Ali *et al.,* Babcock Univ. Med. J.2026 9(2):239-245
https://doi.org/10.38029/babcockuniv.med.j..v9i2.1432
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

In-vitro fertilisation as an independent risk factor for bilateral cleft lip and palate: A multicentre clinical and maxillofacial analysis

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Submitted: 1st December 2025
Accepted: 7th March 2026
Published: 30th June 2026
ID: Orcid ID

Abstract
Objective: To determine whether in-vitro fertilisation (IVF) is associated with increased rates and severity of cleft lip and/or palate (CLP), and to identify associated maxillofacial and perinatal factors
Methods: A retrospective multicentre clinical study was done using 250 children with cleft lip, cleft palate and combined cleft lip and palate, who received treatment in maxillofacial surgery centres. Out of them, 80 children were conceived by IVF, and 170 were conceived naturally. The medical records gathered data on clinical characteristics such as cleft type, maxillofacial features, maternal age, birth weight and pregnancy-related factors. The chi-square and independent t-tests were used to compare statistical differences across groups. The multivariate logistic regression analysis was used to determine the independent predictors of bilateral cleft lip and palate.
Results: Children conceived through IVF had significantly higher rates of bilateral CLP compared to naturally conceived children (25% vs. 11.8%, p=0.02). The IVF group also showed more severe maxillary involvement, including wider alveolar clefts (47.5% vs. 30.6%, p=0.03) and greater maxillary hypoplasia (37.5% vs. 22.4%, p=0.02). IVF remained an independent risk factor for bilateral CLP after multivariate analysis (adjusted OR 2.4, 95% CI 1.1-5.1, p=0.03).
Conclusion
IVF conception is associated with more severe, bilateral forms of CLP, independent of maternal and perinatal factors. These findings support enhanced prenatal counselling and multidisciplinary planning for families undergoing IVF.

Keywords: In-Vitro Fertilisation (IVF), Cleft Lip, Cleft Palate, Craniofacial Development, Maxillofacial Surgery

Plain English Summary

This paper has investigated the existence of a difference in cleft lip and palate patterns of children who were conceived through in vitro fertilisation IVF and those who were conceived naturally. Through the review of medical records of several maxillofacial centres, we detected that children who were conceived using IVF demonstrated a greater ratio of bilateral cleft lip and palate with additional severe involvement on the maxillary side. These results indicate that the initial embryonic states related to assisted reproductive technologies could affect craniofacial development. The findings create the significance of prenatal counselling and multidisciplinary management of families undergoing IVF.

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Introduction

Cleft lip and /or palate (CLP) is one of the most prevalent congenital craniofacial abnormalities across the globe, with about 700 live births per 1000 affected. Such conditions pose serious functional and psychosocial problems, such as feeding disorders and speech disorders, dental problems and facial developmental abnormalities that may need lifelong multidisciplinary care both in childhood and adulthood (1, 2). The pathogenesis of CLP is multifactorial and multifaceted and includes interplay between genetic vulnerability, exposure to environmental factors, maternal health outcomes, and epigenetic control processes that affect craniofacial morphogenesis in early embryonic development (1, 2).

