

# Pregnancy Unawareness and Risk Factors in Cleft

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**Background :** The etiology of the cleft lip and palate (CLP) are still debated among researchers. Early pregnancy awareness is essential since the facial formation occurs in the first eight-week of gestation period. This study aims to compare pregnancy awareness and risk factors associated with CLP.

**Method :** A descriptive cross-sectional study on 103 mothers whose child suffered from non-syndromic CLP (cases) was compared to 157 mothers whose child is normal (control). Parameters evaluated were pregnancy awareness during early pregnancy and CLP risk factors, including oral contraceptive (OC), absence of vitamin supplementation, smoking, and alcohol use within the first eight-week of gestation period. Family history and maternal age were also assessed.

**Result :** The rates of late pregnancy awareness were 10-folds higher in cases, with the scale of 65% compared to 6.5% (p value <0.0001). The use of OC in cases group were 22.6-folds higher (13.6% versus 0.6%), the absence of vitamin supplementation were found to be 123-folds higher as well (73.8% compared to 0.6%). An inverted data were found in the smoke exposure parameter, which was higher in control (27.7% versus 10.7%). In confounded factors, advanced maternal age in the cases soared (37.9% compared to 25.3%), positive family history of cleft were discovered in 24.3% of mother with cleft children.

**Conclusion :** Most cases were categorized in late pregnancy awareness. Higher rates of positive family history and advanced maternal age in cases group were also found.

**Keywords :** *pregnancy awareness, risk factors, cleft lip palate.*

**Latar Belakang :** Etiologi dari sumbing bibir dan langit-langit (CLP) masih menjadi perdebatan diantara para peneliti. Menyadari kehamilan dini penting, karena formasi wajah terjadi pada 8 minggu pertama periode gestasi. Studi ini bertujuan membandingkan kesadaran kehamilan dan faktor resiko kejadian sumbing.

**Metode :** Studi deskriptif cross-sectional ini melibatkan 103 ibu yang memiliki anak dengan CLP tanpa sindrom dibandingkan dengan 157 ibu dengan anak normal. Parameter yang dievaluasi meliputi pregnancy awareness dan faktor resiko terhadap CLP, termasuk konsumsi kontrasepsi oral, absensi suplementasi vitamin, serta paparan rokok dan alkohol di 8 minggu pertama kehamilan. Faktor resiko lainnya yaitu adanya riwayat keluarga dan umur ibu saat hamil.

**Hasil :** Frekuensi *late pregnancy awareness* pada ibu dengan anak sumbing 10 kali lipat lebih tinggi daripada ibu dengan anak normal dengan skala 65% berbanding 6.5% (p value <0.0001). Penggunaan OC pada grup kasus 22.6 kali (13.6% berbanding 0.6%), tidak adanya suplementasi vitamin memiliki nilai 123 kali lipat lebih tinggi pada kelompok kasus (73.8% berbanding 0.6%). Data yang terbalik ditemukan pada paparan terhadap rokok, di mana pada kelompok kontrol memiliki frekuensi paparan yang lebih tinggi (27.7% berbanding 10.7%). Pada kelompok faktor resiko lain, ditemukan kenaikan jumlah faktor resiko usia ibu yang tua pada saat hamil.

**Kesimpulan :** Sebagian besar ibu dari anak dengan sumbing sadar akan kehamilan setelah 8 minggu umur kehamilan. Frekuensi dari riwayat keluarga yang positif menderita sumbing serta usia ibu hamil di atas 30 tampak lebih tinggi pada grup kasus

**Kata Kunci :** *Pregnancy awareness, risk factors, cleft lip palate.*

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**T**he etiology of the cleft lip and palate (CLP) are debated among researchers, several studies have been published to find out the role of either genetics or the environment in the etiology of the CLP. Some researchers postulated that the role of folic acid,

and that of other vitamins, in the prevention of CLP is necessary.<sup>1</sup> Some studies associate oral contraceptives with the risk of CLP, while others claimed oral contraceptives was not the potential risk of CLP.<sup>2</sup> Another studies have found that maternal exposure to alcohol,

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smoking, toxic material and certain drugs may increase the risk for CLP and so do the maternal age, pregnancy complication may contribute to the development of CLP. In addition, one of the strongest relative risk for having a baby born with CLP was the history of CLP in family.<sup>3</sup> The exposure of several risk factors in the first trimester of gestation may lead to the anomaly, as the embryological facial formation occurred in the first trimester, approximately in the 8th week of gestation period.<sup>4</sup>

