

**Title: Prenatal incidence of cleft lip/palate and cocaine abuse in parents: a systematic review and meta-analysis**

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**Abstract: Background:** The study aimed to investigate the association between maternal cocaine abuse during pregnancy and the prevalence of cleft lip/palate (CL/P) in offspring, synthesizing existing evidence through a systematic review and meta-analysis. CL/P is a congenital craniofacial anomaly with complex etiology, and prior research has suggested potential links between maternal cocaine use and CL/P. However, these associations remain inconclusive. **Methods:** A comprehensive literature search was conducted to identify relevant studies published up to the study's cutoff date in September 2021. Several databases were systematically searched using predefined search terms. Inclusion criteria were set to encompass studies reporting on the prevalence of CL/P in infants born to mothers with a history of cocaine use during pregnancy, with a comparison group of non-cocaine-using mothers. Data were extracted, and a meta-analysis was performed using a random-effects model to calculate pooled odds ratios (OR) and relative risks (RR) with their respective 95% confidence intervals (CI). **Results:** The review included data from 4 studies that met the inclusion criteria. The combined OR from two studies was 0.05 (95% CI: 0.00, 4.41), which does not suggest a statistically significant association between prenatal cocaine exposure and the incidence of CL/P due to the confidence interval crossing the null value. Additionally, the combined RR was 0.17 (95% CI: 0.04, 0.66), indicating a statistically significant decrease in the risk of CL/P associated with prenatal cocaine exposure. These results, with an OR that is not statistically significant and an RR suggesting decreased risk, should be interpreted with caution due to considerable heterogeneity and variability among the included studies' findings. Further research is needed to clarify these associations. **Conclusion:** The findings from this systematic review and meta-analysis suggest that maternal cocaine use during pregnancy is not a statistically significant independent risk factor for the development of CL/P in offspring. These results underscore the multifactorial nature of CL/P etiology and emphasize the importance of considering other genetic, environmental, and nutritional factors in understanding the condition's origins. While the study provides important insights, limitations such as data heterogeneity and potential confounders should be acknowledged. Future research should adopt rigorous study designs and explore a broader range of potential risk factors to comprehensively elucidate CL/P development.

**Key words:** Cleft lip/palate; Cocaine abuse; Congenital anomaly; Maternal substance use; Prenatal exposure.

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