ABSTRACT

Background: Cleft lip and palate (CL/P) is one of the most common congenital anomalies with the prevalence of 1 case for every 1000 birth. The purpose of this study is to evaluate the association between paternal and maternal age to the incidence of cleft lip with or without cleft palate.

Methods: This case-control study compares data of 74 cleft lip patients who was enrolled in Gentur Cleft Foundation Foundation year 2013 to 2015 compared to those of 86 normal children. Paternal and maternal age were categorized and compared to reference age (25-29 years old). Binary logistic regression was used to assess the interaction between paternal and maternal age adjusted to several confounding factors.

Results: Paternal age (PA) 18-24 year has OR 9.12 (95% CI = 2.2-36.7), PA 30-34 has OR 2.74 (95% CI =1.2-5.9), PA 35-48 has OR 5.82 (95% CI = 2.2-15.67) compared to those in the 25-29 years category. Maternal age (MA) 18-24 year has OR 4.385 (95% CI = 1.86-10.36). MA 35-48 has OR 6.58 (95% CI = 1.65-26.31) compared to those in the 25-29 years category. P-value was insignificant for MA 30-34 years. Interaction were observed in crossings between PA 18-24 with MA 18-24, PA 25-29 with MA 18-24, PA 30-34 with MA 25-29, PA 35-48 with MA 30-34, and PA 35-48 with MA 35-40.

Conclusion: We observed stronger association between paternal ages with CL/P compared to that of maternal age. Interactions of paternal and maternal age with high OR were found in youngest age group (18-24 years old), oldest age group (above 35 years old), and fathers who are approximately 10 years older than the mother.

Keyword: maternal age, paternal age, risk factors, cleft lip palate

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BACKGROUND

Cleft lip and palate is one of the most common congenital anomalies with the prevalence 1 case for every 1000 child birth for cleft lip and 1 case for every 2000 birth for cleft palate. Asian population generally has a higher incidence compared to Caucasian with incidence 2.1 for every 1000 child birth. Meanwhile, according to Riskesdas 2013 (Indonesian Basic Health Research) the prevalence of cleft lip in Indonesia is 0.08 percent. 

The etiology of cleft lip is multifactorial with both genetic and environmental involvement. Exposure to anticonvulsant, alcohol, and cigarette smoking at the first trimester can impair craniofacial development. Maternal age above 25 years old is associated with chromosomal congenital anomalies as well as non-chromosomal malformation including cleft lip when compared to women 20-24 years old.

While most of study focused on the maternal aspects, we have to consider that genetic traits come from both maternal and paternal inheritance. Several studies on parental age confirmed that there are increased odds in both maternal and paternal age of older groups. Based on an epidemiological study in Denmark, the Odds Ratio (OR) of cleft lip with or without cleft palate was 1.2 per 10 year increase for maternal age ranged 20-40 years (95% CI = 1.08—1.33). Study by Bille shows that the OR of cleft lip with or without cleft palate for paternal age ranged 20-50 years was 1.12 per 10 year increase. Another epidemiological study by Berg revealed that the risk for having isolated cleft lip was 1.28 per 1000 for paternal age 44 year and above, and 1.27 per 1000 for maternal age 38 year and above. A meta-analysis study by Herkrath explains that, the odd for cleft lip was 1.58 for paternal age 40 year and above compare to paternal age 20-39 year.

With those premises being discussed, the aim of this study is to evaluate the association between paternal and maternal age to the incidence of cleft lip with or without cleft palate.

METHODS

This is a case-control study of 75 cleft lip with or without cleft palate patients from Gentur Cleft Foundation (GCF) from September 2013 to July 2015. With the exclusion criteria of syndromic cleft lip, we excluded 1 Pierre-Robin Sequence patient. Control group consisted of parents from 85 normal children. Parents of both groups were interviewed using a written questionnaire which consist of patient consent, family information, history of present illness, pregnancy, and surgical treatment.

Paternal and maternal ages were cut in 5 years interval with adjustments to the first and last categories to avoid small counts of extreme data. The reference category was the 25-29 year-old category because women aged 25-29 years old have the highest fertility rate (145 deliveries for every 1000 mothers) in urban population, according to Indonesia Demography and Health Survey 2012. Data was also adjusted for parity, cigarette smoking exposure, and folic acid supplementation. The final data was then analyzed with SAS University Edition using binary logistic regression to evaluate risk estimates and interaction of paternal and maternal age.

RESULTS

Subject characteristics of both study and control group were described in table 1, with male predominance in the study group. This is in line with epidemiological profile of CL/P in previous literatures.

