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Relationship of Risk Factors to the Success of Single MTX Therapy in Low Risk Gestational Trophoblastic Neoplasia Patients

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ABSTRACT

Introduction: Gestational trophoblastic neoplasia (GTN) is a group of cancers that develop from the growth of abnormal cells normally found in the placenta. It can be diagnosed after a complete or partial pregnancy, miscarriage, or molar pregnancy, which is when the placenta does not develop normally and forms a tumor. In Indonesia, the incidence of GTN is quite high, namely 1:1000 pregnancies. Women with a previous history of hydatidiform mole have a tendency to experience the risk of developing GTN in subsequent pregnancies. Early knowledge of the risk factors in the form of age, history of pregnancy, serum levels of β-HCG and calculating the correct FIGO score will affect the success of therapy in order to prevent resistance treatment.

Method: This study is a retrospective cohort study to assess the relationship of risk factors to the success of single MTX therapy in low-risk GTN patients at HAM Hospital from 2016 - 2021. Initial HCG β assessment, age, history of previous pregnancy, FIGO score, success of therapy with MTX were taken from medical records. Data were tested statistically with Fisher's exact method.

Results: This study obtained 31 GTN subjects *low risk*with an average age of 38.39 years and an average level of β-HCG*pretreatment*117,996.74 IU/mL and the average β HCG*posttreatment*was 104,031.64 with a successful remission of 64.5%. Based on age and history of pregnancy such as abortion and moles, there was no association with single MTX administration (p=0.452 and p=0.527). Conversely, there is a relationship between initial β HCG (p=<0.001; RR=7.125; 95% CI 1.845-27.512) and FIGO score (p=<0.001; RR=6.519; 95% CI 2.221-19.131) with the success of single MTX therapy .

Conclusion: There is relationship between the initial β HCG and the FIGO score on single MTX therapy. However, there is no relationship between age and history of pregnancy on single MTX therapy in low-risk GTN patients.

Keywords: *low risk* GTN, β HCG, methotrexate, MTX, FIGO score

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is a group of cancers that develop from the growth of abnormal cells normally found in the placenta. It can be diagnosed after a complete or partial pregnancy, miscarriage, or molar pregnancy, which is when the placenta does not develop normally and forms a tumor.[1]

GTN patients in most parts of the world have a ratio of about 1 per 1000 pregnancies in 100,000 pregnancies. In high-income countries, the incidence of GTN is approximately 1-3 per 1000 pregnancies. Epidemiological studies report wide regional variations in the incidence of GTN. Studies conducted in North America, Australia, New Zealand, and Europe show the incidence of GTN is 0.57-1.1 per 1,000 pregnancies, while studies in Southeast Asia and Japan show a high incidence of 2 in 1,000 pregnancies. In Europe and North America, GTN occurs in 1 per 40,000 pregnancies and 1 per 40 pregnancies with hydatidiform mole developing GTN, whereas in Southeast Asia and Japan the incidence is higher, namely 9.2 and 3.3 per 40,000 pregnancies. In Indonesia, the incidence of GTN is quite high, namely 1: 1000 pregnancies. In Europe and North America, GTN occurs in 1 per

40,000 pregnancies and 1 per 40 pregnancies with hydatidiform mole that progresses to GTN, while in Southeast Asia and Japan the incidence rates are higher at 9.2 and 3.3 per 40,000 pregnancies. In Indonesia, the incidence of GTN is quite high at 1 : 1000 pregnancies.[1]

Women with a previous history of hydatidiform mole have a tendency to experience the risk of developing GTN in subsequent pregnancies. The risk of developing GTN in subsequent pregnancies is 10-20 times more risky, in fact some studies report up to 40 times higher compared to populations without a history of molars..2 The risk of patients with a history of previous pregnancy having a complete hydatidiform mole increases 2 times in women over 35 years of age, and 7.5 times in women over 40 years for the possibility of GTN. In adolescents have double the risk of experiencing GTN.[3]