Early pregnancy awareness can be missed by most of pregnant women especially in cases of unplanned pregnancy. In this condition, unaware pregnant women may be unconsciously exposed by several risk factors associated with CLP. Usually the sign is often seen with having missed period. Another signs and symptoms due to the rising level of HCG (Human Chorionic Gonadotropine) hormone such as minor fatigue, some nausea and vomiting can vary among women, which will cause the late awareness in asymptomatic pregnancy. In addition, in some women who take oral contraceptives will tend to ignore the missing period as they might have irregular period due to hormonal changes.

The first week of pregnancy is the week of last menstrual period before pregnancy. The conception will take place in the third week of pregnancy, while the missing period sign will be known in the fourth week of pregnancy. Pregnancy awareness is necessary in the first trimester since the essential fetal development occurs within this trimester. This study aims to compare pregnancy awareness and risk factors associated between women with normal child and women who have child with CLP.

## METHODS

A descriptive cross-sectional study on 103 mothers whose child enrolled in Gentur Cleft Foundation with non-syndromic CLP was compared with 157 mothers whose child is normal. The parameters were the mother's pregnancy awareness which related to the risk factors exposed during the first trimester, such as oral contraceptive (OC) consumption, the absent of vitamin which is folic acid supplementation, smoke exposure, and alcohol

use. The parameter of late pregnancy awareness was described as mother's awareness on more than eight-week of gestation period. Another confounded factors including family history and maternal age were also assessed.

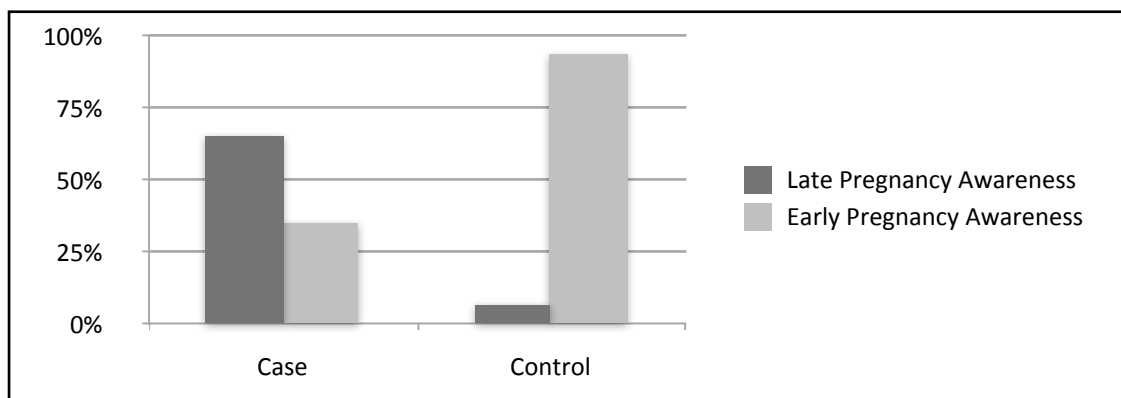
## RESULTS

In this study, there were 67 mothers from 103 mothers (65%) among cases group categorized as late pregnancy awareness, while it is only 10 mothers from 157 mothers (6.5%) in control group categorized as late pregnancy awareness (Figure 1). The statistical analysis showed significant difference between percentage of cases and control group in this study ( $P$  value  $< 0.001$ ).