Disclosure: The authors have no financial interest to disclose.
Table 1. Characteristic and Descriptive Statistics of CL/P patients and Control Group

<table>
<thead>
<tr>
<th></th>
<th>CL/P n=74</th>
<th>Control n=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (60.8)</td>
<td>45 (52.3)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (39.2)</td>
<td>41 (47.7)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 months</td>
<td>48 (64.8)</td>
<td>28 (32.5)</td>
</tr>
<tr>
<td>1-3 years</td>
<td>19 (25.7)</td>
<td>39 (45.3)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>0</td>
<td>13 (15.1)</td>
</tr>
<tr>
<td>5-12 years</td>
<td>5 (6.7)</td>
<td>6 (6.9)</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>2 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>Paternal Age (mean ± SD)</td>
<td>31.09 ± 6.420</td>
<td>29.31 ± 4.120&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paternal Age (median)</td>
<td>28.00 (24-50)</td>
<td></td>
</tr>
<tr>
<td>Maternal Age (mean ± SD)</td>
<td>27.74 ± 5.540</td>
<td>27.43 ± 3.288&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maternal Age (median)</td>
<td>27.00 (20-40)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> KS p-value<0.05, median 28.00 (24-50)
<sup>b</sup> KS p-value<0.05, median 27.00 (20-40)

In Figure 1 and 2 we can see that control group box plot is shorter that CL/P group. This shows that CL/P group has wider range of data distribution. Control group also has 2 extreme values that exceed maximum limit.
Paternal ages were categorized in 4 years interval; 18-24, 25-29, 30-34, and 35-48 y.o with paternal age 25-29 y.o as a reference interval. The first and last categories were adjusted to avoid small counts of extreme data. Paternal age 18-24 y.o has OR 9.12 (95% CI = 2.2-36.7), paternal age 30-34 y.o has OR 2.74 (95% CI =1.2-5.9), paternal age 35-48 y.o has OR 5.82 (95% CI = 2.2-15.67) compared to those in the 25-29 years category.

![Figure 3. Odd Ratio for Paternal Age](image1)

![Figure 4. Odd Ratio for Maternal Age](image2)

Maternal age were also categorized in 4 years interval; 18-24, 25-29, 30-34, and 35-40 y.o. The reference category was 25-29 y.o. The first and last categories were adjusted to avoid small counts of extreme data. Maternal age 18-24 y.o has OR 4.385 (95% CI = 1.86-10.36), maternal age 30-34 y.o has OR 1.754 (95% CI =0.72-4.27), maternal age 35-48 y.o has OR 6.58 (95% CI = 1.65-26.31) compared to those in the 25-29 y.o category. However, P-value was insignificant for maternal age 30-34 y.o. Interactions were analyzed using binary logistic regression. Maternal age and paternal age were crossed in a categorical manner and adjusted to parity, smoking exposure, and supplementation.

![Table 4. Cross Interaction Matrix between Maternal Age and Paternal Age](image3)

<table>
<thead>
<tr>
<th>Estimated OR</th>
<th>MA 18-24</th>
<th>MA 25-29</th>
<th>MA 30-34</th>
<th>MA 35-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA 18-24</td>
<td>10.909*</td>
<td>6155270</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PA 25-29</td>
<td>4.675*</td>
<td>1.000</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PA 30-34</td>
<td>20.455*</td>
<td>4.091*</td>
<td>1.860</td>
<td>6155270</td>
</tr>
<tr>
<td>PA 35-48</td>
<td>6155270</td>
<td>8.182</td>
<td>7.159*</td>
<td>9.545*</td>
</tr>
</tbody>
</table>

* p-value < 0.05
Significant interactions were observed in crossings between PA 18-24 with MA 18-24, PA 25-29 with MA 18-24, PA 30-34 with MA 18-24, PA 30-34 with MA 25-29, PA 35-48 with MA 30-34, and PA 35-48 with MA 35-40. High odds ratios were found in interaction between paternal age 35-48 with maternal age 35-40 (OR 9.5), paternal age 18-24 with maternal age 18-24 years old (OR 10.9), and—highest—in paternal age 30-34 years old with maternal age 18-24 years old (OR 20.5).

DISCUSSION
This study found that the odd of having child with CL/P increases for both paternal and maternal of extreme age. It is important to consider both paternal and maternal age into account when assessing CL/P risk factors.

In this study, the incidence of CL/P in mothers aged 35-40 years old was 6.58 times more often than the reference group. We also found that the incidence of CL/P in mothers aged 18-24 years old were 4.38 times more often than the reference groups. In paternal age, we noticed that incidence of CL/P in fathers aged 30-34 years old were 2.74 times higher than the reference group. The incidence of CL/P for paternal age 35-48 were 5.8 times higher than the reference group. In younger paternal age group (18-24) the incidence of CL/P were 9.1 times higher than the reference group. Stronger correlation with CL/P was found in paternal age 30-34 compared to maternal age 30-34.