GTN arises from an abnormal placenta and spans a spectrum of premalignant to malignant disorders. The diagnosis of GTN is based on the clinical picture, quantitative evaluation of serum B HCG, radiological findings, karyotype and histopathology of the evacuated tissue. In addition to histology, molecular genetic studies can assist in the diagnostic pathway. Early detection of molar pregnancies by ultrasound has resulted in a change in clinical presentation and decreased morbidity from uterine evacuation. Following an increase in serum human chorionic gonadotropin B HCG this is important for the early diagnosis of GTN. The duration of β-HCG monitoring varies depending on the type of histology and degree of regression. In persistent GTN, clinical staging and examination of metastases should be demonstrated.[3]

In GTN, a scoring assessment is carried out to assess the severity of the disease and determine the administration of chemotherapy. Internationally and has been adapted worldwide using the scoring from FIGO.[4] Administration of chemotherapy in the low risk group (FIGO < 6) recommended administration of methotrexate (MTX) or actinomycin-D as first-line single agent chemotherapy with a cure response of 60% to 90% in most retrospective study. Although almost 25 - 30% of low risk patients may develop resistance to this single agent chemotherapy, in cases of choriocarcinoma diagnosis, pre-treatment β HCG is higher and there is metastatic disease.[3] In FIGO Score >7, the therapy that can be given is combination chemotherapy, namely: etoposide, methotrexate and dactinomycin followed by cyclophosphamide and vincristine (EMA/CO) is the most widely used regimen for the initial treatment of high risk GTN.[5]

GTN can be a potentially fatal disease, but with better understanding of the disease, availability of sensitive diagnostic tools (radiology and tumor markers) and with the right chemotherapy administration of GTN has an excellent prognosis. Although GTN can be cured, cases that are not monitored or treated may present with life-threatening bleeding or develop into a systemic disease that often fails to be treated due to delays in diagnosis or treatment resistance. GTN should be managed in a dedicated unit or center following standard treatment protocols for optimal results. By knowing early on the risk factors in the form of age, history of pregnancy, serum β HCG levels and proper calculation of FIGO scoring influence the success of therapy to avoid treatment resistance.[6]

METHOD

This study is a cohort study with a retrospective approach to assess the relationship of risk factors to the success of single MTX therapy in GTN patients*low risk*at Haji Adam Malik General Hospital. This research was conducted from 2016 to 2021. In this study, data collection was carried out within the time limit (*point time approach*). The research sample was all patients with GTN*low risk*who were treated at the Department of

Obstetrics and Gynecology at Adam Malik General Hospital in Medan who received a single dose of methotrexate using total sampling. This research has passed an ethical review by the Health Research Ethics Committee of the University of North Sumatra.

Inclusion criteria for research subjects were patients diagnosed with GTN*low risk*(FIGO*scores*<6) and those who received single MTX therapy as well as patients who had routine control at the Gynecological Oncology polyclinic until completion of treatment. While the exclusion criteria were GTN patients in follow-up who experienced pregnancy.

Measurement of β HCG levels was divided into results measuring >100,000 and ≤ 100,000 IU/mL prior to treatment. Maternal age was divided into 20-40 years and >40 years and history of previous pregnancy such as abortion or previous gestational trophoblastic disease from the medical record. For the FIGO score assessment to determine the risk of GTN divided by the results of measuring 0 – 4 and 5 – 6 and the success of therapy which is indicated by β HCG levels after administration of MTX with measuring results of remission and not remission.

The data that has been collected is checked for completeness, then the data is coded, tabulated, and entered into the SPSS 25.00 computer program. The data were then analyzed statistically including descriptive analysis to display the median, mean and standard deviation of the ratio of the basic characteristics of the study sample and correlative analysis to see if there was a relationship between maternal age, history of pregnancy, initial β HCG and FIGO score on therapeutic success in single patient MTX administration. GTN*low risk*. The test used in this study is the Fisher's Exact test. Data is considered to have statistical significance if the p value obtained is $p < 0.05$.

RESULTS

This study was attended by 31 low-risk GTN patients who were treated at the Department of Obstetrics and Gynecology at Adam Malik General Hospital in Medan who received a single dose of methotrexate. All subjects involved in this study met the inclusion criteria.

A total of 20 people (64.5%) of low risk GTN patients were aged 20-40 years with the youngest being 23 years old and the oldest being 55 years old. Based on the history of pregnancy, the majority of 29 people (93.5%) had a previous history of moles.