Assisted reproductive technologies (ART), especially in vitro fertilisation (IVF), have gradually become more frequently applied in the treatment of infertility in recent decades. Even though IVF has helped millions of couples to have successful pregnancies, there are concerns that there may be some effects of early embryonic manipulations on fetal development. Some epidemiological research and meta-analyses have indicated that ART offspring are at a very small risk of congenital anomalies, such as cleft lip and palate, as craniofacial defects (3, 4). Biological plausibility of this association has been attributed to the role of ovarian stimulation, laboratory culture conditions, and gamete manipulation on the critical stages of early embryogenesis. New studies indicate that ART procedures could induce a change in epigenetic control in pre-implantation development. DNA methylation, histone modification and microRNA expression are epigenetic processes which are vital in the regulation of gene expression during craniofacial development (5, 6, 7). These processes can be disrupted and lead to possible interventions with the migration of the neural crest cell, palatal shelf elevation and midfacial fusion, which play a vital role in normal craniofacial development. Embryos and tissues related to orofacial clefts have been found to exhibit abnormal patterns of epigenetics, implicating the possibility that developmental anomalies during early development may be a contributory factor to clefts (8, 9). The possibility that maternal and perinatal factors affect the risk of craniofacial anomalies also exists. The use of advanced maternal age, multiple gestation and low birth weight has been reported more in the case of IVF pregnancies and has been linked to adverse developmental outcomes, including congenital anomalies (10, 11). Besides, the development of prenatal imaging has enhanced the early detection of cleft lip and palate, resulting in the early counselling and multidisciplinary planning of affected infants (12). Despite the accumulated evidence, the results involving the connection between IVF and cleft lip and palate turned out to be inconsistent. Some studies indicate a higher risk in the case of ART, but others indicate no significant difference in the case of adequate control of the maternal and perinatal factors (3, 4). Such discrepancies underscore the importance of more clinical trials that would be able to evaluate the occurrence as well as the severity and maxillofacial appearance of cleft anomalies in children conceived through IVF. Knowledge of the biological and clinical factors of orofacial clefts would be crucial in enhancing prevention measures and treatment. The most recent studies in genetic research have shown that several developmental pathways play a role in the formation of the craniofacial, and a break in any of the pathways can cause structural defects of different degrees (13, 14). In turn, the assessment of the possible connection between reproductive technologies and craniofacial anomalies can help to enhance the process of prenatal counselling, early detection, and planning of multidisciplinary care.

Hence, the current research intended to examine the relationship between IVF conception and the occurrence and severity of cleft lip and/or palate in children who had been treated in maxillofacial surgery units. In particular, the research aimed to compare the prevalence of cleft in the offspring of IVF and natural conception, assess indicators of the severity of maxillofacial appearance, and assess maternal and perinatal factors that could contribute to the prevalence and severity of CLP.

Materials and Methods

Study Design and Setting

The research design used a retrospective analytical clinical study, which took place across multiple maxillofacial surgery centres. The research aimed to determine if in vitro fertilisation (IVF) leads to different rates of cleft lip and/or palate (CLP) occurrence and severity. The research used multiple centres to minimise selection bias while making the study more diverse and increasing its real-world application.

Study Population

The research included children who received cleft lip (CL) and cleft palate (CP) and combined cleft lip and palate (CLP) treatment at participating centres during the study duration. The researchers established two separate groups based on how participants conceived their children.

IVF Group
The research studied children who developed through IVF treatments and associated ART procedures.

Control Group
The research involved children who developed naturally without any medical treatment.
The research studied children from birth to age five because this period includes most initial cleft treatments and enables scientists to obtain vital data about mothers and their childbirth experiences.

Inclusion and Exclusion Criteria
The patients in the study were considered eligible when they were diagnosed with cleft lip (CL), cleft palate (CP), or cleft lip and palate (CLP) through clinical examination and radiographic assessment. The participants were to be eligible if they had full maternal and perinatal information in the medical records, including the mode of conception. Besides, informed consent in written format was required to be signed by the parent(s) or legal guardian before admission to the study. Patients were not included if they presented with syndromic clefts or other congenital anomalies of the system. The cases in which there were no or limited medical records about conception information were also omitted. Moreover, patients whose prenatal exposure to teratogenic medications was documented were excluded from the analysis.

