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ANALYZING PARENTAL AGE TO DETERMINE TYPES OF CLEFT IN HAYANDRA PEDULI FOUNDATION'S PATIENT, INDONESIA

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ABSTRACT

Cleft lip and palate are complex and known to have multifactorial risk factors with a prevalence of 0.2% in Indonesia. Also, there is no specific data about parental age-related to types of a cleft in Indonesia. This study aims to analyze parental age-related to types of cleft in patients treated by Hayandra Peduli Foundation, Indonesia. The data was collected from 2014 to 2018 from social service held by Hayandra Peduli Foundation. The data collected primarily, and 604 subjects were obtained. The results showed that 81.5% of patients were 0-5 of age, with patients' distribution were 356 male patients and 248 female patients. There was no significant correlation between maternal age and each type of cleft. Furthermore, there was no correlation between paternal age and types of cleft based on maternal group age. For young and ideal maternal group age, their p-value showed no significant correlation (p-value 0.393 for young maternal age and 0.941 for ideal maternal age). Surprisingly, the old maternal group age shows significant results, with a p-value of 0.045. In conclusion, we found that cleft palate will occur in infants born from an aging mother (>35 years old).

Keywords: cleft; palate; parental age; Indonesia

INTRODUCTION

Cleft lip and/or palate are the most common congenital anomalies, with a prevalence of 0.2% in Indonesia.[1] Cleft lip and/or palate are complex and known to have multifactorial risk factors, including environmental factors, social factors, and genetic factors.[2] One of the genetic factors that contributed to the cleft incidence is parental age. A study by Rychtarikova J et al. found that the higher odds for cleft lip and palate were seen among fathers and mothers aged 35-39 years.[3] Other researchers, DeRoo et al., concluded that mothers younger than 20 years were twice as likely to have an infant with nonsyndromic cleft lip and palate than those aged 25-29 years.[4]

Several studies also represented the correlation between parental age and cleft incidence. Martelli et al. found an association between maternal age and an increased risk for cleft lip and palate; however, parental age was not significant.[5] Salihu et al. concluded that maternal age is one of the significant potential risk factors for the cleft occurrence, followed by paternal age.[6] A study in China indicated maternal age was significantly associated with cleft lip and palate.[7] One study conducted by Bille et al. showed higher paternal age, but not maternal age increased the risk of cleft palate only[8]. The other study showed the risk of the cleft was increased only when both parents' age was high.[9]

Although many studies were conducted in several countries, there are no specific data about parental age-related to types of the cleft in Indonesia. This study aims to analyze parental age-related to cleft types in patients treated by Hayandra Peduli Foundation, Indonesia.

MATERIAL AND METHODS

For this retrospective study, we collected the data material from the social services conducted by Hayandra Peduli Foundation from 2014 to 2018. During these years, the parents of the subjects were asked voluntarily to fill the previously prepared form. Seven hundred ninety-seven files of subjects had been documented. One hundred ninety-three files were incomplete, so they were excluded from this study. Only nonsyndromic cleft subjects were included in this study.

We recorded the demographic data and analyze parental age to determine the types of cleft patients. The demographic data, including the year when the social services were held, location of social services, patients' age, patients' gender, patients' diagnosis, maternal age, and paternal age. The cleft types were cleft lip; cleft gum; cleft palate; cleft lip and cleft gum; cleft lip and cleft palate; cleft gum and cleft palate; cleft lip, cleft gum, and cleft palate. We categorized three age groups for each father and mother based on the cleft risk factor: young (<20 years old), ideal (20-35 years old), and old (> 35 years old). Young and old parents are known as cleft risk factors. Kruskal-Wallis test was used to analyze the correlation between maternal age and types of cleft, the correlation between paternal age and types of cleft, the correlation between paternal and maternal group age to determine which type of cleft the patient will have. Calculations were performed by using SPSS 23.

