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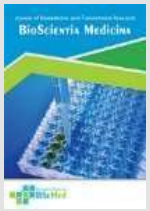

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Study of Analysis of Beta Human Chorionic Gonadotropin (hCG) Levels Before and After Hysterectomy in Gestational Trophoblastic Neoplasia (GTN) Patients: A Single Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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A B S T R A C T

Background: Gestational trophoblastic neoplasia (GTN) is a malignant tumor originating from placental trophoblast which causes mortality due to bleeding. Trophoblast produces beta hormone human chorionic gonadotropin (hCG). Quantitative examination of serum beta hCG is used to support the diagnosis and management of GTN. Hysterectomy is performed in bleeding conditions as the main therapy besides chemotherapy. This study aims to analyze differences in beta hCG levels before and after hysterectomy in GTN patients at Dr. M. Djamil General Hospital Padang. **Methods:** Retrospective observational analytical research design cross-sectional from 21 samples of GTN patients for the period July 2021 to June 2023 at Dr. M. Djamil General Hospital Padang. Quantitative beta hCG level examination is carried out before and after the hysterectomy. The Shapiro-Wilk test was carried out for data normality and continued with the Wilcoxon nonparametric tests to find out significant differences in beta hCG levels. **Results:** The most common characteristics of GTN patients were age ≥35 years, namely 15 (71.4%) patients, multiparity in 14 (66.7%) patients, and indication for hysterectomy due to bleeding in 14 (66.7%) patients. The median beta hCG level before hysterectomy was 46,000 (117.10-653,874) mIU/mL and the median after hysterectomy was 113.3 (0.12-3,693) mIU/mL. Beta hCG levels after hysterectomy were found to be normal (<5 mIU/mL) in five patients (23.8%). There was a significant difference in beta hCG levels before and after hysterectomy ($p < 0.001$). **Conclusion:** Beta hCG levels after hysterectomy decreased compared to before hysterectomy. Hysterectomy therapy is useful for reducing beta hCG levels in GTN patients.

1. Introduction

Mortality and morbidity in pregnant women and childbirth is a major problem in developing countries. Gestational trophoblastic disease (GTD) is a disease in pregnancy that causes maternal mortality due to bleeding. Gestational trophoblastic disease (GTD) is a disease caused by abnormal proliferation of trophoblast cells so that the trophoblast cells produce hormones human chorionic gonadotropin (hCG) in excess.[1] Gestational trophoblastic disease (GTD) based on histopathological features is divided into several types, namely hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ONE).[2] Invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) included in malignant tumors or gestational trophoblastic neoplasia (GTN) and has a tendency to invade or metastasize. Invasive choriocarcinoma and mole are common incidents.[3]

The incidence of trophoblastic disease varies worldwide. Gestational trophoblastic neoplasia (GTN) occurs in approximately 1 per 20,000 to 40,000 pregnancies in the United States.[4] The incidence of choriocarcinoma is higher in Southeast Asia and Japan, namely 3 to 9 per 40,000 pregnancies.[1] GTN research at Dr. Hasan Sadikin General Hospital found 73 cases, from this number it is known that Indonesia has a high number of GTN cases.[5]

Quantitative examination of serum beta hCG is used to support the diagnosis and management of GTN. Evaluation of beta hCG levels is carried out after therapy until it reaches normal levels.[6] Treatment for GTN generally uses chemotherapy but hysterectomy can also be an alternative. Hysterectomy has a limited role in the management of GTN but several studies now suggest hysterectomy may be the first choice. Hysterectomy is performed in cases of lesions limited to the uterus, women aged >35 years, no desire to become pregnant again, uncontrolled vaginal and intra-abdominal bleeding, PSTT and ETT type lesions, and GTN that is resistant to chemotherapy.[1] Research on differences in beta hCG levels before and after therapy with hysterectomy as an option has not been reported at Dr. M. Djamil General Hospital Padang. Beta hCG levels after therapy in GTN patients will be found to decrease, persist, or increase due to its invasive and metastatic nature. The expected result is a decrease in beta hCG levels. This research was conducted to determine the characteristics of GTN patients and analyze differences in beta hCG levels before and after hysterectomy in GTN patients at Dr. M. Djamil General Hospital Padang.