Based on the FIGO score examination, there were 22 people (71%) with a score of 0 - 4 and 9 people (29%) with a score of 5 - 6. Based on the success of therapy, there were 20 people (64.5%) low risk GTN patients with remission results and 11 people (35.5%) with no remission results can be seen in table 1.

Table 1. Demographic Characteristics of Low Risk GTN Patients

FIGO score, n (%)	
0 – 4	22 (71)
5 – 6	9 (29)
Therapeutic Success, n (%)	
Remission	20 (64.5)
No Remission	11 (35.5)

Table 2 shows the β HCG value on examination before and after administration of chemotherapy in low risk GTN patients.The median β HCG value before administration of a single MTX chemotherapy was 117,996.74 IU/mL. After administration of chemotherapy, beta β HCG levels showed a decrease with a median value of 104,031 IU/mL. on β HCG pretreatment >100,000 IU/mL with 12 patients (38.7%), on β HCG ≤ 100,000 IU/mL with a total of 19 patients (61.3%). In β HCG post treatment who achieved remission with β HCG < 5 IU/mL with 20 patients (64.5%) while in no remission ≥ 5 IU/mL with 11 patients (35.5%).

Variable	**n = 31**
β HCG Pretreatment, IU/mL	
Average (SD)	117,996.74 (109,598.39)
Median (Min – Max)	76,596 (8,559-547,230)
>100,000 IU/mL, n (%)	12 (38.7)
≤ 100,000 IU/mL, n (%)	19 (61.3)
β HCG Posttreatment, IU/mL	
Average (SD)	104,031.64 (261011.92)
Median (Min – Max)	1.2 (0.2-1,386,936)
< 5 IU/mL (remission)	20 (64.5)
≥ 5 IU/mL (not in remission)	11 (35.5)

Demographic Characteristics	**n = 31**
Age, n(%)	
20 – 40 years	20 (64.5)
> 40 years	11 (35.5)
Average (SD), years	38.39 (9.37)
Median (Min – Max)	38 (23 – 55)
Pregnancy History, n (%)	
Abortion	2 (6,5)
mole	29 (93.5)

Table 2. Initial and Posttreatment β HCG Levels in Low Risk GTN Patients

Table 3 shows the results of the analysis of the relationship between age and therapeutic success in the administration of a single MTX in low-risk GTN patients. Of the 20 patients aged 20-40 years, there were 6 (30%) who showed non-remitting therapeutic outcomes. Meanwhile, out of 11 patients aged ≥ 40 years, there were 5 people (45.5%) with non-remission therapy outcomes. The results of the analysis using the Fischer's Exact test showed that there was no significant relationship between age and the success of therapy in low-risk GTN patients who received a single dose of MTX chemotherapy (p=0.452).

Table 3. Correlation between age and therapeutic success in single administration of MTX in GTN patients (*low risk*)

Age	Therapeutic success		p.s
	Not Remission (n=11)	Remission (n=20)	
20 – 40 years	6 (30)	14 (70)	0.452*
≥ 40 years	5 (45.5)	6 (54.4)	

*Fischer's Exact

Table 4 shows the results of the analysis of the relationship between pregnancy history and the success of therapy in the administration of a single MTX in low-risk GTN patients. Of the 2 patients with a history of abortion, all experienced remission. Meanwhile, of the 29 patients with a history of previous mole pregnancies, there were 11 (37.9%) who experienced non-remitting therapeutic outcomes. The results of the analysis using the Fischer's Exact test showed that there was no significant relationship between history of pregnancy and the outcome of therapy in low risk GTN patients (p=0.527) who received single doses of MTX chemotherapy.

