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Original article

Cleft lip and palate based on birth order and family history at Mitra Sejati General Hospital, Indonesia

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ABSTRACT

Background: *Cleft lip and palate is one of the most common congenital abnormalities in infants and is caused by more than one factors, which can be genetic and environmental. Defects in a family gene can result in cleft lip and palate. The study found a high family history relationship with the incidence of cleft lip and palate. Birth order studied by several researchers also has different results, which were influenced by folic acid consumption, maternal knowledge, lack of antenatal care visits and maternal age. To determine the cases of cleft lip and palate based on the birth order of the children and family history of the patients at Mitra Sejati General Hospital.* ***Purpose:*** *The study aimed to investigate cleft lip and cleft palate patients by birth order and family history.* ***Methods:*** *This research was a retrospective descriptive study using survey method. Researchers gave 13 questions through a questionnaire and data were collected and counted manually.* ***Results:*** *The results showed that based on the birth, the cleft case in the first birth order amounted to 25 people, the second 30 people, the third 19 people, and the fourth or more as many as 20 people. Based on family history, 27 patients had a family history of cleft lip and palate, while 67 patients did not have family history.* ***Conclusion:*** *The cases of clefts at Mitra Sejati General Hospital happened more frequently in the second child and most incidence did not have family history.*

Keywords: *cleft lip; cleft palate; genetic; risk factors*

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INTRODUCTION

Clefts of the lip and palate are congenital anomalies that take place between the fifth and tenth weeks of fetal life. The lip, alveolar ridge, and hard or soft palates are the most common site affected by oral clefts. Individuals with congenital anomalies may experience problems with teeth, malocclusion, as well as feeding, speaking, hearing, and social integration problems.[1,2]

Globally, the prevalence of cleft lip was 0.3 in every 1000 live births.[3] Meanwhile, in Indonesia, the 2013-2018 Basic Health Research or Riset Kesehatan Dasar (Riskesdas) report showed an increasing the incidence of cleft lips (from 0.08% to 0.12%) among children 24 to 59 months of age.[4,5] In most cases, the causes of cleft lip and palate are multifactorial, including genetic and environmental factors. Medication during pregnancy (amoxicillin, phenytoin, and oxprenolol), nutrient deficiency, radiation, hypoxia, virus, teratogen, smoking, also excess or deficiency of vitamins can be identified as environmental factors. Genetic factor, in addition, is known from the family history.[1,6]

Several studies showed that family history was strongly associated with an increased risk of cleft lip or palate.[7,8] In line with that, an epidemiology study conducted by Acuña-González et al.[9] showed that the presence of cleft lip or palate background for father, mother, or siblings increased the incidence of the anomalies.

Based on the birth order, a study by Noorollahian et al.[10] showed that most of the patients with malformations were first-born children (40.8%), followed by second-born children (28.19%), third-born children (14.97%), and fourth-born children or higher (16.74%). This statement was supported by Jac Okereke who reported that the first-born children accounted for most patients, but didn't have any significance relation to cleft lip and palate.[11] However, Kesande et al.[12] reported that, regarding birth order, most children with orofacial clefts were in the fourth and fifth

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rank (45.0%) compared to one to third rank (25.0%) and those in the sixth to seventh rank (30.0%).

One of the hospitals in Medan that treats patients with clefts is Mitra Sejati General Hospital. It is partner with Smile Train, which is an international children's charity that provides cleft repair surgery and comprehensive cleft care to children in more than 85 countries. According to data from Mitra Sejati General Hospital, in 2019 there were 96 patients with cleft lip or palate and in 2020 there were 107 patients with cleft lip or cleft palate.[13] In a previous study,[14] there was a study on the prevalence of cleft lip and palate regarding gender in other cities and hospitals. However, in this study, the research examined cases of cleft lip and palate regarding birth order, which never had been researched and with no recent information at Mitra Sejati General Hospital, and also regarding family history which was found to have various results. Therefore, this study aimed to provide data on the distribution of cleft lip and palate based on the birth order of the children and family history at Mitra Sejati General Hospital.

MATERIALS AND METHODS

This retrospective descriptive study using survey method was carried out in May 2021 at Mitra Sejati General Hospital as partner of Smile Train, the world's largest cleft-focused organization that provides 100% free cleft surgery. The Research Ethics Commission of Universitas Sumatera Utara approved this study (No.510/KEP/USU/2021). The sample selection was made using the purposive sampling technique and involved 94 samples after we added 10%.

$$n = \frac{Z^2_{(1-\alpha/2)} \times P \times (1-P)}{d^2}$$

$$n = \frac{(1.96)^2 \times 0.33 \times (1-0.33)}{0.1^2}$$

$$n = 84.94$$

It applied inclusion and exclusion criteria. The patients included in the current study had a cleft lip and/or palate diagnosis registered in the hospital from January 2015- December 2020 for surgical treatment or other management. Inclusion criteria were (a) patients who had received a treatment at Mitra Sejati General Hospital; (b) patients with cleft lip and/or palate without systemic conditions; and (c) parents or guardians of the children with cleft lip and/or palate who were willing to be interviewed. The following were excluded: (a) parents or guardians, who do not cooperate or were unwilling to be interviewed; (b) unreachable parents or guardians (i.e., by phone); (c) infants with chromosomal anomalies or other birth defects of known etiology and syndrome such as trisomy 13, Fryns syndrome, Meckel syndrome, and Van der Woude syndrome; and (d) patients who were treated at Mitra Sejati General Hospital but with missing or incomplete medical records. The participants were informed of their right to participate or drop out of the study without affecting their relationship with the investigators. Informed consent was given through digital platform such as Google Form in the beginning of the interview because this study was conducted during of the COVID-19 pandemic.

