

# A Retrospective Cohort Study to Evaluate the Association Between Types of Nonsyndromic Oral Clefts and a Child's Gender and Maternal Age

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ABSTRACT

**Aims:** To evaluate the association between nonsyndromic cleft lip with or without cleft palate (NSCL±P) anomaly and the affected child's gender and maternal age. **Materials and Methods:** Records of 141 newborns received at the orthodontic craniofacial clinic of the Jordanian Royal Rehabilitation Center between 2017 and 2019 were retrospectively analyzed. Two variables were paid attention to: child's gender and maternal age. Five cleft types were considered: unilateral CLP (right; URCLP and left; ULCLP), bilateral CLP (BCLP), isolated cleft palate (CP) and isolated cleft lip (CL). Maternal age was classified into four subgroups: "26–30" years, "31–35" years, "36–40" years, and "above 40" years. Chi-square test and multinomial logistic regression analysis were used to analyze the resultant data. **Results:** A significant occurrence of the NSCL±P in females was found compared with males. The different cleft types were found to be significantly associated with the different maternal age groups investigated. The ULCLP was the most prevalent cleft type for affected children among all maternal age groups except the "31–35" group, at which the BCLP exceeded. **Conclusions:** The children's gender and the maternal age have a significant impact on defining the developing oral cleft types.

**KEYWORDS:** Child's gender, cleft lip, cleft palate, maternal age

## INTRODUCTION

A clear statement regarding congenital malformations is that NSCL±P is the most common form of these anomalies reported in literature, with a prevalence of one to two per 1000 live births.<sup>[1]</sup> Although several potential risk factors have been researched, no specific causative was reported and a multifactorial etiology with more emphasis on genetic impact was found.<sup>[2-4]</sup>

However, such malformations are of great importance from biologic and public health points of view not only for general populations but also for health providers. For this, researchers have continuously considered any factors of concern to clearly find a relation to the occurrence of the NSCL±P and its types or presentations. Maternal age and the affected

child's gender were considered as influencing factors in this issue besides other factors such as the maternal usage of certain medications, smoking and alcohol consumption during pregnancy, intrapartum interval, and folic acid deficiencies.<sup>[5-8]</sup> However, conflicting reports on whether older maternal age is associated with oral cleft types have been found. Some studies found a positive correlation with increasing maternal age for the different cleft types,<sup>[9-11]</sup> whereas others found no association.<sup>[12-14]</sup> Similarly, defining whether the specific affected child's gender is associated with the occurrence of oral cleft and the type of this cleft is also important. As was previously found, CLP is more

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common in males whereas isolated CP is more common in females; males with CLP tend to have a more severe cleft than females.<sup>[6,15]</sup> However, the influence of this variable needs to be researched more with regard to the different cleft types encountered.

In fact, the impact of such variables on the occurrence of the NSCL±P and its types was superficially investigated by researchers and comprehensive work is needed to investigate these variables only without the presence of any other genetic or environmental causatives.

In Jordan, a distinctive clinic for management of craniofacial anomalies, including primarily the CLP, is found to be one of the specialized centers of the Royal Medical Services (RMS) hospitals providing a centralized team approach free of charge treatment at the national level. The aim of this study was to evaluate the relationship between the affected child's gender and maternal age and the types of NSCL±P.

## MATERIALS AND METHODS

Records of newborns with NSCL±P received at the craniofacial orthodontic clinic at the Jordanian Royal Rehabilitation Center of the RMS between the years 2017 and 2019 were retrospectively evaluated. The records were taken by carefully examining and screening the newborns received at the clinic for the presence of any associated anomalies or syndromes by a team of qualified specialists. A questionnaire having the child's gender and age, cleft description, presence of any associated anomalies, and maternal age was used to collect the needed data for this study from the available records.

The selection criteria for this retrospective cohort study targeted patients with oral clefting without the presence of any other anomalies and congenital malformations and with no history of consanguinity or familial NSCL±P. From a total of 220 patients, 141 children were found to comply with the study demands.

The clefts were classified with the incisive foramen as reference,<sup>[16]</sup> so that five cleft types were considered: right URCLP and left ULCLP, BCLP, CP, and isolated CL. A few mothers were found to be younger than 26 years. For this, maternal age was classified into the following

four subgroups: "26–30" years, "31–35" years, "36–40" years, and "above 40" years. The subgroups were divided with a shortened age interval of five years, so that more precise results with homogenous data could be obtained. Informed consent was obtained for each patient from the parents or guardians. Data were then collected and transferred for the purpose of the needed analyses.

