© Curr Gynecol Oncol 2020, 18 (2), p. e34–e38
DOI: 10.15557/CGO.2020.0007

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Received: 05.07.2020
Accepted: 15.10.2020
Published: 31.12.2020

B-hCG and H-hCG levels in patients with gestational trophoblastic neoplasia

Stężenie B-hCG i H-hCG u pacjentek z ciążową neoplazją trofoblastu

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Abstract

Objective: Gestational trophoblastic disease is a term that encompasses a spectrum of disorders all arising from the placenta. Human chorionic gonadotropin (hCG) hormone has an essential role in the diagnosis and management of gestational trophoblastic neoplasia. Measuring beta-hCG (B-hCG) levels is the only standard method of monitoring treatment response in patients on chemotherapy. Serial B-hCG levels are also helpful in defining the suitable approach and the dosage of chemotherapeutic drugs. Unfortunately, this marker may not be helpful in some cases. Therefore, the present study was conducted to determine the results of the ratio of B-hCG and hyperglycosylated human chorionic gonadotropin (H-hCG) in patients with gestational trophoblastic neoplasia. **Materials and methods:** This was a cross-sectional study in 22 patients with gestational trophoblastic neoplasia who were referred to an oncology clinic of an academic hospital of Mashhad University of Medical Sciences in Iran from December 2017 to May 2018. Inclusion criteria were plateau level of B-hCG (during 4 weeks) or persistent low level of hCG. After ruling out other etiologies, H-hCG level was measured and the H-hCG/total hCG ratio was evaluated. If the proportion was more than 20%, active gestational trophoblastic neoplasia was diagnosed, and if it was less than 20%, quiescent gestational trophoblastic neoplasia was diagnosed. In patients with active gestational trophoblastic neoplasia, interventional procedures involved a change in the dose intensity or chemotherapy or proposing a surgery. However, only serial follow-up was recommended in patients with quiescent gestational trophoblastic neoplasia. Then, the patients were followed during the therapy and the condition of patients was followed and recorded. **Results:** The mean age of patients was 31.36 ± 8.01 years. Hydatidiform mole was the most common diagnosis, accounting for approximately 64% (14) of patients. A total of 81% of patients were undergoing chemotherapy. The interval time between the onset of chemotherapy until plateau or persistent low level of hCG was 11.26 ± 4.03 weeks. The mean B-hCG level was 36.6 mIU/mL and the mean H-hCG/total hCG ratio was 6.24%. This proportion was less than 20% in 82% of patients. Among these patients, 14 patients (77.8%) had spontaneously normalized levels of B-hCG during a 6-month follow-up. Two cases underwent chemotherapy due to increased B-hCG. Other patients are still under follow-up without disease progression. Among 4 patients with a H-hCG/total hCG ratio >20%, hysterectomy was recommended to one patient duo to multiparity and the fact that the tumor was localized in the uterus. In the other patients, an increase in the dose of methotrexate or a change of chemotherapy regimen was performed, which caused a decrease in B-hCG level to normal. All patients are still under follow-up without disease progression. **Conclusion:** The data in this study suggests the use of H-hCG as a tumor marker in patients with persistent low level of B-hCG, which is useful to distinguish between quiescence gestational trophoblastic neoplasia, which does not need treatment, from active gestational trophoblastic neoplasia. However, further studies with larger sample size are needed to confirm and generalize the above findings.

Keywords: gestational trophoblastic disease, human chorionic gonadotropin, hyperglycosylated hCG, B-hCG

Streszczenie

Cel pracy: Ciążowa choroba trofoblastyczna to termin obejmujący spektrum zaburzeń wynikających z nieprawidłowego rozwoju łożyska. Ludzka gonadotropina kosmówkowa (*human chorionic gonadotropin*, hCG) odgrywa kluczową rolę w diagnostyce i leczeniu ciążowej neoplazji trofoblastu. Jedyną standardową metodą monitorowania odpowiedzi na leczenie u pacjentek otrzymujących chemioterapię jest pomiar stężenia beta-hCG (B-hCG). W wyborze sposobu leczenia i dawki chemoterapeutyku pomocne są również seryjne oznaczenia B-hCG. Niestety, marker ten może nie być pomocny w niektórych przypadkach. W związku z tym celem niniejszej pracy było określenie stosunku podtypu beta gonadotropiny kosmówkowej (B-hCG) do hiperglikozylowanej ludzkiej gonadotropiny kosmówkowej (H-hCG) u chorych z ciążową neoplazją trofoblastu. **Materiał i metody:** Przeprowadzono przekrojowe badanie z udziałem 22 pacjentek z rozpoznaniem ciążowej neoplazji trofoblastu, skierowanych do kliniki onkologicznej szpitala akademickiego Uniwersytetu Medycznego w Mashhad w Iranie w okresie od grudnia 2017 do maja 2018 roku.