The primary data were conducted by interviewing parents or guardians via phone. The interview was voice recorded to help countercheck any information missing. There were 13 questions in each questionnaire, which related to things experienced by the mother during pregnancy. Information was obtained from questions number one to four regarding the birth order of the children and questions number five to seven regarding the family history of cleft lip and palate. The remaining questions were administered to figure out the risk factors of the cleft incidence. The medical records were collected at Mitra Sejati General Hospital with the visit year of 2015-2020 as the secondary data, which included information on name, age, gender, ethnic, address, telephone and birth order. There were two observers involved in this study to minimize the bias and, before the interview, the investigators were provided brief and training for the calibration. Data processing was manually put in Microsoft Excel, the information was tabulated, by which frequencies and percentages were calculated.

RESULTS

The socio-demographic data is shown in Table 1. Of 94 patients with cleft incidence, 25 patients were first-born children (26.60%), 30 patients were second-born children (31.91%), 19 patients were third-born children (20.21%), and 20 patients were fourth-born children or higher (21.28%). Based on the family history, 27 patients (28.72%) had parents or siblings with cleft lip and/or palate, while 67 patients (71.28%) showed negative family history of oral clefts.

The distribution of cleft incidence regarding birth order is shown in Table 2. Cleft lip and palate were the most common cases found among all groups. The majority of cleft cases from first-born until last were cleft lip and palate 80%, 86.67%, 84.21%, and 80%, respectively. The prevalence of cleft lip and palate was studied in the first-degree relatives and found to be 25% in patients with affected fathers and 12.50% in affected mothers, then followed by siblings as shown in Table 3.

The distribution of cleft incidence regarding the family history of second-degree relatives is shown in Table 4. The result showed that cleft lip and palate were mostly patients with affected grandparents. In addition, the incidence of oral clefts was found patients with affected uncles/aunties, where one patient had a cleft palate, while the other six patients had both cleft lip and palate. In the third-degree relatives, a total of nine patients (100%) had cousins with clefts. Four patients suffered from cleft lip only, while five patients suffered from both cleft lip and palate as shown in Table 5.

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Table 1. The characteristics of study subjects (n=94)

Respondent characteristic		n (people)	%
Birth order of the children	1	25	26.60
	2	30	31.91
	3	19	20.21
	≥4	20	21.28
Family history	Yes	27	28.72
	No	67	71.28

Table 2. The distribution of clefts incidence based on the birth order of the children (n=94)

Cleft cases	Birth Order							
	1		2		3		≥4	
	n	%	n	%	n	%	n	%
Cleft lip only	5	20	3	10	2	10.53	2	10
Cleft palate only	0	0	1	3.33	1	5.26	2	10
Cleft lip and palate	20	80	26	86.67	16	84.21	16	80
Total	25	100	30	100	19	100	20	100

Table 3. The distribution of clefts incidence based on the family history of first-degree relatives

Cleft cases	First-degree relatives							
	Father		Mother		Sibling		Child	
	n	%	n	%	n	%	n	%
Cleft lip only	0	0	0	0	1	20	0	0
Cleft palate only	0	0	0	0	2	40	0	0
Cleft lip and palate	2	100	1	100	2	40	0	0
Total	2	25	1	12.5	5	62.5	0	0

Table 4. The distribution of clefts incidence based on the family history of second-degree relatives

Cleft cases	Second-degree relatives									
	Grandparents		Uncle/ Aunt		Nephew/Niece		Step sibling		Grandchildren	
	n	%	n	%	n	%	n	%	n	%
Cleft lip only	0	0	0	0	0	0	0	0	0	0
Cleft palate only	0	0	1	14.29	0	0	0	0	0	0
Cleft lip and palate	6	100	6	85.71	0	0	0	0	0	0
Total	6	46.15	7	53.85	0	0	0	0	0	0

Table 5. The distribution of clefts incidence based on the family history of third-degree relatives

Cleft cases	Third-degree relatives							
	Great grandparents		Great Uncle/Aunt		Great grandchildren		Cousin	
	n	%	n	%	n	%	n	%
Cleft lip only	0	0	0	0	0	0	4	44.44
Cleft palate only	0	0	0	0	0	0	0	0.00
Cleft lip and palate	0	0	0	0	0	0	5	55.56
Total	0	0	0	0	0	0	9	100