## STATISTICAL ANALYSIS

Chi-square test was used to separately evaluate the association between the NSCL±P and each of the variables researched. With regard to categorical variables, the multinomial logistic regression model was fitted to help predict the dependence of the cleft types on the two variables (child's gender and maternal age ranges). Main effect and two-way stepwise interaction for the logistic regression model were performed. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed, which turn down the chance of occurrence of any type of the clefts in relation to another one taken as a reference with respect to the variables investigated. All statistical tests were performed by using the statistical software SPSS version 21 (SPSS Inc., Chicago, USA). The level of significance was set at  $P < 0.05$ .

## RESULTS

Table 1 shows the distribution of NSCL±P according to the children's gender. Of the 141 children included in the study, CLP had the highest prevalence ( $n = 124$ ; 87.9%), with the left side being affected more than the bilateral type and then the right one, followed by CP ( $n = 15$ ; 10.6%) and CL ( $n = 2$ ; 1.4%). Although males showed more prevalence of URCLP followed by BCLP and CP as compared with females, who were having more ULCLP and isolated CL types, more significant occurrence of the NSCL±P as an overall in females was found compared with males (54.6%, 45.4%) as  $P$  value was 0.006.

The distribution of NSCL±P according to type and maternal age is shown in Table 2. The age group "above 40" was more prevalent (49.6%) than the other age groups: "36–40" years with 24.8%, "31–35" with 19.9%, and 5.7% for maternal age of "26–30" years.

**Table 1: Distribution of non-syndromic cleft lip and/or palate according to type and gender**

Gender	ULCLP		URCLP		BCLP		CP		CL	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Females	51	66.2	6	7.8	12	15.6	6	7.8	2	2.6
Males	25	39.1	14	21.8	16	25.0	9	14.1	0	0
Total	76		20		28		15		2	

\* $P = 0.006$ .

The different cleft types were found to be significantly associated with the different maternal age groups investigated ( $P = 0.002$ ). The ULCLP was the most prevalent cleft type for affected children among all maternal age groups except the “31–35” group, at which the BCLP predominated.

Using the multinomial logistic regression models [Table 3], the two variables were entered as independent predicting categorical factors. The CL parameter was excluded from further analyses, as it was redundant. The result of step summary and model fitting information showed that the combined effect of the two variables significantly impacted the dependent variable (cleft types), as the resultant P value was 0.001 by using the likelihood ratio test. Separately, as a result of the main effect model, both variables were found to significantly predict the occurrence of the cleft types as the P value for the maternal age was 0.005 and that for the child's gender was 0.033.

When calculating the ORs, the CP variable was taken as a reference to which other cleft types were compared. In the gender variable, prediction of occurrence of the cleft types in males was in reference to females holding the maternal age constant; however, in the maternal age variable, the age groups were referenced to the “above 40” group with holding the gender variable constant. With reference to the “above 40” group, we found that the maternal age groups “26–30”, “31–35,” and “36–40” were significantly impacting the occurrence of

ULCLP type by 0.035, 0.083, and 0.098 lesser times, respectively, compared with CP. Males compared with females were 1.813 times more likely to have URCLP opposed to CP. However, this result was not statistically significant. All other predictions for the cleft types by either the maternal age groups or the gender variable differences had less time of occurrences compared with the reference groups, and all were found to be statistically insignificant.

The combined interaction effect of both variables on the prediction of the cleft types by using the two-way stepwise interaction is shown in Table 4. Having a male newborn with a maternal age of 26–30 years has a significantly higher prediction of 1.755 times, as opposed to a female newborn with a maternal age older than 40 years, to develop URCLP compared with CP. Male children with maternal age groups of 31–35 and 36–40 years compared with females with mothers older than 40 years have a significantly less time to develop ULCLP compared with CP by 0.026 and 0.060 times, respectively. Male and female children with mothers older than 40 years do not have any statistically significant difference in developing any of the cleft types compared with the CP type. This is also the same for the female interaction group (31–35 years). However, female children with mothers in the age group 26–30 years have a significantly less risk of occurrence of ULCLP (OR= 0.026) and more chance of occurrence (OR= 2.320) of URCLP in reference to CP compared with females with a maternal age older

**Table 2: Distribution of non-syndromic cleft lip and/or palate according to type and maternal age**

Maternal age	ULCLP		URCLP		BCLP		CP		CL	
	n	%	n	%	n	%	n	%	n	%
26–30	2	25.0	1	12.5	2	25.0	2	25.0	1	12.5
31–35	8	28.6	5	17.9	9	32.1	5	17.9	1	3.6
36–40	14	40.0	7	20.0	8	22.9	6	17.1	0	0
Above 40	52	74.3	7	10.0	9	12.9	2	2.9	0	0

\* $P = 0.002$ .