Data Collection Procedures
Statistical Analysis
Diagnosis was made by clinical examination and imaging. Electronic medical records and parental interviews were used to extract data that was standardised. The variables obtained consisted of a number of child, maternal, and perinatal variables. The data unwound the child-related information, including age, sex, cleft type, cleft laterality, cleft maxillofacial, and surgical history. Mother variables were age at conception, parity, infertility in the past, lifestyle, and pregnancy complications. Perinatal birth information, including gestational age, birth weight, mode of delivery and multiple gestation, was also recorded. Data on IVF procedures were taken where possible; this involved incidences of ovarian hyperstimulation and preimplantation genetic diagnosis (PGD). The clefts with lip and palate were categorised with the Veau classification system based on the standard morphological criteria. Assessment of maxillofacial features was done by clinical assessment, panoramic radiograph, and three-dimensional computed tomography (3D CT) when accessible.
Analysis of data was done through the SPSS program. Frequencies and percentages were used to show the categorical variables, whereas means and standard deviations (SD) were used to show the continuous variables. Independent t-tests of the continuous variables and Chi-square tests of the categorical variables were used to differentiate the two groups of IVF-concepted and naturally conceived. Multivariate logistic regression analysis was used to determine independent predictors of cleft lip and palate severity by adjusting for maternal age, parity and multiple gestation. The p-value below 0.05 was taken as significant.

Results
Study Population Characteristics
A total of 250 children diagnosed with cleft lip and/or palate (CL/CP/CLP) met the inclusion criteria. Out of the 250 children, 80 children (32 per cent) were conceived through in-vitro fertilisation, and 170 children (68 per cent) were conceived naturally. The mean age of the children at the time of assessment was 2.3 ± 1.1 years. The male-to-female ratio was approximately 1.2:1. showing the male predominance that is often reported in cleft epidemiology (Table 1).

Table 1. Baseline demographic characteristics of IVF-conceived and naturally conceived children with CLP

Variable	IVF Group (n = 80)	Natural Conception (n = 170)	p-value
Mean age (years)	2.4 ± 1.0	2.3 ± 1.2	0.52
Male (%)	45 (56.3%)	90 (52.9%)	0.61
Birth weight (kg)	2.8 ± 0.5	3.1 ± 0.4	0.01
Maternal age (years)	34.5 ± 4.2	28.7 ± 3.8	<0.001
Multiple gestation (%)	18%	3%	<0.001

In Table 2, compared with the naturally conceived group, the IVF group demonstrated significantly higher maternal age, lower mean birth weight, and a higher rate of multiple gestation. Significant differences were observed between the two groups. Unilateral clefts were common in both groups. Bilateral cleft lip and palate (BCLP) was more frequently observed in the IVF group. The

higher rate of BCLP in the IVF group points to a shift toward severe facial and jaw involvement.

Table 2. Distribution of Cleft Types Among IVF and Naturally Conceived Children

Cleft Type	IVF Group (n = 80)	Natural Group (n = 170)	p-value
Unilateral cleft lip	15 (18.8%)	40 (23.5%)	0.45
Bilateral cleft lip	5 (6.2%)	10 (5.9%)	0.91
Cleft palate only	20 (25%)	60 (35.3%)	0.12
Unilateral CLP	24 (30%)	48 (28.2%)	0.73
Bilateral CLP	20 (25%)	20 (11.8%)	0.02

The results demonstrated that IVF children developed BCLP at a rate which exceeded twice that of the control group (25% vs. 11.8%), and the difference reached statistical significance (p = 0.02). Research indicates that cleft severity develops based on particular embryonic conditions which emerge during ART treatment.

Maxillofacial Severity Indicators

The IVF group needed extensive treatment because their maxillary problems were more severe than those of the other groups. The children required advanced surgical procedures for their first maxillary repair because they presented with wider alveolar gaps and major maxillary growth deficiencies (Table 3).

Table 3. Maxillofacial severity indicators among IVF and naturally conceived children

Maxillofacial Parameter	IVF Group	Natural Group	p-value
Alveolar cleft width > 5 mm	38 (47.5%)	52 (30.6%)	0.03
Maxillary hypoplasia	30 (37.5%)	38 (22.4%)	0.02
Mandibular anomalies	6 (7.5%)	11 (6.5%)	0.78

The repeated pattern of maxillary involvement in IVF cases indicates that embryos might have genetic or environmental weaknesses which affect their development.

