

Parental Age and the Risk of Cleft Lip and Palate in a Nigerian Population - A Case–Control Study

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Abstract

Introduction: Orofacial clefts are one of the most common congenital malformations in the facial region. Older maternal or paternal age presents higher odds of a child with an orofacial cleft. The objective of the study was to assess the association between parental age and risk of orofacial cleft. **Materials and Methods:** This was a case–control study among 110 parents of children with orofacial cleft (case group) and 110 parents of children without orofacial cleft (control group). Information on maternal age, paternal age, and type of orofacial cleft in the children were obtained. The results were analyzed using descriptive statistics, Chi-square analysis, and bivariate logistic regressions to measure the association between parental age and orofacial cleft. The value of *P* was <0.05, with a 95% confidence interval (CI). **Results:** Information on 219 children (109 cases and 110 controls) was analyzed, of which 52% were females. One respondent from the case group withdrew from the study. The odds of a child with orofacial cleft was statistically significantly lower in mothers aged 26–35 years compared to mothers aged 25 years and less (odds ratio [OR]: 0.32; 95% CI: 0.16, 0.79). Similarly, fathers aged above 35 years had statistically significantly lower odds of children with orofacial cleft than those 25 years and less (OR: 0.18; 95% CI: 0.02, 0.99). **Discussion:** Our findings suggest that mothers aged 26–35 years may have lower odds of giving birth to babies with orofacial clefts, compared to younger mothers. Similarly, fathers aged above 35 years may have lower odds of giving birth to a child with orofacial cleft compared to fathers aged 25 years and less.

Keywords: Cleft lip, cleft palate, maternal age, paternal age

INTRODUCTION

Orofacial clefts are one of the most common congenital malformations in the skull and facial area.^[1–3] The global incidence of cleft lip and palate (CLP) is reported to be 1 in 700 among Asians, 3.6/1000 live births in American Indians, and 1/1000 live births among Caucasians.^[4] Reports of prevalence from the African populations vary widely,^[5] from 0.5/1000 reported in Nigeria^[6] to 0.2/1000 reported in Ethiopia.^[7] Globally, the prevalence is highest in oriental populations and lowest in Africans.^[4]

Orofacial clefts can present clinically as an isolated defect or as part of a syndrome when associated with (usually two or more) malformations in recognizable patterns.^[2,3] The etiology of orofacial cleft is generally believed to be as a result of an interaction between genetic and environmental factors.^[8] With advances in genetics and molecular biology, more studies identifying the combined genetics

and environmental risk factors responsible for CLP are emerging.^[3,8] Genes such as those encoding transcription factors (MSX1) and growth factors (TGFA and TGFB3) have been implicated in the etiology of CLP,^[3,9] while environmental risk factors such as maternal exposure to tobacco smoke,^[10,11] alcohol,^[1,3] folic acid deficiency,^[1,8] birth order,^[1] and maternal diseases such as diabetes^[10] have been reported to play a role.

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The relative uncertainty surrounding the effect of parental age presents a gap in our understanding of risk factors for orofacial cleft. There is no consensus on whether or not it is a risk factor for CLP.^[1,12] Investigating the relationship with parental age will expound on the etiology and support a biologic and a public health perspective on preventive measures for orofacial clefts.^[12]

A few studies have been conducted according to the recommendation of the International Consortium for oral clefts genetics investigating the relationship between parental age and the incidence of orofacial clefts.^[12,13] In the United States, a population-based study carried out in California showed that women older than 39 years had twice the risk of having a child with CLP when compared to mothers between 25 and 29 years.^[14] Similarly, DeRoo *et al.*^[15] found an association between cleft palate (CP) and women below 20 years. These findings support other studies^[1,12] which found various associations between parental age and orofacial cleft. On the contrary, several studies^[1,16,17] have found no such association between orofacial cleft and parental age. Further, meta-analytic studies by Vieira *et al.*^[17] and Herkrath *et al.*^[18] have given conflicting reports on the relationship between orofacial clefts and parental age. In Africa, the relationship between orofacial cleft and parental age remains unclear, with several studies detailing increased risk with advanced parental age^[19,20] and others the opposite.^[21,22]

The aim of this study is to assess the relationship between parental age and the risk of orofacial clefts in our population. Findings from this study will enable us to test the hypothesis that older maternal or paternal age results in a higher risk of giving birth to babies with orofacial clefts.

