PERINATAL JOURNAL

Original Article

Perinatal Journal 2026; 34(2):294-298

https://doi.org/10.57239/prn.26.03420028

Association of maternal random blood glucose and blood pressure with cleft lip and palate and microtia in newborns: A retrospective cohort study

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Abstract

Cleft Lip And/Or Palate (CLP) and microtia are congenital craniofacial anomalies with multifactorial etiologies. Maternal metabolic and vascular disturbances such as hyperglycemia and hypertensive disorders have been proposed as potentially modifiable risk factors for congenital malformations. This study was conducted to evaluate the association between maternal Random Blood Glucose (RBG) levels and blood pressure parameters (systolic, diastolic, and mean arterial pressure/MAP) and the occurrence of CLP, microtia, or combined CLP + microtia in newborns. A retrospective cohort study with total sampling was conducted using medical records from two tertiary referral centers in Surabaya, Indonesia (January 2023 – December 2024). Maternal Random Blood Glucose (RBG) levels and blood pressure during pregnancy were compared across three outcome groups: CLP, microtia, and combined CLP + microtia. RBG was analyzed using the Kruskal–Wallis test, while blood pressure variables were analyzed using one-way ANOVA. Statistical significance was defined as $p < 0.05$. A total of 27 newborns met the inclusion criteria (CLP n=21, microtia n=6, and combined CLP + microtia n=3). Maternal RBG levels did not differ significantly among the outcome groups (Kruskal–Wallis, p=0.344). Similarly, systolic, diastolic, and MAP values showed no significant differences (ANOVA, p=0.930, p=0.280, and p=0.340, respectively). In this retrospective cohort, maternal RBG levels and blood pressure parameters were not significantly associated with the occurrence of CLP, microtia, or combined CLP + microtia. Further large-scale prospective studies incorporating standardized metabolic assessments and additional maternal–environmental covariates are warranted.

Keywords: Association of maternal, Random blood glucose, Blood pressure with cleft lip

1. Introduction

Microtia and Cleft Lip And/Or Palate (CLP) are congenital abnormalities in the craniofacial region. CLP has a prevalence of approximately 1–7 per 1,000 births [1]. Gender variation is also observed with 2:1 male-to-female gender predominance for CL/P versus a 1:2 male-to-female gender predominance for isolated cleft palate. Delayed fusion of the palatal shelves in females has been proposed as a contributing factor for the higher incidence of isolated cleft palate in females [2]. The global incidence microtia is commonly reported between 0.8 and 4.3 per 10,000 live births, with a male predominance and a tendency for unilateral right-sided involvement; cases may occur in isolation or as part of syndromic associations [3,4].

Epidemiologic evidence suggests that cleft lip with or without Cleft Palate (CL/P) is associated with several maternal exposures and conditions. The most consistent findings include maternal active smoking and pre-pregnancy obesity, both of which demonstrate modest but statistically significant risk increases in meta-analyses [5,6]. Meanwhile, pre-gestational diabetes has been repeatedly associated with markedly higher risks of multiple structural birth defects, including craniofacial anomalies, highlighting the importance of glycemic control before conception [7]. Contemporary literature highlights a range of modifiable maternal risk factors such as tobacco and alcohol exposure, nutritional status including folate intake, maternal obesity or underweight, and medication/teratogen exposure [8,9]. For microtia/anotia, stronger and more reproducible associations have been reported with maternal diabetes and certain teratogenic exposures, particularly isotretinoin/retinoids, which are classically associated to external ear malformations as part of the retinoid embryopathy spectrum [7,10].

Maternal hyperglycemia is a well-recognized

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teratogenic exposure associated with a broad range of congenital malformations. During early pregnancy, hyperglycemia can increase reactive oxygen species and dysregulate developmental gene expression, potentially affecting neural crest cell survival and migration [11,12]. While gestational diabetes is often diagnosed later in pregnancy and may confer modest risk elevations, pregestational type 1 or type 2 diabetes is associated with substantially higher risks of structural birth defects, supporting the concept of a diabetic embryopathy in susceptible pregnancies [12].

