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Malignancy risk factors of hydatidiform mole

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Abstract
Objective: to determine risk factors in hydatidiform mole patients who will develop into Gestational Trophoblast Neoplasm (GTN) in Dr. Mohammad Hoesin Hospital Palembang
Method: An observational analytical study with case control design was conducted in Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin Hospital Palembang / Faculty of Medicine Sriwijaya University Palembang from January 2017 to August 2017. The frequency and distribution of data are described in tables. Bivariate analysis was done to determine correlation between independent variable and dependent variable using Chi Square/Fisher Exact test and multivariate analysis was used to know which independent variable has the biggest influence to the occurrence of Gestational TrophoblastNeoplasm (GTN) post evacuation of hydatidiform mole. Data analysis was done using SPSS version 21.0.
Results: There were 45 patients who fulfilled inclusion criteria with control group and case group ratio 1 : 2 (15 cases and 30 controls). Statistical analysis showed a significant correlation between patient age, pre-evacuation β HCG level, parity, and histopathologic appearance with occurrence of Gestational Trophoblast Neoplasm (GTN) after evacuation of hydatidiform mole ($p < 0,05$). From multivariate analysis, it was found that pre-evacuation β HCG levels ≥ 134,182.5 mIU/ml was a risk factor of Gestational Trophoblast Neoplasm (OR = 77.008, p value = 0.004).
Conclusion: Pre-evacuation β HCG levels ≥ 134,182.5 mIU / ml is a risk factor for the occurrence of Gestational Trophoblast Neoplasm (GTN).

Keywords: age, blood type, hydatidiform mole, hysthopathology feature, GTN, pre-evacuation β HCG level, parity, uterine size.

1. Introduction

Hydatidiform mole is the most common form of gestational trophoblastic disease (GTD). Hydatidiform mole is an abnormal pregnancy in which some or all chorionic villis degenerate into grape-like vesicles [1]. Hydatidiform mole may be malignant or benign. The frequency of hydatidiform mole is generally higher in Asian women (1 in every 120 pregnancies) than in Western women (1 in every 2,000 pregnancies) [2]. In Indonesia, hydatidiform mole is considered an important disease with high incidence (data at hospital in Indonesia, 1 per 40), multiple risk factors, uniform distribution and most of the data is still hospital based [3]. Several theories have been proposed to explain the pathogenesis of hydatidiform mole. According to a theory by Hertig and Mansell, the cause of hydatidiform mole is an inadequacy of fetal blood circulation. Trophoblast cells receive nutrition from the mother through the intervillous chamber then send the liquid to the villi. Due to the dysfunctional villous blood circulation, fluid accumulates in villous mesenchymal tissue and forms small cysts. This continues and will eventually result in hydatidiform mole [4, 5].

Patient with normal pregnancy who has previous history of hydatidiform mole is considered healthy and hence, follow-up supervision is no longer necessary. If malignancy occurs, it is not caused by the former hydatidiform mole, but as a result of the last labor. A theory states a number of trophoblast cells in hydatidiform mole sometimes appear quiet (dormant cells) for some time and the existence of pregnancy (the influence of estrogen) reactivates these cells. In this case, the choriocarcinoma arises not from the last pregnancy, but from the previous mole [4, 5]. Malignancy following evacuation of hydatidiform mole occurs in 15-20%. Post-mole malignancy develops very rapidly with a high mortality number of 31-51% [6, 7]. The risk of malignancy after the evacuation of the mole is not clearly known. Several demographic, clinical and laboratory variables have been studied as malignant risk factors such as age, parity, uterine size, lutein cyst, histopathological features and also pre-evacuation β-human chorionic gonadotropin (β-HCG) level [8-10]. This study aimed to determine risk factors of the occurrence of Gestational Trophoblast Neoplasm (GTN) following hydatidiform mole evacuation, so it can be used to predict whether hydatidiform mole will develop into GTN (Gestational Trophoblastic Neoplasm) or return to normal.