MATERIALS AND METHODS

Study design

We conducted a case–control study among 110 parents of children with orofacial cleft (case group) and 110 parents of children without CL/P (control group). One respondent from the case group withdrew from the study.

Study population and settings

Participants in this study consisted of patients from the orofacial cleft and pediatric outpatient clinics at a university teaching hospital in Lagos, Nigeria. Approval was obtained from the Health Research Ethics Committee of the Hospital.

The case–control study recruited patients from two clinical sites at the hospital – cases from the orofacial cleft clinic and controls from the pediatric outpatient clinics. The period of the study was between January 2017 and January 2019. The parents of the selected cohort of patients for this study had been attending either the orofacial cleft or pediatric clinic for at least 6 months before the beginning of the study. Diagnoses of orofacial cleft were coded according to the International Classification of Diseases (ICD), and the

10th ICD revision was used for this study (ICD 10. Q35–37 code).^[23]

Power analysis

Findings of a previous study conducted by Mbuyi-Musanzayi *et al.*^[19] were used to estimate the least extreme odds ratio (OR) to be detected at 3.5 for maternal age. Ninety-five children were required in each group (orofacial cleft vs. controls) after accounting for 10% attrition rate. Hence, an orofacial cleft to control ratio was 1:1, requiring 95 children with orofacial cleft and 95 controls. This was increased to 110 in each group for better representation as well as to account for nonresponse.

Eligibility criteria

The inclusion criteria were all children born with CL/P aged between 0 and 12 years for cases (syndromic and nonsyndromic) and children born without CL/P aged between 0 and 12 years for controls (with and without other congenital anomalies). The exclusion criteria were cases with Tessier clefts, individuals from whom we were unable to obtain parental/guardian consent to participate in the study, as well as parents of children who could not ascertain their age.

Study variables

The primary outcome was the presence or absence of orofacial cleft in a child patient. In this study, the term orofacial cleft is subsequently defined as cleft lip with or without palate (CL/P). The exposure we investigated was parental age at birth of the child. Parental age as defined in this study referred to the independently measured age of the mother (maternal age) and father (paternal age) of a child with CL/P at birth.

Data collection tool

A pro forma questionnaire that contained information about the parents and children was developed. It was interviewer administered and filled for every individual. Data obtained included bio data of parents and children, the age of the father at the birth of the child, the age of the mother at the birth of the child, and the date of birth of the child patient. Parental age was unmatched. However, to reduce confounding from age, the lower limit and upper limits of parental age were placed at 18 and 60 years, respectively. Maternal age was categorized as 25 years and less, 26–35 years, and above 35 years. Paternal age was categorized similarly. The categorization of maternal and paternal age was adapted from prior studies.^[1,19,21]

Ascertainment of cleft

The presence or absence of CL/P was determined by both active and passive ascertainment methods. First, the patient records were screened for patients who fit the case and control eligibility at the cleft and pediatric outpatient clinics, respectively. After passive ascertainment using patient records, all participants were interviewed and examined during clinic visits by two trained research assistants at the respective clinics. During the clinical examination, a pro forma questionnaire was filled, and information from the patient's records was confirmed before entry.

Statistical analysis

The primary objective of the study was to examine the association between parental age (age of the mother and father independently) and orofacial cleft. Frequencies, percentages (approximated to nearest decimal unit), and Chi-square and logistic regressions were used to compare groups as appropriate. The data were analyzed with the OR for each variable with a 95% confidence interval (CI). Statistical significance was inferred at $P < 0.05$. The analysis was carried out using the STATA 15.0 software (StataCorp LLC Lakeway Drive, College Station, Texas).