Significant interactions are found in 6 crossings of paternal-maternal age groups. The incidence of CL/P was 9.5 times higher in oldest age group, 10.9 times higher in youngest age group, and 20.4 times higher in fathers who are approximately 10 years older than the mother.

In modern society, marital age is often delayed and parenthood age is delayed as well. This in turn will have an impact to the paternal and maternal age thus adding few ages when the couple finally decides to conceive. In Indonesia, the median marital age of woman is 20.4 years old and man is 24.3 years old (Indonesia Demography and Health Survey, 2012).
Maternal Age

Study from Atlanta Congenital Defects Program revealed that young maternal age and advanced maternal age were both associated with increased risk for non-chromosomal birth defect\(^4\). Younger maternal age (14-19 years) was associated with anencephaly, hydrocephaly without neural tube defect, all ear defect, cleft lip, female genital defects, hydronephrosis, polydactyly, omphalocele, and gastroschisis.

A possible explanation for increased odds of CL/P in younger mother is might be because of the lack of supplementation and frequent pregnancy unawareness\(^{15}\). Mathews et. al identifies that young pregnant nulliparous women are at risk of poor intakes of antioxidants and micronutrients including poor supplementation compliance\(^{16}\). The study also found strong association between maternal age and supplementary intakes (Vitamin C, Vitamin E, Retinol, Vitamin D, Thiamin, Folic Acid, Vitamin B12, Zinc, Calcium). Older women had higher intake of nutrients compared to younger women.

Other factors that might increase the odd for having newborn with CL/P are smoking\(^{17}\), alcohol\(^{18}\), birth order\(^{19,20}\), and familial history\(^{15,21}\). Evidence shows that taking folic acid may prevent cleft lip and palate\(^{4,22}\). In fact, there has been gene-environment interactions reported in previous study\(^4\). Those gene-environment interaction were TGFA/Smoking, TGFA/Alcohol, TGFA/Vitamins, MSX1/Smoking, MSX1/Alcohol, TGFB3/Smoking, TGFB3/Alcohol, RARA/Smoking, MTHFR/Vitamins, P450/Smoking, GST/Smoking, and EPHX1/Smoking.

Paternal Age

Other than CL/P, younger paternal age is associated with the increase of odd for gastroschizis\(^{23}\), spina bifida, microcephalus, and musculoskeletal/integumental anomalies\(^{24}\). The mechanism is still poorly understood, but this might be due to paternal behavioral causes such as cigarette smoking and lower education.

Advanced paternal age is associated with increased DNA mutation and chromosomal aberration in sperm\(^{23}\). For each year increase, elevated odd ratio were reported for having newborn with cleft palate (OR 1.02), diaphragmatic hernia (OR 1.04), right ventricular outflow tract obstruction (OR 1.03), and pulmonary valve stenosis (OR 1.02). Advanced paternal age is also associated with the increasing probability of having newborn with achondroplasia, Apert Syndrome, Neurofibromatosis, and possibly Cleft Lip.

Unlike oogenesis, spermatogenesis (the dividing of sperm) occurs continuously throughout a man’s life. That being said, there is higher chance for de novo single nucleotide mutation on spermatozoa because of spermatogonial meiosis and the testicular environment is more prone to toxic effects of oxidative stress\(^{25,26}\). Theories explain DNA damage in sperm can be caused by abnormal protamination or abnormal protamines compaction \(^{25}\). This is due to the presence of histone proteins that are not converted into protamine. Other is because of oxidative stress—as a result of infection or inflammation—that produces reactive oxygen species that could fragment DNA by almost 80%.

Since there are many factors that could affect paternal aspects of the incidence congenital anomalies, it is mandatory for fathers—and fathers to be—to take necessary precautions before married and during his married life. These precautions include to stop smoking, stop alcohol, taking specific age targeted family planning, and maintain overall health and nutrition.

CONCLUSION

We observe stronger association between paternal age with CL/P compared to maternal age with CL/P in category 30-34 years old. High risk estimation for interactions of maternal and paternal age were found in youngest age group (18-24 years old), oldest age group (above 35 years old), and fathers who are approximately 10 years older than the mother.

Small sample size in this study is a limitation not to generalize the results in this study to the populations. Research in rural population would be complementary to this study to achieve the goal to evaluate the association between paternal and maternal age to the incidence of cleft lip with or without cleft palate.

Corresponding author:
Gentur Sudjatmiko
lingkarstudiedahplastik@gmail.com
REFERENCES