2. Methods

This research was conducted at the central laboratory installation, anatomical pathology laboratory, and medical records installation at Dr. M. Djamil General Hospital Padang in the period April 2023 to September 2023. This research uses a retrospective observational analytic method with a cross-sectional design. This design allows researchers to observe variables at a certain time and analyze the relationships between variables without direct intervention. Patients with a diagnosis of gestational trophoblastic neoplasia (GTN) confirmed by a clinician in the period July 2021 to June 2023. This study sample was obtained from a population that met the inclusion and exclusion criteria. The inclusion criteria are patients who underwent hysterectomy, underwent a histopathological examination, had beta hCG levels before and after hysterectomy, and had complete medical record data: age, parity, and indication for hysterectomy. Meanwhile, the exclusion criteria are patients with kidney disease.

Research data was obtained from medical records of patients who met the inclusion and exclusion criteria. Data collected include: Patient age, parity, indication for hysterectomy, beta hCG levels before hysterectomy, and beta hCG levels after hysterectomy. Data analysis was carried out on: 1. Patient characteristics data: processed and presented in the form of a frequency distribution table. 2. Numerical data (beta hCG levels): The Shapiro-Wilk test was carried out to test the normality of the data. The nonparametric Wilcoxon test was carried out to determine significant differences in beta hCG levels before and after hysterectomy. The difference was declared significant if a p-value <0.05 was obtained. The results of data analysis were interpreted to determine the characteristics of patients with GTN at Dr. M. Djamil General Hospital Padang and differences in beta hCG levels before and after hysterectomy in GTN patients.

3. Results

The characteristics of GTN patients who met the inclusion criteria in this study can be seen in Table 1. Table 1 shows the characteristics of 21 gestational trophoblastic neoplasia (GTN) patients who underwent hysterectomy at Dr. M. Djamil General Hospital Padang. The majority of patients (71.4%) were aged 35 years or older, with 6 (28.6%) patients aged under 35 years. This suggests that GTN occurs more frequently in older women. Most patients (66.7%) were multiparous (had 2-4 pregnancies), with 4 (19.0%)

primiparous (had 1 pregnancy) and 2 (9.5%) grand-multiparous (had 5 or more pregnancies). Only 1 (4.8%) patient was nullipara (never pregnant). Abnormal bleeding was the most common indication for hysterectomy in GTN patients (66.7%). Other factors that encourage hysterectomy are age over 35 years (19.0%) and the desire not to get pregnant again (14.3%). These findings suggest that GTN occurs more frequently in older and multiparous women. Abnormal bleeding is the main indication for hysterectomy in GTN patients. Age over 35 years and the desire not to become pregnant again also play a role in the decision to hysterectomy in some patients.

Table 1. Characteristics of gestational trophoblastic neoplasia patients.

Characteristics	n=21	Percentage (%)
Age (years)		
< 35	6	28,6
≥ 35	15	71,4
Parity		
Nulliparous (0)	1	4,8
Primiparous (1)	4	19,0
Multiparous (2-4)	14	66,7
Grand-multiparous (≥5)	2	9,5
Indications for hysterectomy		
Bleeding	14	66,7
Age >35 years	4	19,0
Don't want to get pregnant again	3	14,3

The results of beta hCG levels before and after hysterectomy can be seen in Table 2. Table 2 data shows that the median beta hCG level before hysterectomy is 46,000 mIU/mL with a minimum beta hCG level of 117.1 mIU/mL and a maximum beta hCG level of 653,874 mIU/mL. The median beta hCG level after hysterectomy was 113.3 mIU/mL with a minimum beta hCG level of 0.12 mIU/mL and a maximum beta hCG level of 3,693 mIU/mL. Based on the results of the Wilcoxon Signed Ranks test, there was a change in beta hCG levels before and after hysterectomy in GTN patients with a p-value <0.001. Decreased beta hCG levels after hysterectomy occurred in all research samples. An increase or similar value of beta hCG levels after hysterectomy was not found in the study sample**.** This shows that there is a significant difference in beta hCG levels before and after hysterectomy in GTN patients.

