THE ROLE OF RISK FACTORS AND CHARACTERISTIC OF INFANTILE HEMANGIOMA AT WAVA HUSADA HOSPITAL, MALANG: TWO YEARS OF RETROSPECTIVE STUDY

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ABSTRACT

Introduction: Infantile hemangioma is a prevalent tumor in children. To date, the etiology of hemangioma remains unclear; multiple hypotheses have been proposed regarding the etiology of hemangioma. This study aims to report the role of risk factors and characteristic of infantile hemangioma at Wava Husada Hospital, Malang.

Method: This research is a case control study. The data from January 1, 2019 to December 31, 2021 were processed and presented to assess the incidence and percentage of risk factors for infantile hemangioma. Univariate, bivariate and multivariate analysis was performed using Microsoft Excel SPSS 21 spreadsheet program.

Result: Total sample in this research is 201. The risk factor for mothers aged between 22-30 years to give birth to a child with infantile hemangioma is 4.257 times greater than that of mothers aged less than 22 years. The risk factor for mothers aged more than 30 years to give birth to a child with infantile hemangioma is 9.960 times greater than that of mothers aged less than 22 years. The risk factor for patients with a family history of hemangioma was 14.175 times greater than those without a family history of infantile hemangioma or vascular abnormalities. The risk factor of using preconception drugs during pregnancy had a 4.914 times risk than those who did not use preconception drugs during pregnancy.

Conclusion: Infantile hemangioma is more common in women with average birth weight. Mothers aged 22-30 years are at greater risk of giving birth to a child with infantile hemangioma. Family history of infantile hemangioma carries a greater risk than those without. The use of medications during pregnancy is associated with a greater risk of infantile hemangioma than not.

Keywords: Infantile Hemangioma; Age; Gender; Maternal Medication; Family History; Birth Weight

Latar Belakang: Hemangioma infantil merupakan tumor yang banyak ditemukan pada anak-anak. Hingga kini, etiologic hemangioma masih belum dapat dikeluarkan secara pasti; beberapa hipotesis mengenai penyebab hemangioma telah dikenalkan. Studi ini bertujuan untuk mengetahui peran faktor risiko dan karakteristik dari hemangioma pada Rumah Sakit Wava Husada, Malang.


Kata Kunci: Hemangioma infantil; Usia; Jenis kelamin; Pengobatan Ibu; Sejarah Keluarga; Berat Lahir
INTRODUCTION

Hemangioma is a common benign tumor occurring in newborns and in the age group of children less than one year old (5 - 10%). Typically, hemangiomas are visible from the time of birth (30%) or present a few weeks after birth (70%). Twenty percent of hemangioma lesions are with multiple characteristics with clinical manifestations occurring a few weeks after birth. Other prenatal and perinatal risk factors, such as a history of alcohol consumption, smoking, or drug consumption during pregnancy, have not been evaluated in previous studies.

In Indonesia alone, data on risk factors for infantile hemangioma is still undocumented due to parents' lack of knowledge regarding these lesions. In fact, the availability of demographic data, prenatal and perinatal factors in infantile hemangioma patients can assist clinicians to better explore the pathogenesis of this disorder.\(^5,8,11,18,20\)

According to the International Society for the Study of Vascular Anomalies (ISSVA), it is generally divided into the proliferative phase (0-1 years), the involution phase (1-5 years) and the convalescent phase (5-10 years). More common in the head and neck (60%) and limbs (25%). Their size varies greatly from a few millimeters to centimeters.

Hemangioma can affect visceral organs such as the liver, heart, spleen and even the brain, which can be life-threatening for the sufferer. There are several studies that found multiple hemangiomas on the skin have a higher tendency for the possibility of visceral organ involvement and further examination should be carried out to prove it.

To date, the etiology of hemangioma remains unclear; multiple hypotheses have been proposed regarding the etiology of hemangioma. However, the process of angiogenesis plays an important role. Cytokines, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) have been shown to be associated with angiogenesis. Increased levels of these angiogenesis factors and/or reduced levels of angiogenesis inhibitors such as interferon gamma (γ-IF), tumor necrosis factor beta (TNF-β) and transforming growth factor-beta (TGF-β) are suspected to be the underlying cause of hemangioma.\(^5,12,18,16\)

Some possible risk factors for infantile hemangioma include age, gender, race, low birth weight and preterm birth, maternal age at pregnancy, multiple gestation, history of medication use during pregnancy and family history of vascular disorders and infantile hemangioma itself.\(^1,2,5,6,8,11,13,14,15,18,20,21\)

METHOD

This research is an observational analytic case control study of medical record data from January 1, 2019 to December 31, 2021 at Wava Husada Hospital, Malang.