Table 4. Correlation between Pregnancy History and Treatment Success in Single MTX Administration in GTN Patients (*low risk*)

Pregnancy History	Therapeutic success		p.s
	Not Remission (n=11)	Remission (n=20)	
Abortion	0	2 (100)	0.527*
mole	11 (37.9)	18 (62.1)	

*Fischer's Exact

Table 5 shows the results of an analysis of the relationship between initial beta B HCG levels and the success of therapy in the administration of a single MTX in low-risk GTN patients. Of the 12 patients with initial β-HCG levels >100,000 IU/mL, 9 (75%) showed non-remitting therapeutic outcomes. Whereas of the 19 patients with initial β-HCG levels ≤100,000 IU/mL there were only 2 people (10.5%) with non-remitting therapeutic outcomes. The results of the analysis using the Fischer's Exact test showed that there was a significant relationship between initial β-HCG levels and the success of therapy in low-risk GTN patients receiving single-dose MTX chemotherapy (p <0.001). The Relative Risk (RR) value obtained was 7.125 (95% CI 1.845-27.512), which means that low risk GTN patients with initial β HCG levels >100,000 IU/mL have a risk of getting a therapeutic outcome that is not remission is 7.125 times greater than low risk GTN patients with initial β HCG levels ≤100,000 IU/mL.

Table 5. Correlation of Initial β HCG to Therapy Success in Single MTX Administration in GTN patients (low risk)

β-HCG levels	Therapeutic success		p	RR 95% CI
	Not Remission (n=11)	Remission (n=20)		
>100,000 IU/mL, n (%)	9 (75)	3 (25)	<0.001*	7,125
≤ 100,000 IU/mL, n (%)	2 (10.5)	17 (89.5)		1,845-27,512

*Fischer's Exact

Table 6 displays the results of the analysis of the relationship between the FIGO score and the success of therapy in the administration of a single MTX in low-risk GTN patients. Of the 9 patients with a FIGO score of 5 – 6, 8 (88.9%) showed non-remitting treatment outcomes. Whereas of the 22 patients with FIGO scores 1 – 4 there were only 3 people (13.6%) with non-remission therapy outcomes. The results of the analysis using the Fischer's Exact test showed that there was a significant relationship between the FIGO score and the success of therapy in low-risk GTN patients who received single-dose MTX chemotherapy (p<0.001). The relative risk value (RR) obtained was 6.519 (95% CI 2.221-19.131) which indicates that low risk GTN patients with a FIGO score of 5-6 have a risk of getting a non-remitting therapeutic outcome of 6.519 times greater when compared to low risk GTN patients with a FIGO score of 0-4.

Table 6. Correlation between FIGO score and therapeutic success in single administration of MTX in GTN patients (*low risk*)

FIGO score	Therapeutic success		p.s	RR 95% CI
	Not Remission (n=11)	Remission (n=20)		
5 – 6	8 (88.9)	1 (11,1)	<0.001	6,519
0 – 4	3 (13,6)	19 (86.4)		2,221-19,131

*Fischer's Exact

DISCUSSION

This study was attended by 31 low-risk GTN patients who were treated at the Department of Obstetrics and Gynecology at Adam Malik General Hospital in Medan who received a single dose of methotrexate. All subjects involved in this study met the inclusion criteria. A total of 20 people (64.5%) of low risk GTN patients were aged 20-40 years with the youngest being 23 years old and the oldest being 55 years old. Based on the history of pregnancy, the majority of 29 people (93.5%) had a previous history of moles. Based on the FIGO score examination, there were 22 people (71%) with a score of 0 - 4 and 9 people (29%) with a score of 5 - 6. Based on the success of therapy, there were 20 people (64.5%) low risk GTN patients with remission results and 11 people (35.5%) with no remission results.

The median β HCG value before administration of a single MTX chemotherapy was 117996.74 IU/mL. After administration of chemotherapy, beta β HCG levels showed a decrease with a median value of 104031

IU/mL. on β HCG pretreatment >100,000 IU/mL with 12 patients (38.7%), on β HCG ≤ 100,000 IU/mL with a total of 19 patients (61.3%). In B HCG post treatment who achieved remission with β HCG < 5 IU/mL with 20 patients (64.5%) while in no remission ≥ 5 IU/mL with 11 patients (35.5%). This is related to the study of Mousavi et al which examined patients who had the possibility of chemoresistance in patients with serum B HCG > 100,000 IU/mL (OR = 5.86, 95% CI = 1.07 – 32.02).[7]