Table 2. Differences in levels of beta human chorionic gonadotropin before and after hysterectomy.

Variable	Before hysterectomy	After hysterectomy	p-value
Beta hCG level (mIU/mL)			
Median	46.000	113,30	<0,001
(Minimum;Maximum)	(117,10; 653.874)	(0,12; 3.693)	

4. Discussion

This research was conducted on 21 samples of GTN patients at Dr. M. Djamil General Hospital Padang for the period July 2021 to June 2023 who meet the inclusion and exclusion criteria. The characteristics assessed were age, parity, and indication for hysterectomy. Statistical analysis showed that the largest age group of GTN patients was ≥35 years old, 15 people (71.4%). The minimum age in this study was 27 years and the maximum age was 51 years. Research by Tjokroprawiro et al. (2022) found that the average age of GTN patients was 37 years.[7] Research

by Bolze et al. (2018) found that the average age of GTN patients was 51 years with a minimum age of 47 years and a maximum age of 53 years.[8] Maternal age <20 or >35 years increases the risk of trophoblastic disease which is associated with poor egg cell formation function. The risk of GTD occurrence is almost double for women under 21 years and older than 35 years, and 7.5 times higher for women over 40 years.[9] Women of fertile age have optimal reproductive organs between the ages of 20-35 years.[10] Pregnancy planning needs to be done at a healthy reproductive age so that the pregnancy goes well and reduces the risk of GTN. The highest parity in this study sample was the multiparity group (2-4) with 14 patients (66.7%), followed by primiparous (1) with 4 patients (19%), grand-multiparous (≥5) with 2 patients (9.5%), and nulliparous (0) was 1 patient (4.8%). Gestational trophoblastic neoplasia can occur in all parties in this study.

The most common indication for hysterectomy in this study sample was bleeding at 66.7%, followed by age ≥35 years (14.3%), and not wanting more children (16.7%). This is in line with the research of Ramesan et al. (2020) who concluded that bleeding both intraperitoneally and vaginally and the threat of uterine rupture are the most common indications for hysterectomy (48%) for life-saving procedure because this can cause death. Hysterectomy can be the main choice for patients aged >40 years and who do not want to become pregnant again.[11] Other indications for hysterectomy are lesions limited to the uterus, PSTT, and ETT type lesions, as well as GTN that is resistant to chemotherapy but this was not found in this study. This study found that the median beta hCG level before hysterectomy was 46,000 mIU/mL with a minimum beta hCG level of 117.1 mIU/mL and a maximum beta hCG level of 653,874 mIU/mL. The median beta hCG level after hysterectomy was 113.3 mIU/mL with a minimum beta hCG level of 0.120 mIU/mL and a maximum beta hCG level of 3,693 mIU/mL. This data shows that there was a decrease in beta hCG levels after hysterectomy in 21 study samples. Beta hCG levels after hysterectomy were found to be normal (<5 mIU/mL) in five cases (23.8%) so no further chemotherapy was needed. The maximum beta hCG level is 1,022 mg/dL so the decrease in beta hCG levels is influenced by the beta hCG level before hysterectomy. Beta hCG levels that had not reached normal were found in 16 patients requiring chemotherapy as further therapy (76.2%). Based on the statistical test of the Wilcoxon Signed Ranks test obtained a p-value <0.05. This shows that there is a significant difference in beta hCG levels before and after hysterectomy in GTN patients. The results of this research are in line with research conducted by Tjokroprawiro et al. (2022) found normal beta hCG levels after hysterectomy in only 4 cases out of 12 GTN patients who underwent hysterectomy (33.33%) at Dr. Soetomo Regional General Hospital in 2015-2019. The maximum beta hCG level before the hysterectomy was 378,909 mIU/mL. The maximum beta hCG level after hysterectomy was 136,710 mIU/mL. The mean decrease in serum beta hCG levels was 72,317 mIU/mL. There is a significant difference in beta hCG levels before and after hysterectomy so hysterectomy is an effective measure in reducing beta hCG levels in GTN.[7]