Method

This observational analytic study with case control (retrospective) design was conducted in Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin hospital Palembang/Faculty of Medicine Universitas Sriwijaya Palembang from January to August 2017. Data was collected by gathering medical record data of

hydatidiform mole patients who came and were treated in Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin hospital Palembang from January 1st 2014 to December 31st 2016. Samples were selected using purposive sampling by choosing patient who met the research criteria. The sample was then divided into 2 groups, with 1: 2 proportion between the case group and the control group. The control group was the hydatidiform mole group that have regressed and the case group was the hydatidiform mole group that developed into GTN. Independent variables were age, pre-evacuated HCG levels, blood type, parity, uterine size, histopathologic features.

Univariate analysis was performed on sample demographic characteristics. Bivariate analyzes using chi square or fisher exact test were performed to assess the association between age, pre-evacuation HCG levels, blood type, parity, uterine size, histopathologic features and malignancy occurences in hydatidiform mole. Logistic regression analysis was performed to determine which independent variables had the greatest effect on the occurrence of Gestational Trophoblast Neoplasm (GTN) after hydatidiform mole evacuation.

Result

There were 45 hydatidiform mole patients who met the inclusion criteria. Of the 45 patients hydatidiform mole, 15 patients developed Gestational Trophoblast Neoplasm and 30 patients regressed. Of 45 patients,30 regressed patients(66,7%) have mean age 27,37 ± 7,63 (age range 17-45 years old) and 15 patients who developed into GTN(33,3%) have mean age 35,13 ± 10,01 (age range 17-50 years old). Based on statistical analysis, there was a significant difference of age between regressed patients and GTN patients (p = 0,006).

The mean of pre-evacuation β HCG level in regressed group was 69617,6 ± 38449,7 mIU/ml and mean of pre-evacuation β HCG level in GTN group was 515286,4 ± 346728,0 mIU/ml. From statistical analysis, it was found that there was a significant difference of pre-evacuation HCG levels between the two groups (p = 0,000). No significant difference was found in both groups for other demographic and clinical characteristics (p> 0.05) as shown in Table 1.

Table 1: Characteristics of Subjects

Characteristics	Hydatidiform Mole		P *value*
	GTN	Non GTN	
Age (years), mean ± SD	35,13 ± 10,01	27,37 ± 7,63	0,006*
Education, (n,%) Elementary	0 (0)	2 (6,7)	0,496**
Junior High School	3 (20)	3 (10)	
Senior High School	10 (66,7)	23 (76,7)	
College	2 (13,3)	2 (6,7)	
Occupation, (n,%)			0,106**
House wife	11 (73,3)	25 (83,3)	
Farmer	0 (0)	3 (10)	
University student	0 (0)	1 (3,3)	
Employee	2 (13,3)	1 (3,3)	
Civil servant	2 (13,3)	0 (0)	
Pre-evacuation β HCG Levels, mean ± SD	515286,4± 346728,0	69617,6± 38449,7	0,000***
Blood Group			0,470**
A	6 (40)	10 (33,3)	
B	7 (46,7)	11 (36,7)	
O	2 (13,3)	9 (30)	
AB	0 (0)	0 (0)	
Uterine size			1,000****
Bigger	15(100)	29 (96,7)	
Smaller/appropiate	0 (0)	1 (3,3)	

*Independent T Test, p = 0,05, **Pearson Chi Square, p = 0,05, ***Mann Whitney test, p = 0,05 *****Fisher Exact test, p=0,05

ROC curve analysis was performed to obtain the cut off point with the best sensitivity and specificity values for age, parity and pre-evacuation β HCG level. Based on the ROC curve, the cut off point was 29.5 years for age, the best parity at 1.5 and the best pre-evacuation β HCG level at 134.182,5 mIU / ml. Analysis results from ROC curve for age, parity and β HCG is used to analyze the relationship between the independent variables and the occurrence of Gestational Trophoblast Neoplasm (GTN) in hydatidiform mole patients.

