*
Meta-analysis protocol	09 November 2018 (version 1.1)	*< dd MMM yyyy >*	*[Text]*
Statistical analysis plan	10 September 2018	*< dd MMM yyyy >*	*[Text]*
Draft meta-analysis report	May 2019	*< dd MMM yyyy >*	*[Text]*
Final meta-analysis report	July 2020	First approval: *< dd MMM yyyy >* Last approval: *< dd MMM yyyy >*	*[Text]*

*A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1).

5. Rationale and background

Orofacial clefts are the most common congenital anomalies of the craniofacial regions occurring at a rate of one in 700 births. Earlier animal studies with corticosteroids demonstrated that there is an increased risk of congenital abnormalities if these drugs are used during the first trimester of pregnancy. On the other hand, epidemiological studies have shown contradictory results.

Corticosteroid-containing dermatological preparations have been available in the market for more than six decades. However, despite the long period after their development, most evidence regarding the use of these medications during pregnancy are still based on animal studies with systemic formulations.

Treatment with cortisone leads to cleft palates by interference with development of the condition within the palatine shelves that forces them to alter their alignment from the vertical to the horizontal plane. Consequently, the delay in shelf movement, the apparent inability of the shelves to widen without the stimulus of being fused, along with the continued increase in head width, materialises in a palate in which the shelves are too far apart to touch and fuse when they finally become horizontal (Walker and Fraser, 1957).

The development of OFCs is well documented. Between four to eight weeks of gestation, normal lip development occurs along with frontonasal prominence. Nasal placodes develop and divide the paired medial and lateral nasal processes (Dixon et al., 2011), (Leslie and Marazita, 2013), (Leite et al., 2002). By the end of week six of gestation, the primary palate is formed by the fusion of paired medial processes and developing premaxilla (central upper lip, maxillary alveolar arch and four incisor teeth, and hard palate). From week six to 12, the secondary palate develops along with medial projections of maxillary processes. OFC is a result of the disruption of normal development which could be due to chemical and environmental factors.

Based on the possibility of this potential risk, Bayer adopted a conservative approach by recommending the use of this drug in pregnant and lactating women only after carefully weighing the benefits against the risks.

On the other hand, recent scientific publications based on post-marketing case reports have raised questions about the applicability of these findings to humans. Some epidemiological studies have reported a three to six-fold increased risk of OFC due to corticosteroid use in the first trimester of pregnancy in humans (Carmichael et al., 2007), (Pradat et al., 2003) while some studies have not found this association (Xiao et al., 2017), (Källén, 2003). In the scope of a regulatory procedure, the French Health Authority requested Bayer to conduct a scientific evaluation encompassing all studies investigating a possible increase in the risk of OFCs in neonates of women treated with corticosteroids during the first trimester of pregnancy. For use of these products in pregnancy, the French label currently mentions “oral corticosteroids in pregnant women have not shown a malformation risk superior to that observed in the general population. As a result, these medications may be prescribed during pregnancy if needed”.

This study evaluates the risks of a medicinal product class used in a patient population for which safety information is limited or missing (e.g., pregnant women). Therefore, it is considered as a Post Authorization Safety Study (PASS), in accordance with the European Medicine Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3) (EMA/873138/2011, 2014).

In response to this request, an SLR was conducted to identify relevant studies evaluating the potential association between the exposure to corticosteroids during the first trimester of pregnancy and the occurrence of OFC. Due to the heterogeneity of the findings from the 18 selected publications in the SLR, a meta-analysis was deemed as warranted. Despite the lack of data in the published literature, the current meta-analysis addresses some of the shortcomings found in the previously published meta-analysis (Xiao et al., 2017), such as the confounder effect by sub-group analyses.

6. Research question and objectives

To evaluate if there was an increased risk of OFCs among new-borns of women who were treated with corticosteroids during the first trimester of pregnancy.

6.1. Primary objective

The primary objective in this study was to evaluate if the exposure to corticosteroids during the first trimester of pregnancy was associated with the development of OFCs.

6.2. Secondary objective

The secondary objectives were to perform subgroup analyses for route of administration and types of OFC.

7. Amendments and updates

Not applicable.

8. Research methods

8.1. Study design

A meta-analysis of published literature was conducted with 19 shortlisted observational studies with 12 CCS and seven CS (from 18 publications) identified through a SLR which was conducted using keyword and MeSH terms on Embase and Medline via Ovid®, followed by a supplementary search on the Cochrane database and general sources such as Google Scholar. To identify additional studies that might be relevant to the scope of the search general sources, articles published up to 25 June 2018 were reviewed. The key outcomes reported were relative effect sizes such as OR followed by RR for developing OFCs in neonates due to exposure to corticosteroids in first trimester of pregnant women.

Meta-analysis is a powerful tool to analyse rare outcomes as individual studies provide inadequate power to test rare outcome, and increase precision in estimating effects.

Based on the publications identified by the SLR, the risk of OFC associated with corticosteroid exposure during the first trimester of pregnancy was assessed by OR with corresponding 95% confidence interval (CI).

Quality Assessment: The studies were ranked as high, medium or low quality based on the risk of bias for the studies.

Two reviewers independently extracted data and study characteristics from each citation, and any discrepancies between reviewers was reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this stage; whereas unclear citations were included.

The PRISMA was employed for reporting of included studies. NOS was used to assess and appraise the methodological quality of included studies.

8.2. Setting

Pregnant women exposed to any corticosteroid in the first trimester of pregnancy irrespective of the mode of administration were identified through a SLR from articles published up to 25 June 2018 by pre-specified inclusion and exclusion criteria. (See section 4 of SLR provided in Appendix 2). In total, 18 publications (19 studies) were selected for the meta-analysis with sample size for any route of corticosteroid ranging from 96,512 (23,216 from case-control and 73,296 from cohort) in exposed patients to 2,461,849 (691,315 from case-control and 1,770,534 from cohort) in unexposed patients.

8.2.1. Selection criteria used for the SLR

Inclusion criteria

- Population: Pregnant women
- Intervention: Any corticosteroid use irrespective of the mode of administration
- Comparator: Any/none
- Outcomes: Incidence of OFCs in neonates
- Study Design:
    - Meta-analysis and SLR
    - Observational studies (such as CS, CCS, registries data)
    - Clinical trials – Phase IIb, III, and IV
    - Conference abstracts/posters
- Time period: No period restriction
- Geography: No geographic restriction

Exclusion criteria

- Population: Non-pregnant women
- Intervention: Drugs other than corticosteroid
- Outcomes: Other than Incidence of OFCs in neonates
- Study Design:
    - Animal Study
    - In vitro studies
    - Editorial, letters, comment
    - Clinical trials – Phase I or preclinical
    - Case reports, case series
    - Reviews
- Studies focusing on:

- Diagnosis and surgical procedure for cleft repair
- Impact of increased internal corticosteroids due to stress
- The relationship between genetic mutations and cleft patients
- Adverse events for other drugs
- Safety profiles of corticosteroid

8.3. Subjects

Pregnant women exposed to any corticosteroid in the first trimester of pregnancy irrespective of the mode of administration identified from articles published up to 25 June 2018.