RESULT

Table 1 shows the cleft patient's demographic data in Hayandra Peduli Foundation social services from 2014 to 2018. The highest number of patients occurred in 2015 (172 of 604 patients). The social services were held mostly in Jakarta (301 patients). In general, patients aged 0-5 years filled the highest proportion (81.5%). The distribution of patients' gender was 356 male patients and 248 female patients. Cleft palate was the most common patients' diagnosis (36.1%). The median maternal age in this study was 28 (13-47) years old, while that of paternal age was 32 (15-56) (Table 1). The highest proportion of maternal age was 30 years old (Figure 1), whereas the highest proportion of paternal age was 31 years old (Figure 2) (Table 2).

Table 3 shows the correlation between maternal age and types of cleft, with a p-value of 0.628. It shows that there was no significant correlation between maternal age and each type of cleft. Table 4 presents the correlation between paternal age and types of cleft. A p-value of 0.950 indicates a non-significant correlation between paternal age and each type of cleft.

Table 5 shows the correlation between maternal age and types of cleft based on paternal group age. There were no significant results for each of the paternal group age, with p-value 0.743 for the young paternal age; 0.072 for ideal paternal age; and 0.448 for old paternal age.

Table 6 presents the correlation between paternal age and types of cleft based on maternal group age. For young and ideal maternal group age, their p-value shows no significant correlation (p-value 0.393 for young maternal age and 0.941 for ideal maternal age). Surprisingly, the old maternal group age shows a significant result, with a p-value of 0.045.

Table 1. Demographic data of the cleft patient in Hayandra Peduli Foundation social service from 2014 to 2018

Demographic data	N	%
Year		
2014	163	27
2015	172	28.5
2016	129	21.4
2017	71	11.8
2018	69	11.4
Location		
Ambon	12	2.0
Denpasar	2	0.4
Banjarmasin	14	2.3
Cirebon	14	2.3
Ende	23	3.8
Gorontalo	7	1.2
Jakarta	301	49.8
Kediri	5	0.8
Tanjung Pinang	8	1.3
Kupang	39	6.5
Bandar Lampung	39	6.5
Manggarai	6	1.0
Maumere	14	2.3
Padang	16	2.6
Palangkaraya	17	2.8
Pontianak	19	3.1
Pringsewu	44	7.3
Sintang	10	1.7
Tangerang	14	2.3
Patients' age (years old)		
0-5	492	81.5
6-10	47	7.8
11-17	37	6.1
>17	28	4.6
Patients' gender		
Male	356	
Female	248	
Patients' diagnosis		
Cleft lip (CL)	177	29.3
Cleft gum (CG)	10	1.7
Cleft palate (CP)	218	36.1
Cleft lip and gum (CLG)	27	4.5
Cleft lip and palate (CLP)	71	11.8
Cleft gum & palate (CGP)	10	1.7
Cleft lip, cleft gum, and cleft palate (CLGP)	91	15.1

Table 2. The maternal and paternal age at the birth of the child in Hayandra Peduli Foundation social services from 2004 to 2008

	Median (min-max)
Maternal age	28 (13-47)
Paternal age	32 (15-56)

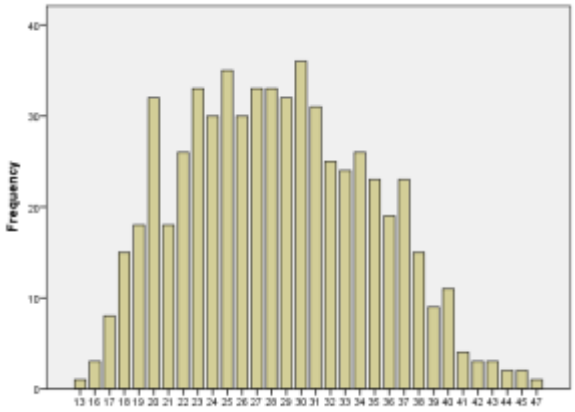

Figure 1. Distribution of maternal age in Hayandra Peduli Foundation social services from 2004 to 2008