In GTN patients the majority (73.3%) of patients was ≥ 29.5 years old whereas in non-GTN patients the majority (66.7%) was<29.5 years old. For parity variables, in GTN patients the majority of patients had a parity of ≥ 1.5 (66.6%) whereas the majority non-GTN patients (73.3%) had parity <1.5. Meanwhile, for the predominant β HCG levels, the majority of patients (93.3%) of the GTN had pre-evacuation β HCG ≥ 134.182.5 mIU / ml, whereas the majority non-GTN patients (93.3%)of had pre-treatment β HCG levels <134.182.5 mIU / ml. Table 2 shows that there is a significant association between age, parity, pre-evacuation βHCG levels and histopathology features and gestational trophoblast neoplasm occurrence in hydatidiform mole patients (p <0.05).

Table 2: Association between age, parity, pre-evacuation β HCG Level, histopathology featureandgestational trophoblast neoplasm occurrence in hydatidiform mole patients

Characteristic	Hydatidiform Mole		Total	OR* (CI 95%)	*P value**
	GTN	Non GTN			
Age (years old)					0,025
≥ 29,5	11	10	21	5,500	
< 29,5	4	20	24	(1,393-21,715)	
Parity					0,024
≥ 1.5	10	8	18	5,500	
< 1.5	5	22	27	(1,434-21,096)	
Pre-evacuation β HCG level					0,000
≥ 134.182,5 mIU/ml					
< 134.182,5 mIU/ml	141	228	1629	196,000 (16,337-2351,532)	
Histopathology Feature					0,000
Moderate-severe proliferation	14	6	20	56,000	
Mild Proliferation	1	24	25	(6,099-514,189)	

* *Fisher Exact test,* p = 0,05

Based on the logistic regression test in table 3, it was found that pre-evacuation β HCG level significantly influenced the occurence of GTN. Risk of progressing to GTN in patients with pre-evacuation β HCG level ≥134.182,5 mIU / ml was 77 times greater than in patients with pre-evacuation β HCG levels <134.182,5 mIU/ml (OR = 77.008, P value = 0.004). While age, parity and histopathology feature have association but not significant (OR ≥ 1, p value <0,05).

Table 3: Risk Factors of Gestational Trophoblast Neoplasm

Variable	Unadjusted*		Adjusted**	
	OR	P value	OR	P value
β HCG level	196,000	0,000	77,008	0,004
Histopathology feature	56,000	0,000	7,423	0,227
Parity	5,500	0,024	5,025	0,295
Age	5,500	0,025	0,813	0,890

**Regression logistic test,p=0,05

Discussion

Gestational trophoblast disease (GTD) is defined as a neoplastic process, derived from fetal chorion during pregnancy [11, 12]. This includes a spectrum of diseases such as molar pregnancy, persistent invasive mole, gestational choriocarcinoma and placental-site trophoblast tumor [13, 14].

Gestational Trophoblast Neoplasm (GTN) is a disease condition where there is clinical evidence of invasive mole or choriocarcinoma. The incidence of gestational trophoblast neoplasm in Indonesia varies between 11.47 - 29.3% [3].

In this study we obtained 45 patients of hydatidiform mole; 15 (33.3%) of which developed into GTN. The number is relatively higher when compared to the incidence of post-mole GTN in Indonesia in previous studies, which range from 11.47 to 29.3% [3]. This may be due to Dr. Mohammad Hoesin Hospital Palembang status as a tertiary health care facility and a regional referral hospital. Hence, many subspesialistic cases that can not be handled at a local hospital can be found in Dr. Mohammad Hoesin Hospital.

Mean age of GTN patients in this study was 35.13 ± 10.01 (age range 17-50), with statistical analysis showed significant difference between mean age of non-GNT patient and mean age of GTN patients where mean age in GTN patients was higher. The results of this study are similar to the study by Azis *et al* who found an increasing incidence of invasive mole and choriocarcinoma in patients over 35-40 years old [15, 16].

Bivariate analysis showed that hydatidiform mole patients age ≥ 29.5 years old were 5.5 times more at risk of progressing to GTN than patients age <29.5 years old. This result is not much different from Soeharyono's research where patients age ≥ 35 years were 6.6 times more at risk of trophoblastic disease. However, a research conducted by Curry did not show a significant relationship between age and post-mole malignancy [13-15].