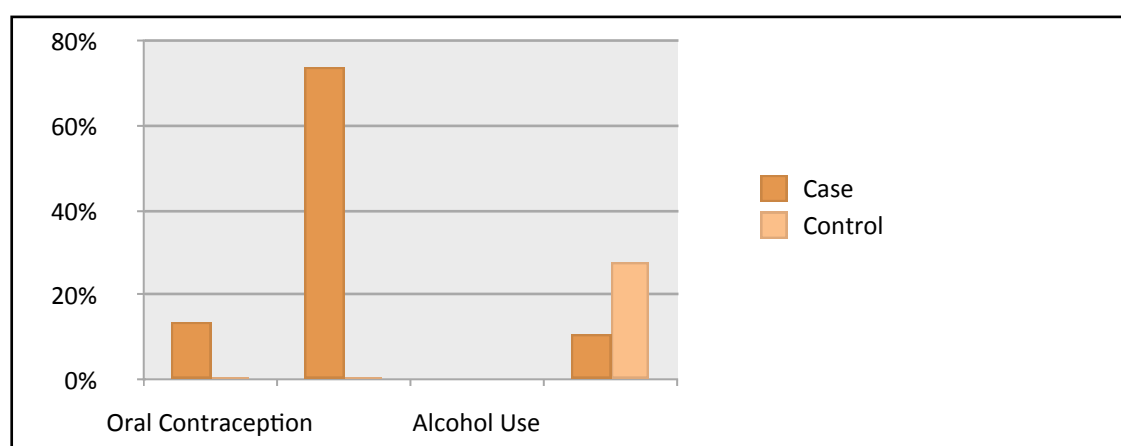
The use of OC on cases mothers was higher than control mothers ( $p < 0.001$ ). There were 14 (13.6%) among 103 mothers with cleft children who consumed OC during their first eight-week of gestation. All of the mothers were categorized in late pregnancy awareness, this might mean they were still consumed OC during the embryological facial formation process. In control mothers, there was only 1 (0.6%) among 155 mothers who consumed OC during pregnancy, but she was aware early on the pregnancy and stopped consuming as soon as she noticed the pregnancy symptom. (Figure 2)

Rates of absence vitamin supplementation consumption during first eight-week gestation were higher in cases mothers than control mothers ( $p < 0.001$ ). There were 76 (73.8%) among 103 mothers with cleft children whom recorded absence of vitamin supplementation, 67 of them were categorized in late pregnancy awareness, while 9 others were aware early on but neglected vitamin consumption with several reasons. While in controls, there was only 1 (0.6%) among 155 mothers with normal children who did not consume any vitamin because she was not aware the pregnancy during the first eight-week of gestation (Figure 2).

There were no mothers who consumed alcohol during their pregnancy in both control and cases. While regarding the smoke exposure parameter, the data showed an inverted result.



**Figure 1.** Pregnancy awareness in case and control group



**Figure 2.** The proportion of risk factors of CLP in cases and control group

Mothers with normal children were exposed to smoke more than those mothers with cleft children ( $p < 0.010$ ). It showed by 11 (10.7 %) over 103 mothers with cleft children and 43 (27.7%) over 155 mothers with normal children who were exposed to smoke (Figure 2).

Another risk factor was family history of cleft, which was showed higher in cases compared to controls ( $p < 0.001$ ). There were 25 (24.3%) of 103 mothers with cleft children. And 14 among them were aware on the pregnancy in the first eight-week of gestation period, while 11 others were categorized in late pregnancy awareness. In controls, 2 mothers (1.3%) among 155 were recorded having family history of cleft, and all of them were aware on the pregnancy in the first eight-week of gestation period (Figure 3).

The amount of mothers who were aged more than 30 years old during pregnancy were slightly higher in cases group compared to

control group and it was significantly different ( $p = 0.03$ ). It was recorded as 39 (37.9%) among 103 in cases and 39 (25.3%) among 155 in controls. Thirty-one over 39 mothers with cleft children who aged more than 30 during conception were categorized in late pregnancy awareness, while another 8 mothers were aware on their pregnancy early. In controls, from 39 mothers, 6 of them were aware on the pregnancy late, while 33 mothers were aware on the pregnancy early (Figure 3). The result of several risk factors and its exposure to mothers was showed in Table 1.

## DISCUSSION

This study found that on case group, the rate of mothers who had late pregnancy awareness is higher (65%) than control group (35%). Late pregnancy awareness in this study means mothers who were aware they were pregnant after the 8<sup>th</sup> week of gestation period.