Maternal and Perinatal Factors

The maternal characteristics between groups showed distinct patterns of variation. The pregnancies from IVF treatments showed three significant differences from natural pregnancies:

The mothers who carried IVF babies were older than average.

The IVF pregnancies resulted in more than one fetus at birth.

The average weight of babies born through IVF was lower than the average.

The development of craniofacial structures shows signs of being affected by these elements.

The analysis included these factors for multivariate regression modelling.

Multivariate Logistic Regression Analysis

The research confirmed that IVF status retained its status as an independent risk factor for bilateral cleft lip and palate after researchers included maternal age, birth weight and multiple gestations and parity in their analysis (Table 4).

Table 4. Logistic Regression Analysis of Predictors of Bilateral CLP

Variable	Adjusted OR	95% CI	p-value
IVF conception	2.4	1.1 – 5.1	0.03
Maternal age	1.08	0.98 – 1.20	0.11
Multiple gestation	1.9	0.9 – 3.7	0.08
Low birth weight	1.4	0.95 – 2.8	0.10

These results suggest that the association between IVF and higher CLP severity is not fully explained by maternal or perinatal variables, pointing toward IVF-related biological processes as plausible contributing factors.

Discussion

This multicentre study demonstrates that children conceived through IVF present with more severe orofacial clefts, particularly the bilateral form, compared to naturally conceived children. The finding that IVF-conceived children had twice the rate of bilateral CLP and more extensive maxillary involvement suggests that factors inherent to

assisted reproductive technologies may influence early craniofacial development. These results align with previous epidemiological studies reporting increased risks of congenital anomalies following ART (1, 2, 3).

Several biological processes can be attributed to the fact that IVF has been associated with more serious cleft phenotypes. In assisted reproductive procedures, the embryos are subjected to diverse unnatural conditions such as ovarian hyperstimulation, in vitro culture conditions and laboratory manipulation of gametes and embryos. These aspects have the potential to affect early embryonic development and change the regulation of genes that regulate the morphogenesis of the craniofacial morphology (3, 4). The dysfunction of the migration of neural crest cells, palatal shelf elevation, or midfacial fusion at early developmental stages could be the reasons behind bilateral cleft lip and palate, which is one of the most terrible forms of orofacial clefting.

Epigenetic regulation is another potential mechanism that has been suggested to be related to the ART procedures and developmental abnormalities. It has been experimentally and clinically proven that patterns of DNA methylation, histone modifications and microRNA expression have central functions in the regulation of craniofacial development (5, 6, 7). A change in these epigenetic processes in early embryonic development can influence any genes that control the proliferation of neural crest cells and differentiation of craniofacial tissue. Recent molecular studies have found abnormal methylation patterns in tissues from patients with orofacial clefts, which do support the hypothesis that epigenetic dysregulation could be part of the pathogenesis of CLP (8, 9).

The maternal and perinatal characteristics were also found in the present study, which patterns are also consistent with previous researchers. The IVF pregnancies were also characterised by higher maternal age, high multiple gestation and low birth weight as compared to naturally conceived pregnancies. These are identified to be the possible contributors to poor developmental outcomes, and they may affect craniofacial development in foetal development (10, 11). The increased risks of the occurrence of chromosome instability and the dysfunction of the placenta have been linked to advanced maternal age, both of which can potentially influence the morphogenesis of the foetus.

These results have important clinical implications, especially in the maxillofacial management of victims. Increased bilateral clefts and greater maxillary hypoplasia in IVF-conceived children imply that these children might need more complicated surgical and orthodontic treatment. The early recognition of extreme patterns of clefts could consequently aid better treatment planning, which entails coordinated surgical correction, orthodontic care, and speech therapy interventions in multidisciplinary cleft care teams (12).

