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**RESEARCH ARTICLES**

# Relationship Between Risk Factors and Incidence of Gestational Trophoblastic Neoplasia at RSUP Dr. M. Djamil Padang Year 2019-2021

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***Abstract***

***Background*** *: Gestational Trophoblastic Neoplasia (GTN) is a tumor originating from cytotrophoblast and syncytotrophoblast that invades myometrium, damages surrounding tissue and blood vessels, and causing bleeding.*

***Purpose*** *: This study aims to determine the relationship between age, history of previous pregnancies, β-hCG levels, parity, and interval with last pregnancy on the incidence of GTN.*

***Method*** *: This research is an observational analytic study with a cross sectional research design. Univariate analysis was carried out which described the frequency distribution of variables and bivariate analysis with the chi square statistical test .*

***Result*** *: The results of this study showed that there was a significant relationship between age, history of previous pregnancies, β-hCG levels and parity) and the incidence of GTN, while the interval with the last pregnancy did not have a significant relationship with the incidence of GTN.*

***Conclusion:*** *It was concluded that age, history of previous pregnancy, β-hCG levels, and parity are risk factors for GTN.*

***Keywords:*** *GTN;Age; β-hCG; Parity*

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## INTRODUCTION

Gestational trophoblastic disease is a group of tumors characterized by abnormal proliferation of the trophoblast which produces the human chorionic gonadotropin (hCG) hormone. Gestational trophoblastic disease is divided into two forms, namely benign and malignant. Hydatidiform mole is benign, while Gestational Trophoblastic Neoplasia(GTN) is malignant. This malignancy can occur after pregnancy but most often occurs after a hydatidiform mole pregnancy. [1]

The incidence of trophoblastic disease varies worldwide. In Southeast Asia and Japan have the highest incidence which is estimated at two in 1000 pregnancies. In the United States occurs in 1 in 1500 pregnancies. However, in Southeast Asia and Japan the choriocarcinoma rate is higher at three to nine per 40,000 pregnancies. [1] Gestational Trophoblastic Neoplasia(GTN) is more common in Asia than in North America or Europe. The reported prevalence of choriocarcinoma varies significantly around the world, from 2 per 100,000 pregnancies in the United States to 202 per 100,000 pregnancy in China. [4] In Asian countries such as Thailand the prevalence is 1.67 to 4.27 per 1000 pregnancies, in Japan 1:538 pregnancies, in South Korea 1:488 pregnancies, and Malaysia 1:357, while in Indonesia it is higher than other countries, namely 1 :40 pregnancy. [5]

Maternal age increases the risk of gestational trophoblastic disease in women younger than 20 years and older than 35 years. Age is related to poor function for the formation of oocytes at reproductive age which can cause complete hydatidiform moles. Increasing maternal age leads to abnormal formation of the zona pellucida in older women, facilitating sperm penetration and leading to the formation of partial hydatidiform moles. [6]

Another risk factor is a history of previous pregnancy. GTN usually occurs after a hydatidiform mole pregnancy. [7] Someone who has had a hydatidiform mole has a higher risk of having another hydatidiform mole or another type of gestational trophoblastic disease. A woman's risk increases if she has had more than one hydatidiform mole. Based on the FIGO scoring in 2000, a history of pregnancy which is also included as a risk factor for GTN is a history of abortion and term pregnancies can also occur GTN. [1]

Other risk factors are the interval from the last pregnancy to the onset of GTN symptoms and high β-hCG levels. When a new woman gives birth, it takes two to three years for her body to recover and prepare herself for the next pregnancy and childbirth. If the distance is too close it will cause damage to the reproductive system. [8] β-hCG level is a marker of malignancy which is very important in trophoblastic disease. The level of β-hCG is also an important part in the management of trophoblastic disease. This hormone is produced by syncytotrophoblast cells. In early pregnancy the concentration of β-hCG will be normal, but the concentration will increase with increasing trophoblastic size. [5]

Based on the description above, the author wants to examine how the relationship between risk factors and GTN events in Dr. M. Djamil Padang. This research was conducted at RSUP Dr. M. Djamil Padang because this hospital is the main referral hospital in the city of Padang.

## METHOD

This type of research is an observational analytic study, namely by looking at the risk factors associated with GTN events in Dr. M. Djamil Padang Year 2019-2021. This research was conducted at the medical record installation of RSUP Dr. M. Djamil Padang. This research was conducted in December 2021-December 2022. The data used in this study is in the form of secondary data that comes from GTN patients at RSUP Dr. M. Djamil Padang Year 2019-2021. Data collected from the medical record included age, history of previous pregnancy, β-hCG levels, parity, and interval with the last pregnancy. The sampling technique used was total sampling in GTN patients who had complete data in the medical records, namely age, history of previous pregnancies, β-hCG levels, parity and interval with the last pregnancy in 2019-2021.