The results of this study are different from the research of Bolze et al. (2018) in 74 GTN patients with hysterectomy as first-line therapy was followed by beta hCG levels reaching normal in 61 patients (82.4%) without chemotherapy as continued therapy, while 13 patients (17.6%) required further chemotherapy.[8] Research by Syafii et al. (2018) showed that of 43 patients after surgery, beta hCG levels decreased in 35 patients (81.4%), remained constant in 1 patient (2.3%), and increased in 7 patients (16.3%).[12] Persistent or increasing levels can be caused by the spread of trophoblast cells due to their invasive and metastatic nature. Metastases via hematogen to various organs such as the lungs, vagina, pelvis, liver, spleen, kidneys and brain. Further examinations are carried out when metastases are suspected, such as chest X-ray, abdominal ultrasonography, Computed tomography scan (CT scan) of the abdomen and brain, as well as other laboratories. Beta hCG levels after

therapy in GTN patients will decrease, persist, or increase. The expected result is a decrease in beta hCG levels. Hysterectomy can reduce the tumor mass so that it can reduce the production of beta hCG.[13]

All samples from this study had histopathological examination results in the form of invasive mole (100%). Choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) were not found. The results of this research are different from the research of Ramesan et al. (2021) obtained histopathological examination results from 26 patients with the highest results being choriocarcinoma in 12 patients (46.2%), followed by an invasive mole in 8 patients (30.8%), PSTT in 2 patients (7.7%), ETT and hydatidiform mole. 1 patient each (3.8%) and 1 patient could not be classified (3.8%).[11] This difference could be due to demographics and the small sample size in this study. Grouping of patients into high risk or low risk was not carried out in this study because of incomplete data in the medical records. The International Federation of Gynecology and Obstetrics (FIGO) and World Health Organization (WHO) combine anatomical staging with a modified WHO prognostic index score for internationally agreed risk assessment and treatment approach, GTN is grouped into two groups, namely the low-risk group (score 0-6) and the high-risk group (score ≥7).[13] Chemotherapy is the main choice given because GTN is very sensitive to chemotherapy. Chemotherapy is given according to low-risk or high-risk categories. Low-risk patients (score 0-6) are given single-agent chemotherapy (Methotrexate or Actinomycin). Patients at high risk are given combination chemotherapy (Etoposide, Methotrexate, Actinomycin, Cyclophosphamide /EMACO regimen).[13,14]

Gestational trophoblastic neoplasia (GTN) is a group of trophoblastic tumors that develop from abnormal pregnancy tissue. This tumor can produce high levels of the hormone beta hCG (human chorionic gonadotropin), which can be used as a diagnostic and prognostic marker. Hysterectomy, the removal of the uterus, is one of the main therapies for GTN. This study shows a significant reduction in beta hCG levels in GTN patients after hysterectomy. GTN originates from abnormal pregnancy tissue, especially trophoblast. Trophoblast produces beta hCG to support pregnancy. In GTN, abnormal trophoblasts continue to produce beta hCG even though the pregnancy is not developing normally. Hysterectomy removes the uterus, including the abnormal trophoblastic tissue. By eliminating the main source of beta hCG production, levels of this hormone are expected to decrease significantly. Beta hCG is metabolized in the liver and kidneys. Hysterectomy does not directly affect beta hCG metabolism in these organs. However, by eliminating the source of its production, the metabolic burden of beta hCG is reduced, making levels of this hormone easier to clear from the body. The decrease in beta hCG levels after hysterectomy does not occur instantly. It takes time for the body to clean up the beta hCG that has been circulating in the blood and eliminate the source of its production. Research shows that the most significant decrease in beta hCG occurs in the first few weeks after a hysterectomy. The decrease in beta hCG levels can continue for several months until they reach normal levels. The rate of decline in beta hCG after hysterectomy can vary between patients. Advanced stages of GTN generally have higher beta hCG levels and may take longer to reach normal levels after hysterectomy. Other medical conditions that affect liver or kidney function may affect beta-hCG metabolism and the rate at which it decreases. If GTN has spread outside the uterus (metastasized), hysterectomy may not completely remove the source of beta hCG production, so the reduction in levels may not be as rapid as in non-metastatic cases. This study shows a significant reduction in beta hCG levels in GTN patients after hysterectomy. This finding is biologically plausible because hysterectomy removes the main source of beta hCG production and reduces the metabolic burden of this hormone. A decrease in beta hCG levels can be used as an indicator of the success of hysterectomy therapy for GTN.[14-19]