8.4. Variables

8.4.1. Exposure definition

The primary exposure of interest is corticosteroid use during the first trimester of pregnancy, defined as at least one prescription for corticosteroids redeemed from the first day of the last menstrual period to the end of gestational week 12.

The primary comparison group includes women not using corticosteroid during the first trimester of pregnancy.

All included publications have considered first trimester pregnancies. Few publications clearly mention the terms “early pregnancy” and “first trimester” interchangeably, while in others the “first trimester” is not clearly mentioned. Also, the terms ‘glucocorticoid’ or ‘corticosteroid’ or ‘steroid’ are synonymously used. For consistency, ‘corticosteroid’ term has been used consistently throughout the report.

8.4.2. Outcomes definition

The primary outcome variable is the incidence of any type of OFC. OFCs are described as cleft lip (CL), cleft palate (CP), cleft lip with/without cleft palate (CLP), or OFC in general without further specification.

OFC types

- OFC => CP +CLP and OFC without any specification, CLP + CP data used for the calculation of OFC, in case OFC was not given in publication
- CLP => CL±CP, data available from the publications
- CL=> isolated CL, no data available from the publications
- CP => isolated CP, data available from the publications

The types of OFCs presented by authors vary across publications as mentioned below:

- CLP (isolated and multiple), CP (isolated and multiple) (Carmichael and Shaw, 1999)
- OFC (Chi et al., 2013)
- CL, CP, cleft lip and palate (Edwards et al., 2003); (Hviid and Mølgaard-Nielsen, 2011)
- Oral cleft (Gur et al., 2004)
- CLP, CP, cleft (Källén, 2003)
- CL, CP, cleft lip and palate, CLP (Robert et al., 1994)
- CP, CLP in rest of the included studies

8.4.3. Covariate definition

Covariates of interest for this meta-analysis are:

- Potency of corticosteroids
- Route of administration

In the studies referred to in the present report, either terms 'topical' or 'dermatological' have been used to describe corticosteroids administration to an outer body surface. As the term 'topical' may also refers to administration to mucous membrane areas (i.e., nasal, ophthalmological), a differentiation was made for the terms 'topical' or 'dermatological' based on the data reported in the publications. Studies mentioning only dermatological (i.e., cutaneous) route of administration have been marked as 'dermatological'. When the author reported a 'topical' route and no further details concerning dermatological or skin use was given, the route was marked as 'topical'. More study details and associated variables have been provided in Annex 2 (Study Details Table).

8.5. Data sources and measurement

8.5.1. Data sources

Embase and Medline via Ovid®, Cochrane database, Google Scholar were used for data collection. All records retrieved from the literature searches were screened for relevancy based on eligibility criteria (inclusion/exclusion). Relevant back references from the shortlisted studies were also reviewed.

8.5.2. Screening steps

- First level: screening based on title and abstracts.

  All the records retrieved from the literature search (using a multi-string search strategy) were screened based on the title and abstract. Two independent reviewers screened each citation, and any discrepancies between the reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this stage, whereas unclear

citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were excluded.

- Second level: screening of full text

  The eligibility criteria were applied to the full-text citations. Each full text was screened by two independent reviewers, and any discrepancies between the reviewers were reconciled through a third independent reviewer. Studies included after this stage were included for the next step, i.e., data extraction.

8.5.3. Extraction of relevant data

Data from included studies were extracted by one reviewer, and the quality of the data was checked by the second reviewer with reconciliation of any differences by a third independent reviewer.

8.5.4. Analysis of relevant results

The evidence for the present SLR was gathered through secondary research on the published studies and meta-analysis. The quantitative data from the research was considered. Based on the evidence identified from SLR, risk association of OFC and corticosteroids exposure during the first trimester of pregnancy was assessed by the OR with corresponding 95% CI. A detailed and comprehensive data extraction table in MS Excel was created to capture the relevant information from the studies identified in the SLR. This was then imported into the R software for meta-analyses.

8.6. Bias

- There may have potential biases (recall and publication bias) inherent from the retrospective CCS design. These types of studies may also have higher sensitivity to detect low-frequency defects.
- Included studies lacked data evaluating the relationship between dosage, potency and duration of medication use and teratogenic effects, which could affect the results of the study.
- Confounding factors assessed and described in the published sources could be an explaining factor for clinical heterogeneity, which includes the decision for specific treatment with corticosteroids, but also other factors could be a reason for heterogeneity. Range of dosages used is relatively wide in included studies which may influence the results.
- Conditions of skin were not reported in all studies which may have an influence on the absorption of corticosteroids and may alter effect outco

8.7. Study size

Nineteen observational studies (18 publications) were selected for meta-analysis based on the eligibility criteria (See Section 9.2). One publication (Skuladottir H, 2014) comprised two different relevant studies (The Norway Cleft Study, and The Norwegian Mother and Child Cohort Study). The

sample size for any route of corticosteroid from 18 publications (19 studies) ranged from 96,512 (23,216 from case-control and 73,296 from cohort) in exposed patients to 2,461,849 (691,315 from case-control and 1,770,534 from cohort) in unexposed patients.

8.8. Data transformation

Measure of relative effect: For the dichotomous outcomes were assessed by OR.

8.9. Statistical methods

- Direct treatment comparison: Any corticosteroid use (any route), irrespective of the mode of administration vs. no use of corticosteroid
- Model: Fixed effect model was used. It is assumed that the underlying effect size for each route of administration is the same across the studies. The differences in observed effects are only due to random error or sampling error within the studies. The observed effects mainly depend on the sample size, and weighted average mean might give a more precise estimation of the overall effect. However, any deviation from this assumption was discussed.
- Measure of relative effect: Dichotomous outcomes were assessed by OR
- Inverse variance method: Studies with less variance or standard deviation were given more weight. The variance of weighted average can be minimized through this method and hence inverse variance method was used to assess the association between treatment and observed OFC occurrence.
- Effect size is assessed by OR as it is a rare outcome.
- Publication bias: Reporting or publication bias was assessed by using the funnel plot (symmetry or asymmetry), and it was confirmed by using the Egger's test (in case of asymmetry of funnel plot). Further, any outliers in the effect size were determined by Galbraith plot.
- Sub-group analyses were planned to be performed for
    - Route of administration:
        - Topical
        - Dermatological
        - Inhalational
        - Systemic
        - Nasal
        - Oral (buccal, local application)
        - Unspecified
        - Any Route

- Types of OFC: CL, CP, CLP, or unspecified OFC

95% CI was used as a measure for the expression of the difference (overlap / no overlap with 1 for OR). Data were analysed by using the meta package in R software version 3.5.1. (RCoreTeam, 2014), (Schwarzer, 2007) (Viechtbauer, 2010).