Hypertensive disorders of pregnancy, including chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome, reflect maternal vascular dysfunction and impaired uteroplacental perfusion. These conditions are also associated with long-term maternal cardiovascular risk [13–15] and have also been investigated for possible relationships with congenital malformations in offspring. A large World Health Organization multicountry study suggested that hypertensive disorders may be associated to increase risks of congenital malformations [16], while more recent cohort data have reported that preeclampsia may increase the risk of nonsyndromic orofacial clefts [17]. The multiple logistic regression model in this study identified several significant risk factors associated with an increased risk of microtia: a maternal history of abortion or stillbirth in a previous pregnancy (4.74–4.96-fold), maternal diabetes (6.46-fold), maternal hypertension (4.18-fold), maternal smoking or exposure to secondhand smoke (2.06-fold), paternal smoking or exposure to secondhand smoke (2.42–2.83-fold), not receiving TORCH vaccination (1.59–2.02-fold), and a family history of microtia (5.36-fold), all of which significantly increased the risk of microtia (p-value < 0.05) [18].

Despite growing international evidence, local Indonesian data exploring the association of maternal metabolic and hemodynamic parameters with CLP and microtia—especially combined CLP + microtia cases—remain limited. This study aimed to assess whether maternal random blood glucose and blood pressure measurements during pregnancy are associated with the occurrence of CLP, microtia, or combined CLP + microtia among newborns treated at two tertiary referral centers in Surabaya, Indonesia.

Methods

This retrospective cohort study employed a total sampling approach using secondary data from medical records of newborns treated at general hospital and university hospital in Surabaya, Indonesia, between January 2023 and December 2024. Eligible participants were newborns diagnosed with Cleft Lip And/Or Palate (CLP), microtia, or concurrent CLP + microtia, provided that maternal random blood glucose (RBG) and maternal blood pressure measurements during pregnancy were documented in the records. Newborns with incomplete documentation of key maternal measurements, particularly missing RBG or blood pressure data, were excluded from the analysis.

The independent variables comprised maternal RBG levels (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and mean arterial pressure (MAP, mmHg). The dependent variable was the newborn condition, categorized into three groups: CLP, microtia, and CLP + microtia. Continuous variables were summarized as mean ± Standard Deviation (SD) for approximately normally distributed data and as median (minimum–maximum) for skewed distributions. Data normality was assessed using the Shapiro–Wilk test given the sample size of fewer than 50 participants.

Maternal RBG were analyzed using the Kruskal–Wallis test, followed by Mann–Whitney U tests for pairwise comparisons when appropriate, whereas maternal blood pressure variables were analyzed using one-way analysis of variance (ANOVA) with post-hoc pairwise comparisons. All statistical analyses were performed using a two-sided approach, and a p-value of <0.05 was considered statistically significant.

Results

A total of 30 newborns met inclusion criteria, comprising 21 cases of CLP, 6 cases of microtia, and 3 cases with combined CLP + microtia. Maternal RBG values were not normally distributed on Shapiro–Wilk testing, whereas systolic blood pressure, diastolic blood pressure, and Mean Arterial Pressure (MAP) showed approximate normal distributions.

Maternal RBG did not differ significantly among the three outcome groups (Kruskal–Wallis p=0.344). Pairwise Mann–Whitney comparisons were also non-significant (CLP vs microtia p=0.641; CLP vs CLP + microtia p=0.150; microtia vs CLP + microtia p=0.634).

Mean systolic blood pressure differed minimally among groups (microtia 122.83 mmHg; CLP + microtia 126.00 mmHg; CLP 126.19 mmHg) and was not significantly different by one-way ANOVA (p=0.930). Similarly, mean diastolic blood pressure (microtia 78.83 mmHg; CLP + microtia 82.33 mmHg; CLP 85.14 mmHg) demonstrated no significant differences (p=0.280). Mean MAP values (microtia 93.53 mmHg; CLP + microtia 96.89 mmHg; CLP 98.82 mmHg) were likewise not significantly different across outcome groups (p=0.340) (see Table 1).

Table 1. Maternal random blood glucose and blood pressure by newborn condition

Variable	CLP (n=21)	Microtia (n=6)	CLP+Microtia (n=3)	p-value
Random blood glucose, median (min–max), mg/dL	103/81	119.50	109.67	0.344*
Systolic BP, mean, mmHg	126.19	122.83	126.00	0.930†
Diastolic BP, mean, mmHg	85.19	77.00	85.33	0.280†
MAP, mean, mmHg	98.85	92.27	86.22	0.340†

*Kruskal–Wallis test. †One-way ANOVA

Discussion

This study evaluated whether maternal random blood glucose and blood pressure during pregnancy were associated with the occurrence of CLP, microtia, or combined CLP + microtia. In this cohort, maternal RBG showed no statistically significant differences among outcome groups, and systolic/diastolic blood pressure as well as MAP similarly did not differ significantly. These findings may indicate that, within the present dataset, single-point maternal metabolic and hemodynamic measurements were not independently associated with the observed distribution of craniofacial outcomes.