RESULTS

Study demographic

This was a case-control study among 109 (49.8%) parents of children with orofacial cleft (case group) and 110 (50.2%) parents of children without the orofacial cleft (control group). One respondent from the case group withdrew from the study [Table 1].

The mean maternal age in cases was 29.7 years (range: 16–45 years), while the mean age for controls was 31.3 years (range: 20–48 years). The mean paternal age in cases was 35.8 years (range: 22–55 years), and for controls, it was 37.2 years (range: 23–52 years) [Table 1].

Maternal age

Table 2 demonstrates a significant association between maternal age and orofacial cleft (<0.05). In the case group, there is a higher proportion (77.3%) of orofacial clefts in mothers aged 25 years and less. The proportion of orofacial cleft decreases with increasing age in cases and inversely in the control group. Bivariate analysis on Table 3 demonstrates that the maternal age of 26–35 years had statistically significantly reduced odds of orofacial cleft compared to ≤ 25 years (OR: 0.32; 95% CI: 0.16, 0.79; P : 0.007). Similarly, the maternal age >35 years had reduced odds of orofacial cleft compared to ≤ 25 years (OR: 0.21; 95% CI: 0.06, 0.66; P : 0.003).

Paternal age

On assessing the association between paternal age and orofacial cleft, there was an inverse relationship between paternal age and orofacial cleft [Table 2]. Chi-square analysis demonstrates that as paternal age increases, the proportion of orofacial cleft reduces and inversely for controls ($P < 0.05$).

Table 3 displays a bivariate analysis which shows reduced odds of orofacial cleft in the age group 26–35 years compared to ≤ 25 years (OR: 0.32; 95% CI: 0.03, 1.75; P : 0.15), however, not statistically significant. On the other hand, the age group >35 years had statistically significantly reduced odds of orofacial cleft compared to ≤ 25 years (OR: 0.18; 95% CI: 0.02, 0.99; P : 0.02) [Table 3].

DISCUSSION

Our findings reject the hypothesis that increasing maternal age is associated with a higher risk of orofacial cleft in a child.

Table 1: Distribution of the study population

Study characteristics	Case (%)	Control (%)
Sex of children		
Female	61 (54.0)	52 (46.0)
Male	48 (44.8)	58 (55.2)
Total	109 (100)	110 (100)
Cleft type		
Cleft lip±alveolus only	41 (37.6)	0 (0)
CLP	35 (32.1)	0 (0)
CP only	33 (30.3)	0 (0)
Total	109 (100)	
Parental age, mean age (SD)		
Maternal age	29.7 (5.6)	31.3 (4.9)
Paternal age	35.8 (6.9)	37.2 (5.5)

SD: Standard deviation, CP: Cleft palate, CLP: Cleft lip and palate

Table 2: Chi-square analysis of maternal and paternal age in cases and controls

	Case (%)	Control (%)	P
Maternal age (years)			
≤ 25	17 (77.3)	5 (22.7)	0.011*
26-35	77 (49.0)	80 (51.0)	
>35 years and above	15 (37.5)	25 (62.5)	
Paternal age (years)			
≤ 25	8 (80)	2 (20)	0.022*
26-35	50 (56.2)	39 (43.8)	
>35 years and above	51 (42.5)	69 (57.5)	

* $P < 0.05$

Table 3: Bivariate analysis of the maternal and paternal age in the “case” and “control” groups

Study characteristics	Case	Control	OR (95% CI)	P
Maternal age (years)				
≤ 25	23	8	1 (reference)	
26-35	73	80	0.32 (0.16-0.79)	0.007*
>35	13	22	0.21 (0.06-0.66)	0.003*
Paternal age (years)				
≤ 25	8	2	1 (reference)	
26-35	50	39	0.32 (0.03-1.75)	0.15
>35	51	69	0.18 (0.02-0.99)	0.02*