8.9.1. Main summary measures

Measure of relative effect: For the dichotomous outcomes were assessed by OR.

8.9.2. Main statistical methods

- Direct treatment comparison: Any corticosteroids use (any route) irrespective of the mode of administration vs. no use of corticosteroids.
- Model: Fixed effect model was used. It is assumed that the underlying effect size for each route of administration is the same across the studies. The differences in observed effects are only due to random error or sampling error within the studies. The observed effects mainly depend on the sample size, and weighted average mean might give a more precise estimation of the overall effect. However, any deviation from this assumption was planned to be discussed.
- Measure of relative effect: Dichotomous outcomes were assessed by OR.
- Inverse variance method: Studies with less variance or standard deviation are given more weight. The variance of weighted average can be minimized through this method and hence inverse variance method was used to assess the association between treatment and observed OFC occurrence.

8.9.3. Missing values

Results as reported for the studies were used, no imputations were done. Potency of corticosteroids was not reported and therefore this analysis was dropped.

8.9.4. Sensitivity analyses

Sensitivity analysis was not performed.

8.9.5. Amendments to the statistical analysis plan

It was mentioned to perform sensitivity analysis and subgroup analysis for the potency of corticosteroids. Both analyses were not performed. The deviation from the planned analysis had occurred due to:

- Potency of corticosteroids - Due to lack of data availability, the analysis was not performed.

- Sensitivity analysis - Due to constrain and limitation of the available analysis time sensitivity analysis was not performed for the included studies.
- Route of administration - Due to inadequate differentiation between topical and dermatological routes in the included studies, a reassignment was made based on available information from the publication (See Section 8.4). In the studies referred to in the present report, either the terms 'topical' or 'dermatological' have been used across publications, based on the data reported for respective subgroups. Studies mentioning only dermatological route or skin related route of administration have been marked as dermatological. Studies reporting topical route (author reported) and no further details about skin or dermatological use were marked as topical, given that other topical routes, such as ophthalmological or nasal could not be excluded.

8.10. Quality control

Two reviewers independently extracted data and study characteristics from each citation, and a third independent reviewer reconciled any discrepancies between the two reviewers. Citations that did not match the eligibility criteria were excluded at this stage; whereas unclear citations were included.

The PRISMA was employed for reporting of included studies.

NOS was used to assess and appraise the methodological quality of included studies.

9. Results

Meta-analysis was conducted with 19 observational studies (18 publications) previously identified through a SLR which was conducted using keyword and MeSH terms on bibliographic databases such as Embase and Medline via Ovid® to identify all studies (including observational studies and clinical trials) published till 25 June 2018 (search date). Additionally, a supplementary search was conducted on the Cochrane database and general sources such as Google Scholar to identify additional studies that might be relevant to the scope of the search. Only 18 publications (19 studies) were shortlisted based on the inclusion /exclusion criteria.

All records retrieved from the literature searches were screened for relevancy based on eligibility criteria (inclusion/exclusion). The results were initially screened by title and abstract, and the shortlisted results were further screened on full text. Most of the included studies were of either high or medium quality, critically appraised using NOS checklist. Relevant back references from the shortlisted studies were also reviewed. The key outcomes reported were relative effect sizes such as OR followed by RR for developing OFCs in neonates due to exposure to corticosteroids in pregnant women in first trimester.

9.1. Participants

Pregnant women exposed to any corticosteroid in the first trimester of pregnancy irrespective of the mode of administration identified from articles published up to 25 June 2018 (Section 9.2 for more details).

9.2. Descriptive data

The number of cases with events and the total population in both exposed and unexposed groups were identified. Quantitative data was extracted for the analysis of the events. Please refer to the Annex 2 section 3 for details.

9.3. Outcome data

The outcomes were assessed by OR with corresponding 95% CI.

9.4. Main results

This study evaluated the association between exposure to corticosteroids by any route of administration during the first trimester of pregnancy with the development of OFCs. All combined routes of administration were regarded as 'any route'. (For details, please refer to Annex 2 MAR, section 3).

- Any route of corticosteroids use: Eighteen publications with 19 studies were identified which evaluated OFC development in pregnant women using corticosteroid by any route. Out of these 19 studies, 11 CCS were for OFCs, nine CCS for CLP and seven CCS for CP. Out of these 19 studies, seven were CS for OFCs, three CS for CLP, and three CS for CP.
    - The current meta-analysis with CCS and CS demonstrated a **significant** risk association between the exposure of corticosteroids and OFC development in exposed group compared to unexposed group (OR: 1.20 [95% CI, 1.05; 1.38]) and (OR: 1.19 [95% CI, 1.01; 1.40]) with fixed effect model by using inverse variance method (Section 9.9.2 for more details).

As secondary objectives, this study evaluated the association between exposure to corticosteroids by various routes of administration (topical, dermatological, inhalational, systemic, nasal, local oral use and unspecified) during the first trimester of pregnancy with the development of OFCs.

- Topical use: Five studies were identified which evaluated OFC development in pregnant women using corticosteroid by topical route. Out of these five studies, four CCS were for OFCs, three CCS for CLP and three CCS for CP. Further, out of these five studies, only one cohort study reported data for OFCs, CLP and CP.
    - The current meta-analysis with CCS demonstrated a non-significant risk association between the exposure of corticosteroids and OFC development in exposed group compared to unexposed group (OR: 1.14 [95% CI, 0.66; 1.95]) with fixed effect model by using inverse variance method. Conducting meta-analysis for cohort study was not feasible.
- Dermatological use: Eight publications with nine studies were identified which evaluated cleft development in pregnant women using corticosteroids by dermatological route. Out of these

nine studies, four CCS for OFCs, four CCS for CLP and three CCS for CP. Further, out of these nine studies, four CS for OFCs, three CS for CLP, and CP.

  - The current meta-analysis with CCS and CS demonstrated a **significant** risk association between the exposure of corticosteroids and OFC development in exposed group compared to unexposed group (OR: 2.72 [95% CI, 1.41; 5.22]) and (OR: 1.36 [95% CI, 1.06; 1.74]) with fixed effect model by using inverse variance method.