The genetic and developmental processes underlying CLP remain critical to understanding prevention and treatment. Recent advances in craniofacial genetics have identified several signalling pathways that govern foetal facial development; disruption of these pathways can produce a range of cleft phenotypes with varying severity (13, 14). Therefore, investigating the interactions between reproductive technologies, genetic susceptibility, and environmental factors could yield valuable insights into the pathogenesis of orofacial clefts. Despite these findings, several limitations must be considered when interpreting the results of this study. It is possible that the retrospective study design will lead to the risk of information bias, especially when it comes to the maternal and prenatal variables. Moreover, the study (despite the control of numerous significant factors) could not consider the impact of other possible confounding variables, such as genetic predisposition, environmental exposures, etc. The prospective multicentre studies in the future that will involve genetic and epigenetic studies can be beneficial in explaining the biological processes that follow the identified relationship between IVF and CLP severity.

On the whole, the findings of the current research can be added to the existing amount of literature that supports the idea that assisted reproductive technologies can have an impact on early craniofacial development. Although the absolute risk is still quite small, the realisation of the possible relationship between cleft severity and IVF could help to enhance prenatal counselling, early diagnosis, and a multidisciplinary management approach towards the impacted children. efts.

Conclusion

This study suggests that in vitro fertilisation may be associated with an increased severity of cleft lip and/or palate, especially when the condition affects both sides of the face. The study found that IVF conception was identified as an independent risk factor for increased cleft severity. The research indicates IVF children develop larger alveolar clefts and significant maxillary problems, which need urgent medical assessment and collaborative treatment from a team of specialists. The study's

retrospective design makes it impossible to establish cause-and-effect relationships, but it shows that future research needs to study how reproductive technology affects facial development.

Study Limitations
In spite of such findings, there are a number of limitations that need to be taken into consideration when interpreting the findings in this study. It is possible that the retrospective study design will lead to the risk of information bias, especially when it comes to the maternal and prenatal variables. Moreover, the study (despite the control of numerous significant factors) could not consider the impact of other possible confounding variables, such as genetic predisposition, environmental exposures, etc. The prospective multicentre studies in the future that will involve genetic and epigenetic studies can be beneficial in explaining the biological processes that follow the identified relationship between IVF and CLP severity.
On the whole, the findings of the current research can be added to the existing amount of literature that supports the idea that assisted reproductive technologies can have an impact on early craniofacial development. Although the absolute risk is still quite small, the realisation of the possible relationship between cleft severity and IVF could help to enhance prenatal counselling, early diagnosis, and a multidisciplinary management approach towards the impacted children.

List of Abbreviations
ART: Assisted Reproductive Technology
BCLP: Bilateral Cleft Lip and Palate
CI: Confidence Interval
CLP: Cleft Lip and/or Palate
CT: Computed Tomography
IVF: In-Vitro Fertilisation
OR: Odds Ratio
SD: Standard Deviation

Declarations:
Ethics Approval and Consent to Participate
The study was ethically approved by the Scientific Committee of the Gilgamesh University (NO.19, 2025). All experiments were performed in accordance with the ethical standards of an institutional/national research committee and the 1964 Helsinki Declaration and its later amendments.

Consent for Publication
All authors gave their consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license.

Data Availability
Data for this work are available from the authors and may be provided upon reasonable request.

Competing Interests
None

Funding Sources
None.

Authors contribution
AHF conceptualised the study, formulated research objectives, and developed the design and methodology. He further analysed and interpreted data, designed and finalised the original manuscript, and executed critical revisions for scientific content and intellectual quality.
MSH did considerable work gathering data, doing experimental procedures like validation of results and an extensive literature review. She also contributed to writing and editing the manuscripts.
Both authors were involved in study design, data collection, analysis and interpretation of data, writing the manuscript and taking full responsibility for the final version of this work.

Acknowledgements
None.

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