**Table 3: Distribution of the cleft types according to gender and maternal age with reference to the CP type as analyzed by using the multinomial logistic regression analysis**

	ULCLP		URCLP		BCLP	
	OR(CI 95%)	P value	OR(CI 95%)	P value	OR(CI 95%)	P value
Gender						
Female	1.00		1.00		1.00	
Male	0.456(0.127-1.637)	0.228	1.813(0.413-8.158)	0.438	0.915(0.231-3.619)	0.900
Maternal age						
26–30	0.035(0.003-0.401)	0.007*	0.156(0.009-2.789)	0.206	0.220(0.018-2.662)	0.234
31–35	0.083(0.013-0.536)	0.009*	0.235(0.030-1.861)	0.170	0.413(0.059-2.899)	0.374
36–40	0.098(0.018-0.547)	0.008*	0.311(0.045-2.134)	0.235	0.299(0.046-1.942)	0.206
Above 40	1.00		1.00		1.00	

OR = odds ratio; CI = confidence interval.

\*Significance at  $p < 0.05$ .

**Table 4: Results of 2-way stepwise interaction between the independent variables on the cleft types (with reference to CP) as analyzed by the multinomial logistic regression**

Interaction	ULCLP		URCLP		BCLP	
	OR (CI 95%)	P value	OR (CI 95%)	P value	OR (CI 95%)	P value
Male/(26–30)	0.130 (0.000-. <sup>b</sup> )	1.000	1.755 (1.023–9.768)	0.000*	7.172 (6.765–9.712)	0.987
Male/(31–35)	0.026 (0.002–0.266)	0.002*	0.500 (0.034–7.452)	0.615	0.240 (0.210–2.790)	0.254
Male/(36–40)	0.060 (0.005–0.661)	0.022*	0.500 (0.028–8.952)	0.638	0.333 (0.025–4.401)	0.404
Male/(>40)	0.333 (0.019–5.717)	0.449	2.500 (0.100–62.605)	0.577	0.800 (0.037–17.196)	0.887
Female/(26–30)	0.026 (0.002–0.417)	0.010*	2.320 (0.023–6.432)	0.000*	0.100 (0.004–2.504)	0.161
Female/(31–35)	0.845 (0.000–8.876)	0.998	0.667 (0.000-. <sup>b</sup> )	1.000	3.615 (0.000-. <sup>b</sup> )	0.998
Female/(36–40)	0.060 (0.005–0.661)	0.022*	0.667 (0.039–11.285)	0.779	0.200 (0.014–2.911)	0.239
Female/(>40)	-	-	-	-	-	-

- = Interaction reference group; <sup>b</sup>Floating point overflow occurred while computing this statistic. Its value is, therefore, set to system missing, \*Significance at  $p < 0.05$ .

than 40 years. The last group (females/36–40) at the table was found to have significantly less prediction of ULCLP in regards with the reference group as compared with CP.

## DISCUSSION

Receiving newborns with oral clefts is a challenging and frustrating experience for parents. Socioeconomic implications are of great importance when dealing with such a situation not only at the personal but also at the national level. Hence, it is the responsibility of the researchers and the specialized health providers to seriously investigate and look for the factors that could play a role in one way or another in the development of these anomalies so that mutual efforts could be obtained to prevent, lessen the severity and simplify the management of these malformations.

In Jordan, a previous study showed that 1.39 per 1000 was the overall prevalence rate for live births with CL, CP, or both, with the CLP type affecting around half of those affected with a higher prevalence rate of boys with oral clefting as compared with girls.<sup>[17]</sup> As compared with this appreciated effort, our results showed that the CLP type was found to be 87.9% compared with the other types. Such an increase in cases at which both lip and palate were affected and the isolated cleft cases were reduced may be worthy of attention. However, the data collected for our colleagues' research targeted newborns between 1991 and 2001, around 20 years ago, so that the results we have gained should represent the picture in a more updated way. Whether the new drugs introduced in the market, the noticed changes in lifestyle as compared with during the past, and the other environmental changes seen nowadays and not found in the past have a role in this issue or not might need investigation. The predominance of CLP over the CP and CL agreed to what was also reported in other studies.<sup>[15,18,19]</sup>

In our study, males had more significant prevalence of URCLP, BCLP, and CP compared with females, who showed more ULCLP and CL cases. The F:M ratio for CLP as a combination was 1.25:1 and for the whole malformation with the addition of the isolated clefts it was 1.2:1. This result is not in line with that previously found for white Caucasians, as the gender ratio for CLP was 1:1.7 (F:M).<sup>[20]</sup> However, the different ratios reported by studies regarding this issue might usually vary between each other. Such ratios of gender differences were found to be affected by multiple factors such as severity of the cleft,<sup>[21]</sup> presence of additional malformations, number of affected siblings in a family, ethnicity, and possibly paternal age.<sup>[22,23]</sup> In our study, only cleft cases of non-syndromic Arab origin with no other associated anomalies and parents without a close relationship were considered and standardized.