- Inhaled use: Eight studies were identified which evaluated OFC development in pregnant women using corticosteroids by inhalational route. Out of these eight studies, five CCS and three CS for OFCs. Four CCS and one CS for CLP and four CCS and one CS for CP were identified (Section 10.1 for more details). These studies reported data for the inhaled route for corticosteroids administration.
  - The current meta-analysis with CCS demonstrated a non-significant risk association between the exposure of corticosteroids and OFC development in exposed group compared to unexposed group (OR: 1.01 [95% CI, 0.84; 1.22]) and (OR: 1.28 [95% CI, 0.98; 1.66]) with fixed effect model by using inverse variance method.
- Systemic use: Eight studies were identified (six CCS and two CS). Six CCS for OFCs, four CCS for CLP, three CCS for CP, and two CS for OFCs were identified which evaluated cleft development in pregnant women using corticosteroid by the systemic route.
  - The current meta-analysis with CCS demonstrated a **significant** risk association between the exposure of corticosteroids and OFC development in the exposed group compared to unexposed group (OR: 1.58 [95% CI, 1.22; 2.06]) with fixed effect model by using inverse variance method.
  - Meta-analysis with CS was not feasible as effect size of only one study (Bjørn et al., 2014) was contributing in calculation of point estimate.
- Nasal use: Two publications with one CS (each for OFC, CLP, and CP) and one CCS (for OFC) were identified which evaluated OFC development in pregnant women using corticosteroid by the nasal route. The meta-analysis was not feasible for nasal route, as it required two similar data sets for comparison, and the publications had different study design and were not comparable.
- Local oral use: Only one publication with a CS (Hviid and Mølgaard-Nielsen, 2011) was identified that evaluated OFC development in pregnant women exposed to corticosteroid by oral local route (A07EA). Another study (Bjørn et al., 2014) reported oral route of administration with ATC codes related to systemic use (H02AB 04, 06, 07, and 09) and hence included in the meta-analysis of systemic route.
- Unspecified route: Four CCS studies for OFCs, CLP and CP each were identified. These studies did not specify the route of administration of the corticosteroids to women.
  - The current meta-analysis demonstrated a non-significant risk association between the exposure of corticosteroids and OFC development in the exposed group compared to unexposed group (OR: 1.54 [95% CI, 0.89; 2.65]) with fixed effect model by using inverse variance method.

9.5. Other analyses

Subgroup analyses were performed for the types of OFC and any route of administration. All combined routes of administration was regarded as 'any route'. The results are presented below (For details, please refer to Annex 2 section 3):

- Any route of corticosteroids use: Eighteen publications with 19 studies were identified which evaluated cleft development in pregnant women using corticosteroid by any route in their first trimester.

  For CLP the analysis was:

  - For CCS a **significant** risk association between the exposure of corticosteroids and Cleft lip and/or palate (OR: 1.48 [95% CI, 1.26; 1.74])
  - For CS a non-significant risk association between the exposure of corticosteroids and Cleft lip and/or palate (OR: 1.08 [95% CI, 0.85; 1.39])

  For CP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CP development (OR: 0.83 [95% CI, 0.62; 1.09])
  - For CS a non-significant risk association between the exposure of corticosteroids and CP development (OR: 1.15 [95% CI, 0.81; 1.63])

As secondary objectives, the study evaluated exposure to corticosteroids for the types of OFC by various routes of administration (topical, dermatological, inhalational, systemic, nasal, local oral use and not specified) during the first trimester of pregnancy with the development of OFCs

- Topical use: Five studies were identified which evaluated cleft development in pregnant women using corticosteroid by topical route during the first trimester of pregnancy.

  For CLP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and Cleft lip and/or palate (OR: 1.17 [95% CI, 0.60; 2.28])

  For CP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CP (OR: 0.87 [95% CI, 0.27; 2.78])

- Dermatological use: Eight publications with nine studies were identified which evaluated cleft development in pregnant women using corticosteroid by dermatological route in their first trimester.

  For CLP the analysis was:

  - For CCS a **significant** risk association between the exposure of corticosteroids and Cleft lip and/or palate development (OR: 3.55 [95% CI, 2.18; 5.77])
  - For CS a **significant** risk association between the exposure of corticosteroids and Cleft lip and/or palate development (OR: 1.41 [95% CI, 1.05; 1.91])

  For CP the analysis was:

- For CCS a **significant** risk association between the exposure of corticosteroids and CP development (OR: 2.78 [95% CI, 1.03; 7.53])

- Inhaled use: Five CCS and three CS for OFCs, four CCS and one CS for CLP and four CCS and one CS for CP were identified. These studies reported data for the inhaled route of corticosteroids.

  For CLP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CLP development (OR: 1.11 [95% CI, 0.88; 1.40])

  For CP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CP development (OR: 0.80 [95% CI, 0.57; 1.13])

- Systemic use: Six CCS for OFCs, four CCS for CLP, and three CCS for CP were identified. These studies indicated the systemic route of administration of the corticosteroids to women in their first trimester.

  For CLP the analysis was:

  - For CCS a **significant** risk association between the exposure of corticosteroids and cleft development (OR: 1.88 [95% CI, 1.37; 2.58])

  For CP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CP development (OR: 0.70 [95% CI, 0.37; 1.34])

- Nasal use: The publications reporting nasal route had different study designs. Thus, meta-analysis was not feasible.

- Local oral use: Only one publication (Hviid A, 2011) reported CLP, CP data for oral route. As there were no identical data sets, meta-analysis was not conducted.

- Unspecified route use: Four CCS for OFCs, four CCS for CLP and four CCS for CP were identified. These studies did not specify the route of administration of the corticosteroids to women in their first trimester.

  For CLP the analysis was:

  - For CCS a **significant** risk association between the exposure of corticosteroids and OFC development (OR: 1.87 [95% CI, 1.04; 3.36])

  For CP the analysis was:

  - For CCS a non-significant risk association between the exposure of corticosteroids and CP development (OR: 1.35 [95% CI, 0.58; 3.13]).

9.6. Adverse events/adverse reactions

Not applicable

10. Discussion

10.1. Key results

The meta-analysis was conducted using the inverse variance method with the fixed effect model assumption. It was based on 12 CCS and 7 CS and deemed as robust. Based on their observational settings, the selected studies could be used for the meta-analysis with the scope of assessing the risk association. The statistical heterogeneity for the CCS was considered moderate to low, whereas for the CS the statistical heterogeneity was high.

The study analysed exposure to corticosteroids during the first trimester of pregnancy by any route of administration as well as by topical, dermatological, inhalational, systemic and not specified route. The meta-analysis was not feasible for nasal and local oral routes. The publications reporting nasal route had different study designs, one was CCS and other was a CS and hence meta-analysis was not feasible. Only one publication reported data for oral route (Hviid and Mølgaard-Nielsen, 2011) and thus meta-analysis was not feasible. Further, for systemic route of administration although there were two publications for CS, meta-analysis was not conducted as only one study (Bjørn et al., 2014) was contributing in calculation of the point estimate. The other study (Gur C, 2004) reported zero events and had zero weightage.

The present analysis demonstrated that the use of corticosteroids in the first trimester of pregnancy is associated with a higher risk to develop OFCs in comparison to non-use. The OR for any route and any type of OFC is 1.2 for CCS and 1.19 for CS and are considered as significant. In addition, dermatological and systemic routes are associated with a higher risk for the development of OFCs. The results also show that the use of corticosteroids (dermatological) in the first trimester of pregnancy is associated with a higher risk to develop OFC, CLP, and CP congenital abnormalities in comparison to non-use. Please refer to the report attached in Annex 2 for detailed discussion of the meta-analysis.