## RESULT AND DISCUSSION

**Table 1** of the relationship between age and the incidence of GTN

| Variable | GTN | | | | Total | | P Value | OR |
|---|---|---|---|---|---|---|---|---|
| | Low Risk FIGO Score < 7 | | High Risk FIGO Score ≥ 7 | | | | | |
| | n | % | n | % | n | % | | |
| 1. Age < 40 years | 12 | 66,7 | 6 | 33,3 | 18 | 100 | | |
| 2. Age ≥ 40 years | 1 | 14,3 | 6 | 85.7 | 7 | 100 | 0.03 | 12.00 |
| **Amount** | **13** | **52** | **12** | **48** | **25** | **100** | | |
| 1. Hydatidiform mole | 11 | 68.8 | 5 | 31,3 | 16 | 100 | | |
| 2. Non hydatidiform mole | 2 | 22,2 | 7 | 77,8 | 9 | 100 | 0.041 | 7,70 |
| **Amount** | **13** | **52** | **12** | **48** | **25** | **100** | | |
| 1. β-hCG level $<10^3$ mIU/mL | 8 | 80 | 2 | 20 | 10 | 100 | | |
| 2. β-hCG level $\geq 10^3$ mIU/mL | 5 | 33,3 | 10 | 66,7 | 15 | 100 | 0.04 | 8.00 |
| **Amount** | **13** | **52** | **12** | **48** | **25** | **100** | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1. Parity < 3 | 11 | 78.6 | 3 | 21,4 | 14 | 100 | | |
| 2. Parity ≥ 3 | 2 | 18,2 | 9 | 81.8 | 11 | 100 | 0.009 | 16.50 |
| **Amount** | **13** | **52** | **12** | **48** | **25** | **100** | | |
| 1. Intervals < 4 months | 9 | 50 | 9 | 50 | 18 | 100 | | |
| 2. Intervals ≥ 4 months | 4 | 57,1 | 3 | 42,9 | 7 | 100 | 1,000 | 0.75 |
| **Amount** | **13** | **52** | **12** | **48** | **25** | **100** | | |

The results of the analysis of the relationship between age and the incidence of GTN found that there were as many as 6 (33.3%) patients aged <40 years experiencing high risk GTN. Meanwhile, among those aged ≥ 40 years there were 6 (85.7%) who experienced high risk GTN. The results of the statistical test obtained a value of p = 0.03, so it can be concluded that there is a relationship between age and the incidence of GTN at RSUP Dr. M. Djamil Padang in 2019-2021. The value of OR = 12.00 indicates that age is a risk factor for GTN, the risk for those aged ≥ 40 years to experience high-risk GTN is 12 times greater than those aged <40 years.

The results of the analysis of the relationship between the history of previous pregnancies and the incidence of GTN showed that there were 5 (31.3%) patients with a history of hydatidiform mole pregnancies who had high-risk GTN. Meanwhile, there were 7 (77.8%) patients with a history of non-hydatidiform mole who experienced high-risk GTN. The statistical test results obtained p = 7 .70 , so it can be concluded that there is a relationship between a history of previous pregnancy and the incidence of GTN in Dr. M. Djamil Padang in 2019-2021. The value of OR = 7.700 indicates that a history of previous pregnancy is a risk factor for GTN, the risk of having a history of non-hydatidiform mole for high-risk GTN is 7.7 times greater than patients with a history of hydatidiform mole.

The results of the analysis of the relationship between β-hCG levels and the incidence of GTN showed that there were 2 (20%) patients with β-hCG levels < $10^3$ mIU/mL who had high risk GTN. Meanwhile, among β-hCG levels ≥ $10^3$ mIU/mL there were 10 (66.7%) patients who had high risk GTN. The statistical test results obtained p = 0.04, so it can be concluded that there is a relationship between β-hCG levels and the incidence of GTN in RSUP Dr. M. Djamil Padang in 2019-2021. The OR value = 8.00 indicates that β-hCG levels are a risk factor for GTN, the risk for patients with β-hCG levels ≥ 10 3 $^{mIU}$ /mL to experience high-risk GTN is 8.00 times greater than patients with β levels -hCG < $10^3$ mIU/mL.

The results of the analysis of the relationship between parity and the incidence of GTN showed that there were 3 (21.4%) patients with parity <3 experiencing high risk GTN. Meanwhile, among parity ≥ 3 there were 9 (81.8%) who experienced high risk GTN. The results of the statistical test obtained a value of p = 0.009, so it can be concluded that there is a relationship between parity and the incidence of GTN in RSUP Dr. M. Djamil Padang in

2019-2021. The value of OR = 16.50 indicates that parity is a risk factor for GTN, the risk of parity ≥ 3 for experiencing high-risk GTN is 16.50 times greater than parity < 3.

