# Observational Study Results Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Overall data disclosed, may differ from published or presented data and are a reflection of the limited information provided here. The results from a single study need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

# 1. Abstract

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| **Acronym/Title** | Risk association of orofacial cleft and Corticosteroids exposure during pregnancy: a meta-analysis (GC_OC) |
| **Report version and date**<br>**Author** | 1.0, 15 Jul 2020<br>PPD PPD<br>PPD PPD<br>PPD PPD<br>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. |

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| **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).<br><br>Data analysis<br>• Direct treatment comparison: Use of any corticosteroid irrespective of route of administration vs. no use of corticosteroids.<br>• 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.<br>• Measure of relative effect: Dichotomous outcomes were assessed by OR.<br>• Inverse variance method was used to assess the association between treatment and observed OFC occurrence.<br>• 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.<br>• 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.<br>• Data was analysed by meta package in R software version 3.5.1.<br>• Outcome results were presented as OR (mean, 95% CI). |

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| | 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.<br>The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) were employed for reporting of included studies.<br><br>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:<br>• OFC: cleft lip and/or cleft palate<br>Route of administration of corticosteroids:<br>• 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'.<br>Data sources:<br>• Embase and Medline via Ovid®, Cochrane database, Google Scholar were used for data collection.<br>• All records retrieved from the literature searches were screened for relevance based on eligibility criteria (inclusion/exclusion). Relevant back |

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| | 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.<br>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).<br>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, |

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| | skin conditions and extent of dermatological application were not reported, which may have influenced the absorption of corticosteroids and potentially altered effect outcomes.<br>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. |
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