The OR for the use of corticosteroids in all combined routes of administration (i.e., dermatological, topical, inhaled, systemic and route unspecified) and any type of OFC were 1.20 (95% CI 1.05 – 1.38) for CCS and 1.19 (95% CI 1.01 – 1.40) for CS and thus considered as significant outcomes. For the dermatological route of administration, the OR for any type of OFC were 2.72 (95% CI 1.41 – 5.22) for CCS and 1.36 (95% CI 1.06 – 1.74) for CS. Apart from nasal and local oral route for which meta-analysis was not feasible, all other subgroup analyses showed the same outcome but with different effect sizes. The increase in risk was smaller with inhalation and topical routes, relatively higher with systemic corticosteroids, and the highest odds were observed with dermatological administration.

The table below presents summary of overall results OR (95% CI) across various clefts for various routes of corticosteroids administration.

Table 2: Summary of overall results based on meta-analysis of included studies

Route of administration	Cleft category	Study type	No. of studies	Total no. of subjects in case/exposed group	Total no. of subjects in control/non-exposed group	OR	OR 95% lower CI	OR 95% upper CI	
Topical	OFC	CCS	4	6,940	588,136	1.14	0.66	1.95	n.s.
	CLP	CCS	3	3,814	24,683	1.17	0.60	2.28	n.s.
	CP	CCS	3	2,076	24,683	0.87	0.27	2.78	n.s.
Dermatological	OFC	CCS	4	1,173	12,064	2.72	1.41	5.22	
	OFC	CS	4	29,565	814,918	1.36	1.06	1.74	
	CLP	CCS	4	865	47,615	3.55	2.18	5.77	
	CLP	CS	3	28,753	807,706	1.41	1.05	1.91	
	CP	CCS	3	386	12,006	2.78	1.03	7.53	
	CP	CS	3	28,691	807,706	1.26	0.81	1.94	n.s.
Inhaled	OFC	CCS	5	13,807	641,138	1.01	0.84	1.22	n.s.
	OFC	CS	3	21,122	1,735,489	1.28	0.98	1.66	n.s.
	CLP	CCS	4	4,371	77,685	1.11	0.88	1.40	n.s.
	CP	CCS	4	2,633	77,685	0.80	0.57	1.13	n.s.
Systemic	OFC	CCS	6	9,287	600,669	1.58	1.22	2.06	
	CLP	CCS	4	4,617	31,628	1.88	1.37	2.58	
	CP	CCS	3	2,248	24,683	0.70	0.37	1.34	n.s.
Unspecified	OFC	CCS	4	7,037	15,417	1.54	0.89	2.65	n.s.
	CLP	CCS	4	4,594	15,417	1.87	1.04	3.36	
	CP	CCS	4	2,443	15,417	1.35	0.58	3.13	n.s.
Any Route	OFC	CCS	11	23,143	655,706	1.20	1.05	1.38	
	OFC	CS	7	73,296	1,770,534	1.19	1.01	1.40	
	CLP	CCS	9	6,580	122,216	1.48	1.26	1.74	
	CLP	CS	3	58,246	807,706	1.08	0.85	1.39	n.s.
	CP	CCS	7	3,500	79,662	0.83	0.62	1.09	n.s.
	CP	CS	3	58,184	807,706	1.15	0.81	1.63	n.s.

n.s. = non-significant. Red highlighted results are significant, green ones are non-significant.
Note: Meta-analysis of nasal and local oral routes was not feasible. 'Any route' comprises all the routes, including nasal and local oral route.

The observed risk of OFC associated with inhaled corticosteroids was found to be lower than with dermatological formulations. However, important information on medical history, indication, characteristics of corticosteroids and pattern of their use is not available. For example, a prolonged, continuous use of potent corticosteroids for diseases like psoriasis, eczema, lichen sclerosus or bullous pemphigoid may result in higher systemic exposure compared with intermittent corticosteroid use for asthma exacerbations.

A few publications analysing the risk are mentioned below:

- A Cochrane SLR observed no casual associations between maternal exposure to dermatological corticosteroids and OFCs, irrespective of potency (Chi, 2015).

- Another SLR mentioned certain association between OFCs and maternal corticosteroids use, irrespective of route. The various confounders were dose, route of application, disease etc. and biases (re-call, loss-to follow-up etc.) that still need to be considered (Xiao et al., 2017).
- Inadequate data to determine risk of OFC associated with corticosteroids exposure in first trimester was reported in a SLR, irrespective of route of administration (Bandoli et al., 2017).
- Evidence from another SLR suggested the use of corticosteroids (inhaled and oral) in first trimester is not associated with an increased risk of OFCs in offspring; but also mentioned that the published estimates were inconsistent (Bjorn 2015).
- A CCS, National Birth Defects Prevention Study could not confirm risk association of OFC and maternal exposure to corticosteroids (inhaled asthma medication), although it found modest increase in odd ratios.
- A meta-analysis (Xiao 2017) suggested a small increase on the risk for CLP associated with the use of corticosteroids during early pregnancy. However, this publication did not specify the route of administration, and presented other shortcomings, such as:
    - Recall and publication bias due to retrospective study.
    - Relationship between dosage and duration of medication were not examined in the included studies that could affect the results of the study.
    - Confounding factors, such as race, maternal age, level of education, economic and social status, smoking, chances of repetitive enrolment of some patients in different studies were not addressed.
    - Dosage of corticosteroid was not discussed.

10.2. Limitations

As occurs with any meta-analysis, this study is based on published articles. As previously discussed, the available studies lack some data, such as potency of corticosteroids and comorbidity. Therefore, subgroup analysis for these variables could not have been performed.

- No sensitivity analysis was conducted for the included studies.
- There may have potential biases (recall and publication bias) inherent in retrospective CCS designs. These types of study may also have higher sensitivity to detect low-frequency defects.
- Included studies lacked data evaluating the relationship between dosage, potency, and duration of medication (leading to a potential under/over estimation of exposure), and teratogenic effects, which could affect the results of the study.
- Conditions of skin were not reported in all studies which may influence the absorption of corticosteroids and potentially alter effect outcomes. Furthermore, information on the extent of dermatological application, particularly under occlusion, that may significantly increase the risk adverse effects of corticosteroids was not available.

10.3. Interpretation

All analyses show higher odds for the development of any form of oral-facial clefts in neonates born to women using corticosteroids in the first trimester of pregnancy. The highest odds are observed in the dermatological administration of corticosteroids. In general, longer courses of higher potency dermatological corticosteroids are avoided in pregnancy, but shorter courses of medium to low potency dermatological corticosteroids are quite common, especially given the need to treat various pregnancy-related dermatoses which quite commonly arise (e.g. atopic eruption of pregnancy, polymorphous eruption of pregnancy, etc.). However, the data from the included publications lack information on the underlying disease, potency and duration of use of corticosteroids. Thus, it cannot be excluded that a few women may have required prolonged cutaneous application of high potency corticosteroids and/or the use occlusive dressing techniques for treating a chronic skin disease (e.g. psoriasis, eczema, lichen sclerosus or bullous pemphigoid) that led to a high level of systemic exposure. Similarly, this finding needs further research.