Of the 20 patients aged 20-40 years, there were 6 (30%) who showed non-remitting therapeutic outcomes. Meanwhile, out of 11 patients aged ≥ 40 years, there were 5 people (45.5%) with non-remission therapy outcomes. The results of the analysis using the Fischer's Exact test showed that there was no significant relationship between age and the success of therapy in low-risk GTN patients who received a single dose of MTX chemotherapy (p=0.452). According to a study by Xiadong Wu et al, the age group that experienced no remissions was in the age group <40 years with a P value of 0.114.[8]

Of the 2 patients with a history of abortion, all experienced remission. Meanwhile, of the 29 patients with a history of previous mole pregnancies, there were 11 (37.9%) who experienced non-remitting therapeutic outcomes. The results of the analysis using the Fischer's Exact test showed that there was no significant relationship between history of pregnancy and the outcome of therapy in low risk GTN patients (p=0.527) who received single doses of MTX chemotherapy. According to the study by Shen Tao et al, patients with a history of hydatidiform moles were more at risk for non-remitting (16.67%) with a P value of 0.409.[9]

Of the 12 patients with initial β-HCG levels >100,000 IU/mL, 9 (75%) showed non-remitting therapeutic outcomes. Whereas of the 19 patients with initial β-HCG levels ≤100,000 IU/mL there were only 2 people (10.5%) with non-remitting therapeutic outcomes. The results of the analysis using the Fischer's Exact test showed that there was a significant relationship between initial β-HCG levels and the success of therapy in low-risk GTN patients receiving single-dose MTX chemotherapy (p <0.001). The relative risk value (RR) obtained was 7.125 (95% CI 1.845-27.512) which means that low-risk GTN patients with initial β-HCG levels >100,000 IU/mL have a risk of getting non-remitting therapy outcomes that are 7.125 times greater than GTN low risk patients with initial β HCG levels ≤100.000 IU/mL. In a study by Sheffield et al evaluating a total of 289 patients with low risk GTN, resistance levels were found in patients with pretreatment β HCG > 100,000 IU/mL compared to <100,000 IU/L (84% vs 34% and P < 0.0001).[10]

Of the 9 patients with a FIGO score of 5 – 6, 8 (88.9%) showed non-remitting treatment outcomes. Meanwhile, of the 22 patients with a FIGO score of 0 – 4, only 3 (13.6%) had non-remission therapy outcomes. The results of the analysis using the Fischer's Exact test showed that there was a significant relationship between the FIGO score and the success of therapy in low-risk GTN patients who received single doses of MTX chemotherapy (p <0.001). The relative risk value (RR) obtained was 6.519 (95% CI 2.221-19.131) which means that low risk GTN patients with a FIGO score of 5-6 have a risk of getting a non-remitting therapeutic outcome which is 6.519 times greater than low risk GTN patients. with a FIGO score of 0– 4.

In the study by Sita Lumsden et al, the effectiveness of single MTX chemotherapy at FIGO score 0 – 4 has better effectiveness than FIGO score 5 – 6 and has a higher probability of experiencing chemoresistance.[11] Osborn et al reported that first-line chemotherapy for GTN is low risk. less effective at FIGO scores of 5 - 6 (CR level 29%) and in patients with choriocarcinoma (CR level 10%). Sheffield et al in 2000 - 2011 evaluated 289 patients

with low risk GTN treated with MTX-FA for 8 days, found 81% (29 of 36 patients) with a FIGO score of 5 - 6 had resistance to MTX-FA when compared to 34% (87 of 253 patients) with a score of 0 - 5 (p 0.0001). Significantly, higher levels of resistance were also found in patients with initial β-HCG levels >100,000 IU/L compared to <100,000 IU/L (84% vs. 34% and p value = 0.0001).[4]

CONCLUSION

There was no significant relationship between age and history of pregnancy with the success of single MTX therapy in low risk GTN. However, there is a significant relationship between high β-HCG, which is > 100,000 IU/mL, and no remittance of low-risk GTN disease who receive a single dose of MTX chemotherapy. There was a significant relationship between the FIGO score (5 – 6) with no remittance of low risk GTN who received a single dose of MTX chemotherapy. Further research is needed regarding the relationship of risk factors to the success of single MTX therapy in low-risk GTN patients with more diverse characteristics and if possible, multicentre studies should be conducted.

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