The results of the analysis of the relationship between the last pregnancy interval and the incidence of GTN showed that there were as many as 9 (50%) patients with gestational intervals <4 months who experienced high risk GTN. Meanwhile, among the last pregnancy intervals ≥ 4 months there were 3 (42.9%) who experienced high risk GTN. The results of the statistical test obtained a value of p = 1.00, so it can be concluded that there is no relationship between the last pregnancy interval and the incidence of GTN in RSUP Dr. M. Djamil Padang in 2019-2021. OR value = 0.75 indicates that the interval with the last pregnancy is not a risk factor for GTN.

The results of the statistical test showed that there was a significant relationship between age and the incidence of GTN, the *p value of which* was 0.03 as well as being a risk factor for GTN. The *OR* result was 12, meaning that someone aged ≥ 40 years would be at risk of experiencing a high-risk GTN 12 times compared to those aged <40 years. [10] The results of research related to age as a risk factor state that age over 40 years will increase the prognostic risk towards high-risk GTN, increasing maternal age correlates with a high incidence of trophoblastic diseases such as hydatidiform mole by 7.5 times. [12] Post-molar patients aged ≥ 40 years also have a high risk of developing GTN

These results are in accordance with the theory which states that women who have a history of 15% -20% hydatidiform mole pregnancies can experience GTN in their next pregnancy. This is because after pregnancy, genetic hydatidiform mole becomes more susceptible to dysregulation of *tumor suppressor genes* , but the pathogenesis is not known with certainty. GTN has an abnormal karyotype in terms of number and structure, so that if the chromosomes increase, decrease or there is an error in their arrangement it will cause the trophoblast to become malignant. [12] A history of previous pregnancies with both hydatidiform mole and non-hydatidiform mole has a chance to become GTN, but the biggest risk is a history of hydatidiform mole pregnancy.

The results of data analysis using the chi square test showed that in this study the levels of β-hCG had a significant relationship to the incidence of GTN as well as being a risk factor with an *OR* of 8.00. Patients with β-hCG levels ≥ 10,000 mIU/mL have an 8-fold greater risk of experiencing high-risk GTN compared to patients with hCG levels < 10,000 mIU/mL. High β-hCG levels in pregnancy can be suspected of GTN. Increased levels of β-hCG can occur in GTN, especially in choriocarcinoma. [5] Malignant Trophoblastic Disease is characterized by abnormal trophoblastic proliferation, so that GTN patients will find high levels of β-hCG due to the secretion of β-hCG in large amounts. [16]

The results of data analysis using the chi square test show that parity has a significant relationship to the incidence of GTN. From the results of the analysis, it was found that *the p value* was 0.009 and *the OR* was 16.5 . Parity ≥ 3 is 16.5 times more likely to experience high-risk GTN compared to parity < 3. This is in accordance with a study

conducted by Huanca et al. (2020) found *an OR* of more than 1, which means that parity is also a risk factor for GTN. This is also in accordance with research conducted by Al-Wahaibi et al. (2020) which states that high parity will increase the risk of GTN formation. [16] This is in accordance with the theory which states that the more pregnant a mother is, the higher the risk of experiencing complications in pregnancy and childbirth. This is in accordance with research conducted by Damongilala et al. (2015) who stated that GTN was found in many patients with high parity. [19]

The results of statistical tests using the chi square test showed that in this study there was no significant relationship between the interval of previous pregnancies and the incidence of Malignant Trophoblastic Disease (GTN). The statistical test results obtained a p value of 1.00 and an OR of 0.75. Based on the OR results, the previous pregnancy interval is not a risk factor for GTN. Research conducted by Ali et al. (2017) found different results. The highest interval results obtained were > 12 months as much as 55%. In 2021 it was also found that the highest interval was > 12 months by 47%. According to the FIGO prognostic scoring system, the longer the previous pregnancy interval, the higher the risk of GTN. [17]

## CONCLUSION

Based on the results of research on the relationship between risk factors and the incidence of GTN at RSUP Dr. M. Djamil Padang in 2019-2021 obtained the following conclusions :

1. There is a relationship between age and the incidence of GTN in RSUP Dr. M. Djamil Padang in 2019-2021
2. There is a relationship between a history of previous pregnancy and the incidence of GTN at RSUP Dr. M. Djamil Padang in 2019-2021
3. There is a relationship between β-hCG levels and the incidence of GTN in RSUP Dr. M. Djamil Padang in 2019-2021
4. There is a relationship between parity and the incidence of GTN in RSUP Dr. M. Djamil Padang in 2019-2021
5. There is no relationship between the interval with the last pregnancy and the incidence of GTN at RSUP Dr. M. Djamil Padang in 2019-2021

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