The absence of significant associations with RBG should be interpreted in light of the broader literature on hyperglycemia and congenital anomalies. Hyperglycemia is known to exert teratogenic effects through oxidative stress, dysregulation of key developmental pathways, and impairment of neural crest cell function during early organogenesis [11,12]. Nonetheless, the magnitude of risk for specific anomalies varies by diabetes subtype, glycemic control, and timing of exposure. In particular, pregestational diabetes is generally associated with substantially higher rates of malformations compared with gestational diabetes, which is often identified later in pregnancy and may carry more modest risk elevations [12]. In our study, RBG values were obtained from routine clinical records rather than standardized HbA1c or oral glucose tolerance testing; therefore, these values may not accurately capture early-pregnancy glycemic exposure during critical windows of craniofacial development.

With respect to blood pressure, hypertensive disorders of pregnancy reflect maternal vascular dysfunction and are associated with long-term cardiovascular morbidity [13–15]. A World Health Organization multicountry survey reported that hypertensive disorders may be associated with congenital malformations in offspring [16], and recent cohort data suggest a relationship between preeclampsia and increased risk of non-syndromic orofacial clefts [17]. However, blood pressure values in clinical records may not adequately classify hypertensive disorders (e.g., transient elevated readings versus chronic hypertension or preeclampsia), and the pathophysiologic mechanisms are likely heterogeneous. It is plausible that only severe or sustained placental vascular compromise contributes meaningfully to craniofacial malformation risk, which might not be reflected by mean blood pressure values alone.

In addition, both CLP and microtia are strongly influenced by non-metabolic factors. Genetic predisposition and a range of environmental exposures—including nutritional status, smoking,

alcohol, and certain medications—have been consistently implicated as risk modifiers [8,9,19]. Therefore, the lack of association in our cohort may reflect residual confounding and the multifactorial nature of these anomalies. The combined CLP + microtia group was small (n=3), further limiting inference for this subgroup.

This study has important limitations. First, the sample size was limited, reducing statistical power and the ability to detect modest associations. Second, the retrospective design relies on data completeness and clinical recording practices, which may introduce measurement error and selection bias. Third, we were unable to adjust for key maternal covariates such as body mass index, smoking status, folate supplementation, medication exposure, infection history, and family history.

Despite these limitations, this study provides preliminary local evidence on maternal RBG and blood pressure in relation to two clinically significant craniofacial anomalies. Future prospective studies with larger sample sizes, standardized metabolic assessments (including fasting glucose, HbA1c, and/or oral glucose tolerance testing), longitudinal blood pressure profiling, and comprehensive evaluation of established maternal risk factors such as pregestational diabetes, gestational diabetes, body mass index, medication exposures, infections, smoking status, nutritional status, and periconceptional folate supplementation, are recommended to clarify the contribution of maternal glycemic and hypertensive exposures to craniofacial anomaly risk in Indonesian populations.

Conclusion

In this retrospective cohort, maternal random blood glucose and maternal blood pressure parameters recorded during pregnancy were not significantly associated with the birth of infants with cleft lip and palate, with or without microtia. Future studies should adopt prospective, adequately powered designs and incorporate standardized metabolic and hemodynamic maternal profiles assessments to clarify the risk spectrum of craniofacial anomalies and provide preventive strategies or risk stratification in antenatal care.

Author contributions: Conceptualization, J.I.H., M.R.H., and I.L.P.; methodology, J.I.H.; software, J.I.H. and I.F.A.; validation, M.R.H.; formal analysis, J.I.H.; investigation, J.I.H.; data curation, J.I.H.; writing—original draft preparation, J.I.H.; writing—review and editing, I.L.P. and M.R.H.; visualization, I.F.A.; supervision, I.L.P.; project administration, I.F.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Acknowledgements: The authors gratefully acknowledge all participants who were willing to participate in this research and all the authors who contributed to this original research.

Ethics statement: None. Studies involving humans and animals must have been performed with the approval of an appropriate ethics committee and provide the reference number.

Conflict of interest: The authors declare that there are no conflicts of interest or competing interests associated with this manuscript.

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