* $P < 0.05$. OR: Odds ratio, CI: Confidence interval

The findings from our study suggest that younger mothers aged 25 years and less have a higher risk of having a child with orofacial cleft compared to mothers above 25 years. Our findings are supported by Olufunmilayo *et al.*^[21] who reported a higher risk of orofacial in the children of mothers younger than 20 years of age. Similarly, Martelli *et al.*,^[1] reported an increased risk for CP in mothers <25 years, compared to mothers above 26 years. Other studies have reported the same association between maternal age and the risk of orofacial cleft.^[15,22]

Multiple studies^[18-20] have also reported a higher risk of orofacial cleft with increasing maternal age. In a

meta-analysis conducted by Herkrath *et al.*,^[18] older maternal age was reported to increase the risk of having a child with nonsyndromic orofacial cleft. In this study,^[18] mothers aged between 35 and 39 years had a 20% higher odds of having a child with nonsyndromic orofacial clefts compared to mothers aged between 20 and 29 years. A possible explanation for this relationship may be accumulating environmental exposures as well as chromosomal mutations in aging mothers. Further, a number of studies have reported no relationship between maternal age and the occurrence of oral cleft lip with or without palate.^[16,17,24-28] Vieira *et al.*^[17] in a review of eight population-based studies found no association between increasing maternal age and the occurrence of orofacial cleft in children. However, limitations such as the nonadjustment for the presence of syndromes and other risk factors pose a challenge in the interpretation of these findings.

A possible explanation for the increased occurrence of orofacial cleft in younger mothers aged 25 years and less may be a lack of physical maturity and deficiency in vitamins, notably folic acid, which has been associated with congenital disabilities.^[15] In addition, teenage pregnancies are more common in low-income families in Nigeria,^[29] and the latter may contribute to nutritional deficiencies resulting in the prevalence of orofacial cleft in this segment of the population.

Our findings on paternal age were less conclusive, as paternal age of 25 years and less was not significantly associated with a higher risk of orofacial cleft compared to older paternal age (26–35 years). A significantly lower risk was however found with paternal age above 35 years compared to paternal age of 25 years and less. Contrary to our finding, Mbuyi-Musanziyi *et al.*^[19] reported a higher risk of orofacial cleft when the paternal age is above 35 years compared to between 26 and 35 years. Similar to the suggested origin of increased risk with older maternal age, the increased risk associated with advanced paternal age may be based on a higher rate of *de novo* mutation in sperm with older age in fathers.^[30,31] Further, in assessing the combined association of both parental ages with orofacial cleft in 2,449,218 births from a Norwegian birth registry between 1967 and 2010, Berg and colleagues^[32] reported that the risk of having a child with orofacial cleft increased only when the age of both parents was advanced.

We identify a limitation in this study. Our case and control populations were not age and sex matched. Nonetheless, a key strength of the present study is that it presents accurate data on selected cases and controls in assessing the association of parental age on the occurrence of CL/P.

CONCLUSION

The findings from our study suggest that maternal age of 25 years and less may pose a higher risk for orofacial cleft than above 25 years. Similarly, paternal age below of 25 years and less demonstrated a significantly higher risk of orofacial cleft than above 35 years. Future studies could consider

the relationship between parental age and different patterns of cleft lip with and without palate, as well as in strictly syndromic or nonsyndromic populations. Further, studies could investigate the interaction of factors such as a parental tobacco smoking, alcohol consumption, the use of folic acid during pregnancy, and with parental age on the risk of orofacial cleft. Epidemiologic studies of orofacial cleft remain relevant to clinical and public health research, as it provides evidence for counseling parents as societal changes are trending towards millennials beginning families relatively later.

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Conflicts of interest

There are no conflicts of interest.

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