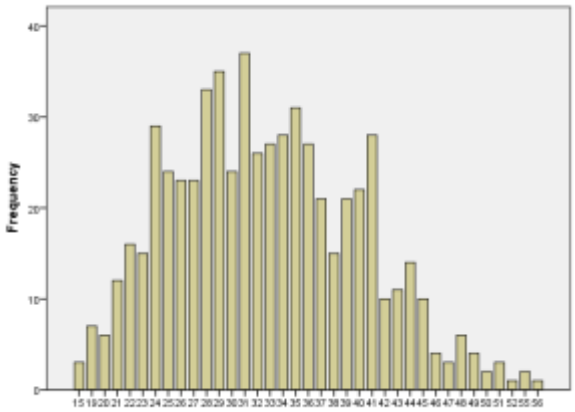

Figure 2. Distribution of paternal age in Hayandra Peduli Foundation from 2004 to 2008

Table 3. Correlation between maternal age and types of cleft

Maternal age (MA)		Young (Y)	Ideal (I)	Old (O)
Types of cleft (n=604)	CL	12 (27.3)	139 (29.7)	26 (28.3)
	CG	0 (0.0)	8 (1.7)	2 (2.2)
	CP	18 (40.9)	172 (36.8)	28 (30.4)
	CLG	1 (2.3)	21 (4.5)	5 (5.4)
	CLP	6 (13.6)	52 (11.1)	13 (14.1)
	CGP	0 (0.0)	9 (1.9)	1 (1.1)
	CLGP	7 (15.9)	67 (14.3)	17 (18.5)
P			0.628	

Kruskal-Wallis test: Mean rank (young maternal age= 307.84; ideal maternal age= 299.13; old maternal age= 317.08).

Table 4. Correlation between paternal age and types of cleft

	Paternal age (PA)	Young (Y)	Ideal (I)	Old (O)
Types of cleft (n=604)	CL	3 (30.0)	113 (29.0)	61 (29.9)
	CG	1 (10.0)	7 (1.8)	2 (1.0)
	CP	1 (10.0)	145 (37.2)	72 (35.3)
	CLG	0 (0.0)	15 (3.8)	12 (5.9)
	CLP	4 (40.0)	45 (11.5)	22 (10.8)
	CGP	0 (0.0)	8 (2.1)	2 (1.0)
	CLGP	1 (10.0)	57 (14.6)	33 (16.2)
P			0.95	

Kruskal-Wallis test: Mean rank (young paternal age= 317.70; ideal paternal age=301.55; old paternal age= 303.58).

DISCUSSION

To our knowledge, this is the first study that analyses the correlation between parental age and cleft risk. Other previous evidence shows the inconsistent result, whether parental age is related to the cleft incidence or not. In our study, most maternal and paternal age is within ideal age (20–39 years old). Median maternal age is 28 years old (13–47 years old), while median paternal age is 32 years old (15–56 years old).

Extreme parental age (too young or old) have been suggested as a risk factor for cleft development. A large study by Bille et al. shows an increase in the risk of cleft lip with or without palate as high as 1.2 every 10-year increase in maternal age. The risk of cleft palate without cleft is increased by 1.16, a 10-year increase in maternal age. Meanwhile, with every 10-year increase in paternal age, the cleft lip risk is also increased to 1.12 and cleft palate without cleft lip increases to 1.24. However, multivariate analysis shows that only the older paternal age is significant.[8]

A meta-analysis of 13 studies by Herkrath et al. show paternal aged 40 years and older have a 58% higher risk of having a cleft palate than ideal paternal age (20–39 years old). Also, maternal age 35–39 years old increases cleft risk as high as 20%, while maternal age 40 years and older has a 28% higher risk than maternal age 20–29. However, this meta-analysis found no significant correlation between younger maternal or paternal age and cleft risk.[10] In contrast, DeRoo et al. concluded maternal age younger than 20 years old may increase cleft risk as twice likely compared to mother within the ideal age.[4]

This analysis found no significant relation between extreme maternal or paternal age and types of cleft. Although most evidence shows a significant relationship between extreme parental age and cleft risk, some studies show no significant relation. Harville et al. show older

parental age is not a significant risk factor for developing isolated cleft in off-spring. However, the syndromic cleft risk is significantly higher in older parents since syndromic and nonsyndromic cleft has different risk factors.[11] Also, Viera et al. show no correlation between maternal age and cleft risk.[12]

Table 5. Correlation between maternal age and types of cleft based on the paternal group age