Pregnancy is a complex physiological process, characterized by various hormonal and anatomical

changes in women. One of the key hormones in pregnancy is beta human chorionic gonadotropin (beta hCG), which is produced by placental trophoblast cells. Beta hCG plays an important role in early embryonic development, maintenance of pregnancy, and suppression of ovulation. In early pregnancy, beta hCG stimulates the corpus luteum in the ovary to continue producing progesterone, an important hormone for maintaining the viability of the endometrium and supporting embryo implantation. Beta hCG also inhibits the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn prevents the release of follicle-stimulating (FSH) and luteinizing (LH) hormones from the pituitary gland. This prevents ovulation during pregnancy. Beta hCG plays a role in angiogenesis, namely the formation of new blood vessels, which is important for supplying nutrients and oxygen to the developing fetus. Beta hCG helps maintain pregnancy by suppressing the mother's immune system and preventing fetal rejection. Measuring beta hCG levels in blood or urine is an important examination in pregnancy. Beta hCG levels increase rapidly in the blood and urine after embryo implantation. Beta hCG examination can detect pregnancy as early as 10-14 days after fertilization. Beta hCG levels continue to increase during the first trimester of pregnancy, reaching a peak around weeks 8-12. After that, the levels gradually decrease until the third trimester. Monitoring beta hCG levels can help assess the progress of a pregnancy and detect potential complications, such as miscarriage or ectopic pregnancy. Beta hCG levels can be used to estimate gestational age with fairly high accuracy, especially in the first trimester. Abnormal beta hCG levels can indicate a pregnancy abnormality, such as hydatidiform mole (molar pregnancy), ectopic pregnancy, or missed abortion. Gestational trophoblastic neoplasia (GTN) is a group of trophoblastic tumors that develop from placental tissue. GTN can occur after miscarriage, molar pregnancy, or vaginal delivery. Checking beta hCG levels plays an important role in the diagnosis, monitoring and management of GTN. High and persistent beta hCG levels after miscarriage or molar pregnancy are a strong indication of GTN. Serial beta hCG testing can help confirm the diagnosis and monitor the patient's response to therapy. Regular monitoring of beta hCG levels after GTN therapy can help detect disease recurrence early. Elevated beta hCG levels after treatment is completed is a potential sign of recurrence. Beta hCG examination can help determine the appropriate dose and duration of therapy for GTN patients. Placental trophoblast cells are the main source of beta hCG production. Beta hCG production levels increase rapidly in early pregnancy and continue to increase during the first trimester. Beta hCG is excreted in the blood and urine of pregnant women. Beta hCG levels in blood are higher than in urine, but urine testing is easier and less invasive. Beta hCG levels are closely correlated with the development of pregnancy. Elevated beta hCG levels indicate normal pregnancy development, while abnormal levels may indicate complications.[20-24]

Hysterectomy was the main treatment option in this study sample because of several indications that have been described previously. The first time the beta hCG level was checked after a hysterectomy was 2 weeks in this study. This is in accordance with the GTN management guidelines, namely follow-up quantitative examination of beta hCG levels is carried out every 1-2 weeks until the results are negative (<5 mIU/mL) for 3 months, then every 4 weeks for 1 year, and every 6-12 months for life or at least 3-5 years. Evaluation of beta hCG levels is carried out after treatment until it reaches normal levels (<5 mIU/mL) and pregnancy prevention is carried out during monitoring.[6] This research has a number of limitations, especially since the research was conducted at only one research center, the small sample size, and the retrospective nature of the research which could result in missing data on the research sample used.

5. Conclusion

This study shows that there is a decrease in beta hCG levels after hysterectomy in GTN patients. Hysterectomy therapy is useful for reducing beta hCG levels in GTN patients. Checking beta hCG levels is one of the important tests carried out in pregnancy to determine normal or abnormal pregnancies such as GTN in addition to ultrasound examination.

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