For the maternal age variable, the development of the NSCL±P was almost increasing with an increase in maternal age. These results are in accordance with other studies that found a positive association with increasing maternal age for oral clefting,<sup>[24-26]</sup> but they are contradictory to other studies that found no association.<sup>[12,14,27]</sup> Once more, the populations tested in each of these studies, besides the inclusion criteria adopted, should not be ignored. Regarding these contradictory researches, the meta-analysis of Veira *et al.* was based at eight population studies of non-Arab origin as it is the case in our study. Also, the work of Baird *et al.* was limited to live births in British Columbia, whereas the last research was performed by using a population of Canadian origin.

Another meta-analysis pertaining to this subject was published in 2012.<sup>[28]</sup> Interestingly, it included data extracted from the Middle East area and of Arab origin too. The results were promising and match ours. The authors concluded that mothers between 35 and 39 years old were more likely to have babies with

cleft palate in comparison with those between 20 and 29 years old. Further, mothers 40 years of age or older were more likely to give birth to babies with CLP.

The results of ORs presented in Table 3 depict the power of impact of the variables on the development of a cleft type compared with the CP. Based on the results found, the significant prediction power of having a baby with ULCLP compared with CP was very obvious as the mother of this baby crossed 40 years of age. Beyond the actual values of times of occurrence, this result agrees with the research by Luo *et al.*,<sup>[29]</sup> who found that mothers aged 40 years or older were 1.56 times more likely to have a baby with CLP compared with those aged between 20 and 29 years; however, this result is not in line with a previous study<sup>[6]</sup> performed with limited subjects, which found that the mothers aged from 26 to 35 years and those older than 35 years had a reduced risk of having CLP when compared with mothers younger than 26 years. At the public level of our research community, the general opinion regarding conception at the age of 40 is that it may bring about risks and complications not only pertaining to the mother's health status but also for the baby. As mothers get older, and compared with younger, they might be having a certain condition or disease that might affect their pregnancy status. Whether this maternal age interval affects the general health of babies in one way or another or not is not our target in this research but it is worth investigation.

Very importantly, our aim is to present the data available [Table 4] regarding the joint interaction of dependence of the cleft types on the child's gender and his mother's age. This gives the power of combining the two variables in predicting the type of the oral clefting developed. For example, for a pregnant woman of age between 26 and 30 years who is at risk of developing oral clefting and compared with another pregnant woman older than 40 years, regardless of whether she will get a boy or a girl, her newborn will be at more risk of having URCLP compared with CP. In fact, little research was performed with the same interaction technique we had investigated. For this reason, we have encountered difficulties in presenting suitable comparisons with other works.

However, the result of classification of the ability of the predicting variables we have researched on the overall prediction percentage of the cleft types was 55.4% (using the statistical classification table of the predictors). This means that the prediction process using only the two variables researched in our study was not adequate and that other variables should be

added to the predictors to sufficiently investigate the factors impacting the cleft types.

Such results should call for governmental and community responses. Based on these results, mothers with an increased age, especially older than 40 years, should be carefully advised regarding their pregnancy plans. There should be special precautions, counseling, and even laws at the national level defining a female's optimum age for either marriage or conception, particularly for those at a higher risk of developing any type of oral clefting.

A possible weakness of the study is that paternal age was not considered. The interaction between maternal and paternal age on the development of the oral cleft types, although previously investigated by multiple researchers, is an important issue; this issue should be focused on in our future plans so that comprehensive data regarding the association between the oral cleft types and paternal age are available for our population not only at the local level but also for global specialized healthcare providers.

## CONCLUSION

The relationship between a child's gender and maternal age variables and the developed type of NSCL±P anomaly was investigated retrospectively. It was found that these variables have a significant impact on defining the developing cleft types as follows:

- 1- More significant occurrence of the NSCL±P in females was found compared with males.
- 2- The different cleft types were found to be significantly associated with maternal age.
- 3- Compared with ages below 40, mothers older than 40 years of age have an increased risk of having a child with ULCLP compared with isolated CP.

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Nil.

## CONFLICTS OF INTEREST

There are no conflicts of interest.

## AUTHORS' CONTRIBUTIONS

Not applicable.

## ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

The research protocol was approved by the Jordanian RMS human research ethics committee in March 2020.

## PATIENT DECLARATION OF CONSENT

Not applicable.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available on request from the corresponding author.

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