Paternal age	Maternal age	Types of cleft							P
		Cleft lip	Cleft gum	Cleft palate	Cleft lip and gum	Cleft lip and palate	Cleft gum and palate	Cleft lip, gum, and palate	
Young	Young	2 (40.0)	0 (0.0)	0 (0.0)		2(40.0)		1(20.0)	0.743
	Ideal	1 (20.0)	1(20.0)	1 (20.0)		2 (40.0)		0 (0.0)	
Ideal	Young	9 (23.7)	0 (0.0)	18(47.4)	1 (2.6)	4 (10.5)	0 (0.0)	6(15.8)	
	Ideal	103 (29.9)	7 (2.0)	126 (36.6)	14 (4.1)	38 (11.0)	8 (2.3)	48 (14.0)	0.072
	Old	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	3 (37.5)	0 (0.0)	3 (37.5)	
Old	Young	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Ideal	35 (29.4)	0 (0.0)	45 (37.8)	7 (5.9)	12(10.1)	1 (0.8)	19(16.0)	0.448
	Old	25 (29.8)	2 (2.4)	27 (32.1)	5 (6.0)	10(11.9)	1 (1.2)	14(16.7)	

Kruskal-Wallis test: Mean rank (young paternal age+young maternal age = 5.80; young paternal age+ideal maternal age= 5.20; ideal paternal age+young maternal age= 201.16; ideal paternal age+ideal maternal age= 192.90; ideal paternal age+old maternal age= 280.63); old paternal age+young maternal age= 31.00; old paternal age+ideal maternal age= 102.50; old paternal age+old maternal age= 103.35).

Moreover, we also analyze the correlation between maternal or paternal age and cleft types based on spouse age. In our study, older maternal age with old or ideal spouse age correlated with cleft incidence (p=0.045). It manifests that no matter how old or young the paternal age, the old maternal age will tend to certain types of cleft. In this study, we found that cleft palate will occur in infants born from old mothers (>35 years old).

Other studies show a correlation between parental age and cleft incidence. Berg et al. show a combination of advanced parental age may increase cleft risk. While only an older mother or father may not significantly increase cleft incidence.[9] Herman et al. conclude that increased parental age may contribute to more severe cleft lip, with or without palate. Older parental age may result in more severe cleft compare to a couple whose one is old, and the other is still young. This result suggests that parental age combination also contributes to cleft severity.[12] An earlier study by Balgir in 1984 shows parental age gaps increase cleft risk.[13]

There is no clear explanation about the exact mechanism of parental age's impact on cleft incidence or severity. Some authors suggest a genetic role as the underlying mechanism. "Copy error" during spermatogenesis or single gene mutation may result in cleft palate.[8,15,16]

While other authors assume that the environment is the main culprit. Bille et al. conclude that older mothers may have a longer duration of toxic and infection exposure. The result supports this hypothesis that increasing birth order is also found to increase cleft risk.[8]

Table 6. Correlation between paternal age and types of cleft based on the maternal group age

Maternal age	Paternal age	Types of cleft							P
		Cleft lip	Cleft gum	Cleft palate	Cleft lip and gum	Cleft lip and palate	Cleft gum and palate	Cleft lip, gum, and palate	
Young	Young	2 (40.0)		0 (0.0)	0 (0.0)	2(40.0)		1(20.0)	0.393
	Ideal	9 (23.7)		18(47.4)	1 (2.6)	4 (10.5)		6 (15.8)	
	Old	1 (100.0)		0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	
Ideal	Young	1 (20.0)	1(20.0)	1(20.0)	0 (0.0)	2 (40.0)	0 (0.0)	0(0.0)	
	Ideal	103(29.9)	7 (2.0)	126(36.6)	14(4.1)	38(11.0)	8 (2.3)	48(14.0)	0.941
	Old	35 (29.4)	0 (0.0)	45(37.8)	7 (5.9)	12(10.1)	1 (0.8)	19(16.0)	
Old	Ideal	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	3 (37.5)	0 (0.0)	3 (37.5)	0.045
	Old	25 (29.8)	2 (2.4)	27 (32.1)	5 (6.0)	10(11.9)	1 (1.2)	14(16.7)	