Majority of patients in this study, both in groups of GTN and non-GTN, have blood type B, followed by blood type A and blood type O. However,no AB blood type was found in both groups. With statistical analysis, there was no difference of blood type groups between the two groups. A research by Soeharyono (1996) showed that most malignancy cases occured in blood type O patients, then blood type B, blood type A, and blood type AB. This difference is probably due to the smaller number of samples in this study compared to Soeharyono's study (321 samples) so the possibility of finding blood type O is higher [13, 16]. In the study by Aziz *et al*, patients with blood type O and B were found to be more likely to develop malignancy than patients with other blood types [13]. While in the research conducted by Martaadisubrata in 2005, it was found that 33.3% of blood type A patients developed into choriocarcinoma [1]. The results of Bagshawe's study found that blood type A had a higher risk for choriocarcinoma when the blood type of the husband was O [17].

The association between parity (gravidity) and post-mole malignancy is still unclear. Some studies have found that the risk of malignancy was higher in higher parity, while other authors did not find a relationship between parity and the risk of post-mole malignancy. [13,16] In this study, we found that hydatidiform mole patients with parity ≥ 1.5 were 5.5 times more at risk of progressing to GTN than patients with parity<1.5. Statistical analysis showed a significant association.

Curry found that patients with larger uterine size and an enlarged ovary have higher risk of post-mole malignancy. However, in this study, no difference of uterine size was found between the two groups. All GTN patients had larger uterine size than gestational age and only 1 non-GTN patient had a uterine size in accordance with gestational age [15, 16, 18].

The serum concentration of β HCG is recognized as an important prognostic indicator of gestational trophoblastic disease. According to FIGO, post-evacuation treatment of

hydatidiform mole involves examining β-HCG every week during the first month until undetectable. The β-HCG level in most cases will return to normal within 8 weeks and the others will return to normal within 14-16 weeks after evacuation. Meanwhile, according to Berkowitz and Goldstein, β-HCG levels in hydatidiform mole patients usually will return to normal within 9-11 weeks after evacuation. However, if, during the follow up, there is an elevated β-HCG level or plateau then the diagnosis ofGTN can be established [13, 19, 20].

In this research, the mean pre-evacuation β HCG level was 515286,4 ± 346728,0 mIu/ml. Then the pre-evacuation β HCG level was divided into ≥134.182,5mIU/ml and <134.182,5 mIU/ml based on analysis results with ROC curve. With bivariate analysis, we found that hydatidiform mole patients with pre-evacuation β HCG level ≥134.182.5 mIU/ml was significantly more at risk (196 times more at risk) of progressing to GTN than patients with pre-evacuation β HCG level <134.182,5 mIU/ml. This result is similar to the study by Goldstein and Berkowitz which concluded that highpre-evacuation β HCGtiter above 100,000 SI / l was a high risk factor for malignancy [14, 15, 17].

In this study, we found that hydatidiform mole patients with moderate-to-severe proliferation from histopathology feature were significantly more at risk (56 times higher) of progressing to GTN than patients with mild proliferation. This result is consistent with the study by Hertig and Sheldon, which found an association between the severity of trophoblastic hyperplasia in hydatidiform mole and the onset of malignancy. The more severe the hyperplasia and anaplasia found in histopathologic examinations, the more likely it is to become malignant. Based on the severity of hyperplasia and trophoblast cell anaplasia, a histologic hydatidiform mole classification was formulated in 1956 and was simplified by Hertig and Mansel [17].

Based on multivariate analysis, the risk factor for the occurrence of gestational trophoblastneoplasm was pre-evacuation β HCG level ≥ 134.182,5 mIU/ml while other variables were not risk factors because no statistically significant correlation was found. The results were slightly different from the studies by Lurain JR and Loh KY *et al*. They reported that the risk factors for post hydatidiform mole malignancy were histopathologic features with severe proliferation, uterine size, lutein cysts> 6 cm and pre-evacuation β-HCG levels> 100,000 mIU / mL [8- 10].

Conclusion

Pre-evacuation β HCG levels ≥ 134,182.5 mIU/ml is a risk factor of the occurrence of gestational trophoblast neoplasm (GTN).

Suggestion

Follow-up studies with prospective cohort designs and large sample, which incorporate other risk factors should be conducted to provide more valid and targeted results and conclusions.

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