**Table 1.** Result of several risk factors of CLP

Characteristics	Overall					Late pregnancy awareness				Early pregnancy awareness			
	Cases		Controls		p-value	Cases		Controls		Cases		Controls	
	N =	103	N =	155		N =	67	N =	10	N =	36	N =	145
<b>Use of Contraceptive Hormones</b>	14	13.6%	1	0.6%	< 0.001	14	20.9%	0	0.0%	0	0.0%	1	0.7%
<b>Absent of Vitamin Supplementation</b>	76	73.8%	1	0.6%	< 0.001	67	100.0%	0	0.0%	9	25.0%	1	0.7%
<b>Alcohol consumption</b>	0	0.0%	0	0.0%	-	0	0.0%	0	0.0%	0	0.0%	0	0.0%
<b>Smoke exposure</b>	11	10.7%	43	27.7%	0.001	7	10.4%	4	40.0%	4	11.1%	39	26.9%
<b>Family History</b>	25	24.3%	2	1.3%	< 0.001	11	16.4%	0	0.0%	14	38.9%	2	1.4%
<b>Mother's Age during Conception &gt; 30 y.o</b>	39	37.9%	39	25.2%	0.030	31	46.3%	6	60.0%	8	22.2%	33	22.8%

It is very crucial since the critical period of lip and palate development is started from conception to the 8<sup>th</sup> week of gestation period.<sup>4</sup> A study by Peter et al. reported that planned pregnancy were associated with a lower risk of orofacial cleft.<sup>5</sup> Therefore, pregnancy awareness as early as possible is essential, as it will affect the life style behavior of an expecting mother. This study indicates several risk factors gave significantly increasing number in the outcome of CLP.

#### Oral Contraceptive Hormones

Based on the present data recorded, more than one fifth (20.9%) of mothers of cleft children which have late pregnancy awareness still consumed the OC hormones when she was pregnant in the first semester. They usually didn't realize they were pregnant due to irregular menstruation they had because of hormonal changes, and kept consuming the OCs. Obviously prior to this event, they tend to take OC in irregular basis causing failure on the whole concept of contraception.

Although some study indicate there were lack of association between OC and oral cleft,<sup>6,7</sup> but there were some study that shown

the moderate risk level.<sup>8</sup> In 1960s, Peterson detected an association of oral contraceptive use during pregnancy and various malformations.<sup>9</sup> Harlap et al also noted a small risk of oral cleft following the use of estrogen and progesterone in early pregnancy.<sup>10</sup>

There was no significant explanation about why the OC might be responsible for development of CLP, but it might associate with evidence of folic acid and vitamin B12 levels depletion in woman taking oral contraceptives. These levels usually do not come back to normal until three months after usage has stopped.<sup>11</sup> Various studies stated that high folic acid levels during early pregnancy have significant role in reducing the risk of CLP.<sup>12-3</sup>

In this study, we found there was statistically significant increasing numbers of risk factor of using OC in mothers of cleft children (20.9%) compared to control (0.6%). There were many studies of association between OC and CLP was done in the past years and failure to proved the absolute risk. This present report indicates we should restart the further study and in-depth research about OC consumption and its association with the incidence of CLP.

### **Absent of Vitamin Supplementation**

Based on this study, the proportion of mothers who were taking vitamin supplements in both case and control groups was in contrast. The rates of absent vitamin supplementation during first eight-week gestation were higher in mothers with cleft children (73.8%) compared with mothers with normal children that only 0.6%. Among mothers with cleft children that had absented of vitamin supplementation, most of them were in late pregnancy awareness.

Multiple studies had reported that multivitamin and folic acid supplementation had the protective effect against various congenital birth defect, especially Neural Tube Defect (NTD).<sup>14</sup> Since then, it was postulated a possibility that folic acid supplementation may reduce the occurrence of CLP. Cheizei et. al (1994) found the protective effect of folic acid to be significant for all types of cleft,<sup>15</sup> whereas Shaw et al (1995) found this only applied to the isolated CL/P alone.<sup>16</sup> A study in 2007 reported there was a decrease in isolated CL/P risk by a third with using folic acid supplementation and other vitamins during early pregnancy.<sup>12</sup> However, a study in 2008 showed no strong evidence for an association between CLP and folic acid intake alone, but the use of multivitamin in the early pregnancy may produce protective effect of CLP although this association may be confounded by other lifestyle factors such as family history.<sup>17</sup> Study in high-prevalence region in China in 2012, reported a daily maternal consumption of 400 µg without other vitamins started before mother's last menstrual period was associated with reduced risk of CLP.<sup>13</sup>

This present study suggests the importance of pregnancy awareness of expectant mothers. The sooner they were aware that they were pregnant, the better the mothers will take special care of their nutrition, include the vitamin supplementation. Other than pregnancy awareness, we should also consider of the understanding and awareness of pregnant mothers about the importance of vitamin and folic acid supplementations during pregnancy. A literature has described how an understanding of folic acid consumption has not been well studied, particularly in

developing countries.<sup>18</sup> There was a study in Iran, a developing country, which stated the awareness of folic acid supplementation is low among pregnant woman.<sup>19</sup> Indonesia is also a developing country that has many under-educated people with lack of health information. Therefore, it's a necessity for all the health providers to pay special attention to educate woman in reproductive age about the benefit of folic acid supplementation for preventing congenital birth defect, include CLP.