Kruskal-Wallis test: Mean rank (young maternal age+young paternal age = 24.60; young maternal age+ideal paternal age= 22.64; young maternal age+old paternal age= 6.50; ideal maternal age+young paternal age= 236.00; ideal maternal age+ideal paternal age= 233.25); ideal maternal age+old paternal age= 238.05; old maternal age+ideal paternal age= 64.00; old maternal age+old paternal age= 44.83)

CONCLUSION

In this study, we found that cleft palate will occur in infants born from an old mother (>35 years old), although most other studies show a different result. This inconsistency may result due to different methods and lack of confounding factors control. Therefore, a study protocol is needed to equalize further studies, which allows for resolving this question. Further research is required to assess parental age's impact on cleft types and severity in Indonesia.

REFERENCES

1. Wahyuni N, Latifah S. Kondisi Lingkungan di Nusa Tenggara Timur dan Prevalensi Kejadian Celah Bibir dan Celah Langitan. *BIMKMI.* 2016;**4(1)**:7.
2. Natsume N, Tolarova MM. *Epidemiology of Cleft Lip and Palate*. Tokyo: Quintessence Publishing Co., Ltd, 2006.
3. Rychtarikova J, Gourbin C, Sipek A, Wunsch G. Impact of parental ages and other characteristics at childbearing on congenital anomalies: Results for the Czech Republic, 2000-2007. *Demograph. Res*. 2013;**28**:137-176.
4. DeRoo LA, Gaudino JA, Edmonds LD. Orofacial cleft malformations: associations with maternal and infant characteristics in Washington State. *Birth Defects Res A Clin Mol Teratol*. 2003; **67(9)**:637-42.
5. Martelli DRB, Cruz KW, Barros LM, Silveira MF, Swerts MSO, Junior HM. Maternal and Paternal Age, Birth Order, and Interpregnancy Interval Evaluation for Cleft Lip-Palate. *Braz J Otorhinolaryngol*. 2010;**76(1)**:107-12.
6. Salihu S, Krasniqi B, Sejfija O, Heta N, Salihaj N, Geci A, et al. Analysis of Potential Oral Cleft Risk Factors in the Kosovo Population. *Int Surg*. 2014;**99**:161-5.

7. Luo YL, Cheng YL, Gao XH, Tan QS, Li JM, Wang W, et al. Maternal Age, Parity and Isolated Birth Defects: A Population-Based Case-Control Study in Shenzhen, China. *Plos one*. 2013;**8**:1-6.
8. Bille C, Skytthe A, Vach W, Knudsen LB, Andersen AMN, Murray JC, et al. Parent's Age and the Risk of Oral Clefts. *Epidemiol*. 2005;**16(3)**:311-316.
9. Berg E, Lie RT, Sivertsen A, Haaland. Parental Age and the Risk of Isolated Cleft Lip : A Registry-Based Study. *Annals of Epidemiol*. 2015;**xxx**:1-6.
10. Herkrath AP1, Herkrath FJ, Rebelo MA, Vettore MV. Parental age as a risk factor for nonsyndromic oral clefts: a meta-analysis. *J Dent*. 2012;**40(1)**:3-14.
11. Harville EW1, Wilcox AJ, Lie RT, Abyholm F, Vindenes H. Epidemiology of cleft palate alone and cleft palate with accompanying defects. *Eur J Epidemiol*. 2007;**22(6)**:389-395.
12. Hermann NV, Darvann TA, Munch A, Kreiborg S. Parental age in relation to the severity of cleft lip and/or palate. *Orthod Craniofac Res*. 2018;**21(4)**:236-241.
13. Vieira AR, Orioli IM, Murray JC. Maternal age and oral clefts: a reappraisal. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002;**94**:530–535.
14. Balgir RS. Parental age and incidence of cleft lip and cleft palate anomalies. *Acta Anthropogenet*. 1984;**8(3-4)**: 231-5.
15. Penrose LS. Parental age and mutation. *Lancet*. 1995;**269**:312-3.
16. Keightley PD. Rates and fitness consequences of new mutation in human. *Genetics*. 2012;**190**:295-304.