10.4. Generalizability

The study is generalizable as the data was collected from secondary research through published studies with no geographical restrictions. The included patient population comprised pregnant women who were exposed to corticosteroids in their first trimester regardless of the age, ethnicity, and underlying comorbidity. The non-syndromic OFCs developed in the exposed and unexposed mothers were considered to exclude genetic anomalies.

11. Other information

Not Applicable

12. Conclusion

The studies in this meta-analysis lacked relevant information across multiple clinical domains, and therefore no definite conclusion could be established. This meta-analysis demonstrates a potential association between exposure to systemic and dermatologic formulations of corticosteroids in the first trimester of pregnancy and suggests an increased risk of developing OFCs, whereas increased risk was not observed for other routes of administration. However, these results are not definitive and, to date, large-scale, prospective, well-designed studies assessing this risk have not been conducted, and these findings accordingly should be interpreted with appropriate caution.

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Appendices

Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name*	**Final version and date**
Meta-analysis report	V 1.0, 15 May 2020
SAP	V 1.0, 10 September 2018
Signature Page	25. Jan 2024

Annex 2: Additional information

Study Details Table

Summary of study details included in the SLR and considered for meta-analysis.

Study Name	Study Design	Study Population	Definition of Orofacial Cleft	Route of Administration Details	Derma/Topical Route Sub-Groups Details	Definition of exposure		Adjustment for confounding (method of adjustment and list of confounding variables)
						How and by whom assessed	When assessed	
(Bjørn et al., 2014)	Cohort Study	Women who gave birth to a live-born singleton in northern Denmark, in 1999–2009 were considered	Diagnoses are coded by medical doctors according to the International Classification of Diseases, eighth revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter Oral clefts were defined as diagnoses of cleft lip with or without cleft palate or isolated cleft	Systemic corticosteroids	Not applicable	Through Danish medical registries, we identified prescriptions for corticosteroids, congenital malformations, and covariates To identify prescriptions for corticosteroids, we used the Aarhus University Prescription Database (tracks prescriptions for reimbursed drugs redeemed at the regions' community pharmacies)	From 30 days before estimated conception to the end of the first trimester (12 completed gestational weeks)	Confounding factors were unknown, but they could not be ruled out and could have been the ones that mask the risk of congenital malformation associated with the use of corticosteroids. Further, the estimates for congenital malformations overall were further adjusted for maternal smoking during pregnancy, maternal age at delivery, and diabetes

Study Name	Study Design	Study Population	Definition of Orofacial Cleft	Route of Administration Details	Derma/Topical Route Sub-Groups Details	Definition of exposure		Adjustment for confounding (method of adjustment and list of confounding variables)
						How and by whom assessed	When assessed	
			palate (CLP or CP)					
(Carmichael and Shaw, 1999)	Case-control Study	Case Identification: (Deliveries of infants and fetal deaths in 1987 and 1988 were eligible for study) - 1999 (Data collection continued for pregnancies ending in 1989) Controls: were selected randomly from eligible liveborn infants (i.e., born to a mother who was a resident in the same counties in which cases were ascertained and had no reportable birth	Orofacial cleft cases were those infants or fetuses with cleft palate without cleft lip (CP) and cleft lip with or without cleft palate (CLP) confirmed by surgical or autopsy report. Orofacial clefts were classified further into the following phenotypic groups for analyses: isolated cleft lip with or without cleft palate (ICLP), isolated cleft palate (ICP), multiple cleft lip with or	Unspecified	Not applicable	Information on medication use was collected via maternal telephone interviews in English or Spanish and were asked about various exposures during the 4-month periconceptional period The California Birth Defects Monitoring Program reviewed medical records at all hospitals and genetic counseling centers. Case eligibility was determined by medical geneticists using detailed diagnostic information and cases were confirmed by surgical or autopsy report.	4-month periconceptional period, early pregnancy	Small sample size limited the ability of the study and previous ones to examine potential confounders

Study Name	Study Design	Study Population	Definition of Orofacial Cleft	Route of Administration Details	Derma/Topical Route Sub-Groups Details	Definition of exposure		Adjustment for confounding (method of adjustment and list of confounding variables)
						How and by whom assessed	When assessed	
		defect before the 1st birthday) Telephonic interviews for case and control confirmation: On the average, interviews took place 3.7 years after the date of delivery for cases and 3.8 years for controls	without cleft palate (MCLP), and multiple cleft palate (MCP)					
(Carmichael et al., 2007)	Case-control Study	Cases included infants or fetuses who were born with cleft lip with or without cleft palate (CLP) or cleft palate (CP) [October 1997 to December 2002]. Each case received an additional	Orofacial cleft: cleft lip±cleft palate (CLP), cleft palate (CP) CLP cases were further classified as bilateral, unilateral, central, or not otherwise specified	Systemic Any Nasal spray or inhaled use Other or not otherwise specified use	Data presented for topical route No further details mentioned	Data on deliveries from the National Birth Defects Prevention Study (October 1997 to December 2002) Exposures were assessed by telephone interviews	Medication exposures were assessed from 12 weeks before conception through the date of delivery. Date of conception was derived by subtracting 266 days from the woman's EDD	Analyses that were adjusted for all covariates were very similar to the unadjusted results (data not reported)

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		review by 1 clinical geneticist to ensure that cases from each study center met standard eligibility criteria.						
(Chi et al., 2011)	Cohort Study	Pregnant women exposed and unexposed to GC 2000-2006	Orofacial cleft (cleft lip ± palate (CLP) and cleft palate alone (CP)). The diagnostic codes for identifying the outcomes are available from the authors.	Dermatological	Data presented for dermatological route No further details mentioned	UK General Practice Research Database (GPRD) The prescription records were used to identify the timing, potency, and dosage of topical corticosteroids prescribed	85 days before last menstrual period (LMP) to delivery or fetal death	Known confounding was minimized in the study. Confounding from maternal age and year of pregnancy was controlled by matching; maternal disorder (hypertensive disorder, diabetes mellitus etc.), indication for topical corticosteroid, exposure to FDA pregnancy risk category D and X medicines (that may affect pregnancy outcomes), and smoking were adjusted in statistical analysis. Maternal drinking, body mass index and socioeconomic factors were not adjusted. Parity and paternal height were