### **Alcohol and smoking**

Based on this reported data, there were no mother who consumed alcohol during their pregnancy in both control and cases. This event might be due to the eastern culture issues. Merely, Indonesia is known as the world's most populous Moslem country, which prohibits their followers to drink alcohol. Alcohol, however, has known to be one of the risk factors that can lead to CLP. Several studies revealed an association between various levels of alcohol use during first trimester of pregnancy and incidents of CLP.<sup>20-3</sup> DeRoo et al (2007) reported compared to the non-drinkers, mothers who had binge-level drinking (>5 drinks per sitting) were more likely to have infant with CLP.<sup>24</sup>

Unlike alcohol, smoking in Indonesia is very common. In Indonesia, 67.4% men and 4.5% of women, comprising 36.1% of the population (61.4 million) currently smoking. The rates of second-hand smokers in Indonesia were also high, whereas among all adults, 78.4% (133.3 million) were exposed to tobacco smoke at home.<sup>25</sup> In this study we found no smoking mothers, but there were many second-hand smoker mothers who were profusely exposed by the smokers at home and their environment. Second-hand smokers also played an important role to the incidence of congenital malformation. According to a review article in 2011, pregnant women who are second-hand smokers were estimated to be 13% more likely give birth to a child with a congenital malformation.<sup>26</sup>

With this reported data, we found an inverted yet significant result. We found mothers with normal children (27.7%) were exposed to smoke more than those mothers with cleft children



(10.7%). This data is inconsistent and might be an indication of more samples still needed in this study.

The association between maternal smoking during pregnancy and the development of CLP has been inconsistent across different studies, and most of the studies failing to reach statistical significance.<sup>8</sup> A multivariate analysis study showed an increased risk of CLP associated with smoking. This risk increased with the number of cigarettes smoked.<sup>27</sup>

### Family history of cleft and advanced pregnancy age

A family history of CLP accounted to be one of the strongest relative risk factor of CLP.<sup>3</sup> The risk depends on what type of clefts were the parents had and how many affected children do the family had.<sup>28</sup> There was an evidence that the risk of having CLP is increasing for more than a six-fold in first-degree relatives.<sup>29</sup> In this study, we found 24.3% mothers (25 of 103 mothers) with cleft children had a positive family history of CLP and more than half among them (17 of 25 mothers) categorized in late pregnancy awareness. This data is lower than studies in US and Brazil that found a prevalence of CLP in family members for 42% and 26.3%,<sup>30-1</sup> but higher than study in Thailand that found only 17.7% had positive family history of CLP.<sup>32</sup>

Previous studies have shown an advanced maternal age of more than 30 year-old have been linked to the development of CLP.<sup>33-4</sup> Another study also suggested that mothers <20 years of age of being almost twice likely to have their offspring with CLP compared with mothers 25 to 29 years of age.<sup>35</sup> In this study we discovered that the mothers with maternal age of more than 30 years old during pregnancy were higher in cases mothers (37.9%) compared to control (25.3%). This study differs with study in Brazil that noticed reduced risk of CLP with maternal age intervals of 26 to 35 years and >35 years.<sup>36</sup>

### CONCLUSION

In our study, we found most mothers with cleft children were aware of their pregnancy after the 8<sup>th</sup> week of gestation. It

made an unaware exposure of several risk factors of CLP, include exposure of oral contraceptives (13.6%), smoke (10.7%), and also the absent of vitamin supplementation (73.8%) in the first 8<sup>th</sup> week of gestation period. The rates of positive family history in mothers with cleft children were 24.3% and there were 37.9% mothers with cleft children who have an advanced maternal age (more than 30-years-old).

Limitation of this present study is that the data cannot be generalized due to minimum sample we've had and the cases were obtained only from Gentur Cleft Foundation's database recorded within March 2012 to January 2013. In the future, we would like to continue this study using case-control study with more samples to associate between risk factors and the outcome of CLP.

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