Univariate and bivariate analysis will be performed on the data. Bivariate analysis uses the chi-square test with a significance level of p < 0.05. After collecting all the data, the data were entered into Microsoft Excel spreadsheet program SPSS 21.0 for windows. The data were categorized according to type, either nominal, scaled, or ordinal. Age group, diagnoses, and risk factors were classified as nominal data.

RESULT

The study subjects consisted of 201 patients, comprising 67 infantile hemangioma subjects and 134 non-infantile hemangioma subjects at the Plastic Surgery Outpatient Installation of Wava Husada Hospital Malang from 2019 to 2021.

From the results of the distribution of hemangiomas based on birth weight; it was found that low birth weight (<2500 grams) was 10 patients (14.9%), medium birth weight (2500 grams - 4000 grams) 48 patients (71.6%), and high birth weight (>4000 grams) 9 patients (13.4%). In the group without infantile hemangioma, there were 32 patients (23.9%) with low birth weight (<2500 grams), 66 patients (49.3%) with medium birth weight (2500 grams - 4000 grams), and 36 patients (26.9%) with high birth weight (>4000 grams).

Among all patients, there were 22 boys (45.3%) and 45 girls (67.2%) patients with hemangioma. In the control group, there were 69 (51.5%) boys and 65 (48.5%) girls (Table 2). After
performing the chi-square test (2 categories) to assess the relationship between gender and the incidence of infantile hemangioma, the continuity correction was 0.019 (<0.05).

Table 1. Hemangioma based on birth weight

<table>
<thead>
<tr>
<th></th>
<th>HI</th>
<th>Non HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>10 14.9%</td>
<td>32 23.9%</td>
</tr>
<tr>
<td>Medium birth weight</td>
<td>48 71.6%</td>
<td>66 49.3%</td>
</tr>
<tr>
<td>High birth weight</td>
<td>9 13.4%</td>
<td>36 26.9%</td>
</tr>
</tbody>
</table>

For the age of the mother during pregnancy and the incidence of infantile hemangioma, there were 5 patients (7.5%) in the age group of less than 22 years, 49 patients (73.1%) in the age group between 22 and 30 years, and 13 patients (19.4%) in the maternal age group of more than 30 years. In the control group, there were 24 patients (17.9%) in the group of mothers aged less than 22 years, 49 patients (72.4%) in the age group of 22 to 30 years, and 13 patients (9.7%) in the maternal age group of more than 30 years (Table 3). After performing the Pearson chi-square test (3 categories) to evaluate the association of maternal age during pregnancy with the incidence of infantile hemangioma, the result was 0.035 (<0.05), thus it was concluded that there was a significant difference or association between maternal age during pregnancy and the incidence of infantile hemangioma.

Table 2. Hemangioma based on gender

<table>
<thead>
<tr>
<th></th>
<th>HI</th>
<th>Non HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>22 32.8%</td>
<td>69 51.5%</td>
</tr>
<tr>
<td>Girls</td>
<td>45 67.2%</td>
<td>65 48.5%</td>
</tr>
</tbody>
</table>

Meanwhile, in the control group, there were 32 patients (23.9%) with a history of preconception drug use and 102 patients (76.1%) without the use of preconception drugs during pregnancy (Table 6). The chi-square test (2 categories) was then conducted to see the association, with continuity correction of 0.00 (<0.05). Therefore, we concluded that there was a significant difference or association between the history of preconception drug use during pregnancy and the incidence of infantile hemangioma.

Table 4. Hemangioma based on the history of conception drug use

<table>
<thead>
<tr>
<th></th>
<th>HI</th>
<th>Non HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug use</td>
<td>38 56.7%</td>
<td>32 23.9%</td>
</tr>
<tr>
<td>Without drug use</td>
<td>29 43.3%</td>
<td>102 76.1%</td>
</tr>
</tbody>
</table>

Regarding data on the family history of hemangioma or vascular disorders, there were 27 patients (40.3%) with a family history of vascular disorders and 40 patients (59.7%) with no family history of vascular disorders. Meanwhile, in the control group, there were 8 patients (6%) with a family history of vascular disorders or hemangioma and 126 patients (94%) with no family history of vascular disorders or hemangioma (Table 5). Subsequently, the chi-square test (2 categories) was performed to determine the correlation between the two variables, and the result on continuity correction was 0.00 (<0.05). Therefore, it was concluded that there is a significant difference or relationship between family history of vascular disorders and the incidence of infantile hemangioma.