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								not recorded in the GPRD and were thus not controlled.
(Chi et al., 2013)	Cohort Study	An early exposed group limited to women ≥1 dispensed prescription for topical corticosteroids during the first 12 gestational weeks was used for the analysis of orofacial cleft 1989-2006	Orofacial cleft	Dermatological	Data presented for dermatological route No further details mentioned	United Kingdom National Health Service Health Informatics Centre (HIC) data sets from 1989 to 2006. HIC manages a database of anonymized longitudinal medical records from National Health Service (NHS) In the UK NHS, all community prescriptions are written by general practitioners, sometimes on the basis of the advice of referred hospital dermatologists. number. Pharmacy records to identify the timing, potency, and dosage of topical corticosteroids dispensed	First 12 gestational weeks	Confounders included maternal smoking during pregnancy, socioeconomic levels, maternal comorbidities, acute skin conditions, previous exposure to topical corticosteroids within 1 year before pregnancy, lupus erythematosus, antiphospholipid syndrome, hypertension, diabetes mellitus, renal disease, thyroid disorder, thrombophilia, cholestasis of pregnancy, human immunodeficiency virus infection, asthma, and exposure to other medications that may affect Pregnancy outcomes(drugs classified as USFDA pregnancy risk category D or X)
(Czeizel and Rockenb	Case-control Study	The Hungarian Case-Control Surveillance of	Not mentioned	Topical	Not applicable	The prenatal care physicians were obliged to record all drug uses	The maximum of ointment treatments was	Confounding Factors: maternal age, birth, proportion of threatened

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auer, 1997)		Congenital Abnormalities (HCCSCA), 1980 - 1994 Group of controls represents 1.9% of the Hungarian pregnant population (1,923,413 total births) during the study period				and diseases during pregnancy in the logbook, which was looked after by the mothers. Data for conditions unrelated to pregnancy, prescribed by general practitioners/other physicians/self-medication were collected by questionnaire	in the first month of gestation	abortion, preterm birth, maternal disorders, other drug uses
(Edwards et al., 2003)	Case-control Study	Cases were classified as syndromic or nonsyndromic (isolated cleft) Invitations, information, and consent forms with stamped return address envelopes were mailed to parents of 190 present and past patients ascertained at a	Cleft lip and palate and CP and were classified as syndromic or nonsyndromic (isolated cleft).	Dermatological	Data presented for dermatological route No further details mentioned	Questionnaires were also sent to 405 control families of babies selected from delivery suite records by date of birth as close as possible to each case's date of birth in the same hospital. All cases had been assessed by a geneticist and a pediatrician in the clinic and were classified as syndromic or nonsyndromic (isolated cleft).	First trimester	Although there were potential confounders and differences between the groups at baseline (e.g., income), adjustment for these using multiple regression appeared to increase the strength of the association

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		multidisciplinary cleft palate clinic between 1990 and 2000 Questionnaires were also sent to 405 control families of babies selected from delivery suite records by date of birth as close as possible to each case's date of birth in the same hospital.						
(Garne et al., 2015)	Case-control Study	Cases were defined as EUROCAT registrations with at least 1 of the signal malformations: spina bifida, cleft palate, cleft lip with or without cleft palate, severe congenital heart defects,	As per EUROCAT Guide 1.3 and reference documents (Instructions for the Registration and Surveillance of Congenital Anomalies) al102: EUROCAT	Inhaled	Not applicable	Data from the EUROmediCAT database for 13 EUROCAT population-based congenital anomaly registries. EUROCAT registries clinical geneticists are involved in the evaluation of most patients with multiple malformation, dysmorphic features, or both). Information on	First-trimester exposure to asthma medication	There was limited information on potential confounding factors, but because registries collect standardized data on congenital anomalies for both exposed and unexposed cases and information on medication was obtained prospectively, the potential for bias was reduced

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		tetralogy of Fallot, esophageal atresia, gastroschisis, omphalocele, hypospadias, and anorectal atresia, stenosis, or both Cases and controls both enrolled from EUROCAT registries (1995 - 2010)	subgroup: Cleft lip with or without palate (ICD10-BPA Q36, Q37; ICD9-BPA 7491, 7492) al103: EUROCAT subgroup: Cleft palate (ICD10-BPA Q35; ICD9-BPA 7490) Added from link reported in article (EUROCAT Guide 1.3; http://www.eurocatnetwork.eu/content/EUROCAT-Guide-1.3.pdf)			medication exposure by obstetric/midwife records, created before birth and other additional sources (medical records, maternity passports, maternal interviews before or after birth, prescription data, and prescription redemption records)		
(Gur et al., 2004)	Cohort Study	Case: All women who contacted (directly or through their health care providers) the	Oral cleft	Systemic	Not applicable	Standardized data collection forms were used to record information by telephone and when the mother reported a malformation, she was asked to send	First trimester	No cases of OFC and adjustment for confounding factors were reported

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		Israeli Teratogen Information Service (TIS) between the years 1988 and 2001 for information about gestational systemic exposure to different GCS in the first trimester of pregnancy or to non-teratogenic agents were prospectively enrolled in the study				medical documents verifying the diagnosis. Alternatively, an attempt was made to contact the child's physician for verification.		
(Hao et al., 2015)	Case-control Study	Cases were patients with orofacial clefts in Heilongjiang Province and the surrounding areas attend	Cases were divided into two groups: patients with cleft palate only (CPO group) and cleft lip with or without cleft palate	Dermatological	Data presented for dermatological route No further details mentioned	Information of case and control mothers was extracted from interviewer-administered questionnaires The interview was administered by a trained interviewer and addressed exposures	From one month before conception through the end of the first trimester	Confounding was based on multivariable regression that used a standard set of covariates

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		clinics 2009-2014	(CL/P group). (Cleft lip and cleft lip with cleft palate share a common development process.)					
(Hviid and Mølgaard-Nielsen, 2011)	Cohort Study	Infants with orofacial clefts (clefts) were identified through the National Hospital Discharge Register Control was not defined by author. We have considered the cases and population, not using corticosteroids	ICD-10 was used to code OFC: -Cleft lip ± palate: Q36, Q37 -Cleft palate: Q35 -Q35: Cleft palate -Q36: Cleft lip -Q37: Cleft - palate with Cleft lip	Local oral (A07EA) -Nasal spray -Inhaled -Other topical form - Dermatological	Data presented for: - Dermatologic -Other topical forms No further details mentioned	ATC codes gave information on all corticosteroids. Each record was indexed using the recipient's personal identification number and included date on which the prescription was filled, the ATC code of drug Drug information obtained from Prescription Drug Register which contains information on all prescription drugs purchased from Danish pharmacies	First trimester (was defined as the first 12 weeks after the start of pregnancy)	Included information on many potential confounders: Maternal age, Parity status, Smoking status, Maternal morbidities, Concomitant medications, History of birth defects. Covariables that were potential confounders were included in the regression models if they were significant risk factors for clefts in univariable analyses
(Källén, 2003)	Nested case-control Study	From Swedish Medical Birth Registry, infants diagnosed with an orofacial	Orofacial cleft -Type of clefts and controls were not defined	Topical administration as a dermatological preparation	Data presented for topical route No further	Anatomical drug names coded into Therapeutic Chemical Classification (ATC) codes Names of drugs that woman stated using	The data represented first-trimester exposures, as reported in early pregnancy	Not reported