DISCUSSION

The present study showed that clefts incidence was found to be more prevalent in second-born children compared to other groups. Similarly, a study by Acuña-González et al.[9] also stated that the prevalence of cleft lip and/or palate in first or second-born children was higher compared to third or fourth-born children. However, a study conducted by Noorllahian et al.[10] showed a different result, where the incidence of cleft lip and/or palate was the highest in first-born children. This may be due to consanguineous marriages between two individuals who are related as first cousins or closer from both paternal and maternal sides. Consanguineous marriages can lead to various disorders, such as congenital abnormalities, stunted growth, epilepsy, mental retardation or learning disabilities, blood disorders, unexplained neonatal death, and an increase in autosomal recessive disorders.[15] We also reported a different result from a study conducted by Kesande et al,[12] where the fourth and fifth-born children had the highest prevalence of oral clefts. These results may be influenced by several factors, such as approximately 20% of mothers have a history of

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abortion and most of them live in hillside areas.[12,16] A higher maternal age is also associated with the risk of cleft incidence, where the energy in embryonic development decreases. As a result, deformity during the cell division stage to the organogenesis stage may occur.[17]

The deficiency of folic acid during embryonic development and the lack of maternal knowledge can affect the incidence of cleft lip or palate. Folic acid is well-known for its role as a one-carbon donor, which is essential for DNA synthesis and proliferation. It also plays an important role in synthetizing *enzyme methylenetetrahydrofolate reductase* (MTHFR) for folate-dependent metabolism of homocysteine. As a result of low MTHFR activity due to polymorphisms, higher homocysteine or lower plasma folate cells may occur, of which both are associated with neural tube defect.[18] The deficiency of folic acid may also lead to the inability of methionine production; hence, the production of antioxidants (glutathione) and sulfur-containing amino acid that eliminate toxins in the body, strengthens tissues, and maintains cardiovascular health also decreases.[19,20] In addition, lack of maternal knowledge about prenatal nutrition, such as folic acid and zinc, can affect fetal growth and development.[8,9,21] Deficiency of zinc, for instance, causes impaired reabsorption of folate which affects the production of methionine.

Other possible factors are the impact of unwanted pregnancy among married women, which affects the mother's mental and psychological condition in the process of child care and nutrition.[22] During pregnancy, psychological stress causes disruption in endocrine, nervous and immune systems. It can strongly activate the hypothalamo-pituitary-adrenal (HPA) stress response, increases corticotropin-releasing hormone (CRH), and stimulates the production of inflammatory cytokines. As a result of altered immune system due to stress, mothers are more susceptible to infection and illness during pregnancy.[23]

The majority of the patients with oral clefts do not have positive family history of the anomalies. The result was similar to a study conducted by Figueiredo et al.[8] where clefts incidence mostly occurred in patients without positive family history and it was statistically significant. It was assumed that environmental factors, such as exposure to cigar smoke or mothers who did not take folic acid, played a bigger part than the genetic factors.[8] According to Kummet et al.,[24] passive smoking women have a greater risk of giving birth to children with clefts. Smoking is one of the risk factors for cleft lip and palate. Cigarettes contain nicotine, polycyclic aromatic hydrocarbons, tar, carbon particles, and carbon monoxide. Exposure to cigarette smoke to embryonic tissue depends on the number of cigarettes smoked, the frequency of inhalation, and the depth of inhalation. The mechanism by which cigarette smoke affects pregnancy is still not well-understood.[25] Several studies also reported significant relationship between tobacco exposure and development of orofacial clefts. However, the mechanism by which cigarette smoke affects pregnancy is not well-understood.[25–27]

Most of the cleft cases this study were cleft lip and palate, where 78 people were affected. In line with that, Lin et al.[28] also reported a similar study result. Among all possible factors, it may be related to maternal level of knowledge and age during pregnancy.[28] According to Bui, et al.,[26] cleft lip and palate were the most cases if compared to cleft palate, which were caused by father or mother's smoking. Based on the result in Table 3, 4 and 5, cousins had the most frequencies of cleft lip and palate. Similarly, Martelli et al.[2] reported that cousins were the most affected by clefts incidence. The plausible factor is autosomal recessive inheritance, where both parents of cousins are a carrier that inherits clefts incidence. Autosomal recessive inheritance occurs when two individuals with a recessive allele meet, so that the newborn individuals have a phenotype. When both parents have recessive type, there is a chance whereby 25% of the babies will inherit the anomalies, 50% will be a carrier, and 25% will be normally born. In the present study, we may assume that both parents have carrier gene since most of the patients do not have positive family history of clefts incidence.[29]

This study, however, had several limitations because we found it hard to obtain more detailed information from medical records at Mitra Sejati General Hospital due to inefficient medical record storage system and also respondents who were less fluent in sharing information, so that it can affect the interview process with researchers. We suggested this research can be a theoretical base for further research and a guideline for regional health services, especially Mitra Sejati General Hospital, to provide guidance and first aid to babies with cleft lip and palate, and hope this study can be used as additional education material to add new information and knowledge to public for increase awareness about the risk factors for the occurrence of cleft lip and palate. In conclusion, the highest distribution of cleft lip and palate regarding birth order at Mitra Sejati General Hospital in 2015-2020 was among second-born children with a total of 30 people (31.91%), individuals with negative family history with a total of 67 people (71.28%), and cousins who were affected by clefts (100%).

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