Table 3. Hemangioma based on age of the mother during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>HI</th>
<th>Non HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22</td>
<td>5 7.5%</td>
<td>24 17.9%</td>
</tr>
<tr>
<td>22-30</td>
<td>49 73.1%</td>
<td>97 72.4%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>13 19.4%</td>
<td>13 9.7%</td>
</tr>
</tbody>
</table>

Based on the history of conception drug use in patients with hemangioma, there were 38 patients (56.7%) with a history of drug use, 29 patients (43.3%) patients without using preconception drugs during pregnancy.

Logistic regression analysis in this study is divided into two stages, the first being bivariate and multivariate logistics. Bivariate logistic regression aimed to examine the association of each predictor factor with the incidence of infantile hemangioma. This bivariate test was performed as a variable screening. If the test results had a significance value of <0.250, the independent variables or predictors were processed for multivariate logistic regression.
The role of risk factors and characteristic for infantile hemangioma testing. The method used for the bivariate logistic regression test is the enter method. The following is a summary of the bivariate logistic regression test results.

**Table 6. Result regression analysis bivariate**

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>Sig.</th>
<th>95% C.I for EXP (B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>age of the mother during pregnancy</td>
<td>0.768</td>
<td>0.012</td>
<td>1.187, 3.916</td>
<td></td>
<td></td>
</tr>
<tr>
<td>history of family</td>
<td>-2.364</td>
<td>0.000</td>
<td>0.040, 0.223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of conception drug use</td>
<td>-1.430</td>
<td>0.000</td>
<td>0.128, 0.448</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results of bivariate analysis indicated that variables with a significance level of less than 0.250 were maternal age group during pregnancy, family history of vascular disease or hemangioma and history of periconceptional drug use. With these results, these variables were processed further into the multivariate analysis.

**Table 7. Based on logistic regression in variable**

<table>
<thead>
<tr>
<th>Var.</th>
<th>Parameter coding</th>
<th></th>
<th>F</th>
<th>(1)</th>
<th>(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the mother</td>
<td>&lt; 22 yo</td>
<td>29</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22-30 yo</td>
<td>146</td>
<td>1.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 30 yo</td>
<td>26</td>
<td>0.000</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>History of conception drug use</td>
<td>Yes</td>
<td>70</td>
<td>1.000</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>131</td>
<td>0.000</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>History of family</td>
<td>Yes</td>
<td>35</td>
<td>1.000</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>166</td>
<td>0.000</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

The highest OR value was obtained by the risk factor variable with a family history of infantile hemangioma or vascular abnormalities. With this result, the most common cause of infantile hemangioma is a family history of infantile hemangioma or vascular abnormalities.

**DISCUSSION**

In this study, the age of the patients varied, suggesting a wide age range at the time of treatment. The majority of patients were found to be in the moderate birth weight group.

There were 45 female infantile hemangioma cases. This indicates that many cases occur in women, which is in accordance with previous studies that mostly reported cases in women. This is probably due to the suspected inheritance relationship associated with the X chromosome, although it is generally known that the inheritance pattern is autosomal dominant 13. For maternal age during pregnancy more...
than 30 years has a risk factor of 2 times higher. This is in accordance with previous research, where infantile hemangioma is more prevalent in mothers over 30 years of age. It is also associated with a higher incidence of preconception complications including preterm birth, low birth weight, and pre-eclampsia in mothers over 30 years of age.

The use of drugs during pregnancy has a great influence on the incidence of infantile hemangioma. In this study, data were obtained from 38 patients with a history of preconception drug use. This is in accordance with research by Li et al (2011) where the use of drugs during pregnancy is associated with an increase in cases of infantile hemangioma. These drugs are generally prescribed and non-prescribed drugs, categorized as follows: antibiotics, Chinese herbal medicines, antifungal drugs, progesterone, and other drugs including oral contraceptive drugs, nonsteroidal anti-inflammatory drugs, clomiphene, and ethamsylate.

In other words, the risk factor for patients with a family history of infantile hemangioma is 14.175 times greater than those without a family history of hemangioma or vascular abnormalities. This finding is in accordance with previous research by Holland & Drolet (2010) which suggests that patients with family members who have vascular disorders will have a higher tendency to experience infantile hemangioma. This is related to genetic effects, due to the autosomal dominant nature of the disease.

CONCLUSION

Hemangioma is more prevalent in females compared to males, infantile hemangioma often occurs in infants with adequate birth weight, the risk factor for mothers aged between 22 years and 30 years to give birth to children with infantile hemangioma is 4.257 times greater than the age of the mother less than 22 years, risk factors in patients with a family history of infantile hemangioma have a risk of 14.175 times greater than those without a family history of hemangioma and risk factors for the use of preconception drugs during pregnancy have a risk of 4.914 times greater than those who do not use preconception drugs during pregnancy.

REFERENCES

The role of risk factors and characteristic for infantile hemangioma…


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