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		cleft were identified -Control were not defined by author. Control was calculated by subtracting population of exposed groups (all routes of corticosteroids), from total study population)		-Nose drops -Inhalation -Systemic	details mentioned	during pregnancy before the antenatal visit, were recorded by attending midwife		
(Källén and Olausson, 2007)	Cohort Study	Infants were identified from the Swedish Medical Birth Register (1995-2004) Hospitalizations up to the end of 2004	Orofacial clefts are divided into isolated median cleft palate (CP) and cleft lip with or without cleft palate (CLP)	Inhaled	Not applicable	Infants were identified from the Swedish Medical Birth Register (from 1995 - 2004) where drug use reported at the first maternal health care visit is recorded. Congenital malformations among the infants born were identified from that register, the Swedish Register of Congenital Malformations, and the Hospital Discharge Register. Patient identification was through unique personal	Early Pregnancy (Week 10-12)	Confounding factors (year of birth, maternal age, parity, smoking habits, and number of previous miscarriages) were adjusted but not further specified

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						identification number given to everyone born in or immigrated to Sweden. By record linkage with the Swedish Birth Register (Statistics Sweden), the complete identification number of the child was obtained and used for further linkage with the Hospital Discharge Register		
(Pradat et al., 2003)	Case-control Study	Cases were defined as infants presenting with a malformation belonging to one an oral cleft Controls were defined as infants presenting with any other birth defect Large multicentric MADRE database (that collects data yearly on	9th revision of the World Health Organization (WHO) International Classification of Diseases, adapted by the British Paediatric Association, known as ICD9/BPA (British Paediatric Association, 1987) Oral cleft: code 749 (cleft	Topical Dermatological Inhaled Systemic Other use (Unspecified use)	Data presented for: - Dermatologic -Topical No further details mentioned	Exposure was defined by the use of corticosteroids (alone or in combination). ATC codes gave information on all corticosteroids.	First trimester	Not reported

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		malformed infants exposed to drugs in different parts of the world) data collected from 1990-2002 was analysed	palate or cleft lip); group II: code 749.0 (cleft palate); and group III: code 749.1 or 749.2 (cleft lip or cleft lip with cleft palate)					
(Robert et al., 1994)	Case-control Study	Cases have been reported by eight programs: Australia, Central-East France, Israel, Italy IPIMC, Italy IMER, Japan Red Cross Hospitals, Japan Maternal Health and Welfare, and South America. By searching this databank for associations between drugs and	9th revision of the WHO International Classification of Diseases (ICD9)/ British Paediatric Association (BPA) (for drugs and malformations, respectively) CL, CP, cleft lip and palate, CLP	Systemic	Not applicable	International Clearinghouse for Birth Defect Monitoring Systems is named MADRE: Malformation Drug Exposure surveillance The MADRE collects data continuously on malformed infants exposed to drugs in different parts of the world. This paper reports on the analysis of material accumulated during the first 2 years.	First trimester	Not reported

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		malformations, specific relationships can be detected. In 1990 and 1991 reports came from eight programs, all collecting exposure data retrospectively and reporting monthly, quarterly or once in every 6-month period						
(Rodríguez-Pinilla and Luisa Martínez-Frías, 1998)	Case-control Study	Data was derived from the Spanish Collaborative Study of Congenital Malformations (ECEMC) based on a hospital-based case-control study and surveillance system. For	Cleft lip (with or without cleft palate)	Systemic	Not applicable	Staff examined the children within the first 3 days of life to identify major and/or minor/mild defects.	First trimester of pregnancy	Adjusted/controlled for potential confounder factors, such as maternal smoking, maternal hyperthermia, first-degree malformed relatives with cleft lip with or without cleft palate, and maternal treatment with antiepileptics, benzodiazepines, metronidazole, or sex hormones during the first trimester of pregnancy

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		each malformed baby, the next nonmalformed infant of the same sex born in the same hospital is selected as a control subject. April 1976 - December 1995						
(Skuladottir et al., 2014a) (MoBa)	Cohort Study	Cases within the cohort were identified by linking all cohort members with the Medical Birth Registry, which includes information on all defects recorded during the newborn's hospital stay 1999 – 2008	Cleft lip with or without cleft palate (CLP), and cleft palate only (CP)	Dermatological	Data presented for dermatological route No further details mentioned	Mothers in the study were asked to complete self-administered questionnaires at pregnancy week 15, 22 and 30. We used information from the 15-week questionnaire, which focuses on maternal health and use of medications 6 months before pregnancy and during the first 15 weeks of pregnancy.	First trimester of pregnancy	The timing of exposure (spanning from 6 month prior to pregnancy to the 15th week) is reported for each condition/symptom and not for each medication. Adjustment were made for: folic acid use (400 ug/day or none), smoking (none, passive only, active smoker), mother's education (less than high school, high school or more) and alcohol consumption (none or any)
(Skuladottir et al.,	Nested case-	Information for cases on accompanying	Total clefts and the two main cleft	Dermatological Other use	Data presented for	Information on medications was collected for only the first	First-trimester (first three months of	Adjusted for the following potential confounders: mother's

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2014a)(NCS)	control Study	birth defects or syndromes was obtained from three sources: medical records at the hospital performing corrective surgery, the Medical Birth Registry, and the mothers' questionnaire. From 1996 - 2001 the families of all newborn infants in Norway referred for clefts surgery were invited to participate in a case-control study. Controls were randomly selected from all live births during the same time	subtypes (cleft lip with or without cleft palate [CLP], and cleft palate only [CP])	(unspecified use)	dermatological route No further details mentioned	three months of pregnancy. Medication was coded according to the Anatomical Therapeutic Chemical Classification System (ATC)	pregnancy, which is the period during which exposures can potentially affect the embryological fusion of the lip (around week 4 - 6 of embryonic life) and palate (around week 7 - 10))	education, work status in early pregnancy (yes/no), alcohol intake (total number of drinks during first 3 months of pregnancy), smoking (none, passive only, cigarettes/day), folic acid supplementation (none, ≤400 ug/day), dietary folates, multivitamin supplementation (yes/no), and calendar year of baby's birth

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		period, sampling from the Medical Birth Registry of Norway. Parents of both cases and controls were recruited within the first three months after delivery.						
(Skuladottir et al., 2014b)	Case-control Study	National Birth Defect Prevention Study (NBDPS), 2003-2009 Ascertainment of cases and controls born since 1997 Infants or fetuses with CLP or CPO were considered -Cases and analyzed separately. Case status was	Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO)	Topical Inhaled Systemic Other use (Unspecified use)	Data presented for topical route No further details mentioned	Medications were coded according to the Slone Epidemiology Center Drug Dictionary	4 weeks before through 12 weeks after conception	Associations were examined after adjustment for several covariates, such as: Maternal, race-ethnicity, Education, Intake of folic acid-containing supplements, Smoking, Study center

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		ascertained either through clinical or surgical records or autopsy reports. Medical records for all cases were assessed by a clinical geneticist who ensured that they fulfilled the eligibility criteria -Controls (live born infants, without birth defects) were randomly selected from hospital birth records or birth certificates at each study center						