Kryteriami włączenia były stężenie plateau B-hCG (przez 4 tygodnie) lub utrzymujące się niskie stężenie hCG. Po wykluczeniu innych patologii dokonano pomiaru stężenia H-hCG i oceny stosunku H-hCG do całkowitej hCG. Jeśli odsetek ten przekraczał 20%, ustalano rozpoznanie aktywnej postaci ciążowej neoplazji trofoblastu, natomiast jeśli był mniejszy niż 20%, rozpoznawano postać nieaktywną ciążowej neoplazji trofoblastycznej. W przypadku pacjentek z aktywną postacią ciążowej neoplazji trofoblastu procedury interwencyjne obejmowały zmianę intensywności dawki lub chemioterapii, ewentualnie proponowano leczenie operacyjne. Natomiast u pacjentek z nieaktywną postacią choroby zalecano jedynie seryjną obserwację. Przez cały okres leczenia prowadzono obserwację pacjentek, monitorując i rejestrując ich stan zdrowia. **Wyniki:** Średnia wieku badanych wynosiła 31,36 ± 8,01 roku. Najczęstszym rozpoznaniem wśród pacjentek był zaśniad groniasty, występujący u około 64% (14) badanych. Chemioterapię otrzymywało łącznie 81% kobiet. Odstęp czasu od rozpoczęcia chemioterapii do momentu osiągnięcia plateau lub uzyskania utrzymującego się niskiego stężenia hCG wynosił 11,26 ± 4,03 tygodnia. Średnia wartość stężenia B-hCG wynosiła 36,6 mIU/ml, natomiast średnia wartość stosunku H-hCG do całkowitej hCG – 6,24%. U 82% pacjentek odsetek ten wynosił poniżej 20%. U 14 spośród tych pacjentek (77,8%) doszło do samoistnej normalizacji stężenia B-hCG podczas 6-miesięcznej obserwacji. W 2 przypadkach z uwagi na podwyższone stężenie B-hCG zastosowano chemioterapię. Pozostałe pacjentki nadal znajdują się pod obserwacją i nie wykazują oznak progresji choroby. U jednej spośród 4 kobiet ze stosunkiem H-hCG do całkowitej hCG wynoszącym powyżej 20% zalecono zabieg histerektomii z uwagi na liczne porody w wywiadzie i ograniczenie choroby nowotworowej do macicy. U pozostałych pacjentek zwiększano dawkę metotreksatu lub dokonywano zmiany schematu chemioterapii, co skutkowało obniżeniem stężenia B-hCG do poziomu prawidłowego. Wszystkie pacjentki pozostają pod obserwacją i są wolne od progresji choroby. **Wnioski:** Dane zgromadzone w przedstawionym badaniu wskazują na zasadność stosowania H-hCG jako markera nowotworowego u pacjentek z utrzymującym się niskim stężeniem B-hCG, pomocnego w rozróżnieniu między nieaktywną postacią ciążowej neoplazji trofoblastu, w przypadku której nie ma potrzeby stosowania leczenia, a jej postacią aktywną. Niemniej jednak w celu potwierdzenia i uogólnienia wyżej przedstawionych wyników potrzebne są dalsze badania z udziałem większej grupy pacjentek.

Słowa kluczowe: ciążowa choroba trofoblastyczna, ludzki hormon gonadotropiny kosmówkowej, hiperglikozylowana hCG, B-hCG

INTRODUCTION

Human chorionic gonadotropin (hCG) is a hormone that has two subunits of alpha and beta. Hyperglycosylated hCG (H-hCG) is a variant of hCG made by cytotrophoblast cells. H-hCG is not a hormone, but acts as an autocrine on cytotrophoblast cells, thereby causing cell growth, differentiation and invasion. H-hCG is as an invasive signal of cytotrophoblast cells[1]. The invasion may involve a replacement of gestational products or the invasion of choriocarcinoma cells, thereby showing that choriocarcinoma cells are the main source of H-hCG. hCG is involved in many stages of placental and fetal development[2,3]. The ratio of H-hCG to total hCG greater than 20% can stimulate invasion. Indeed, the invasive potential of H-hCG has been proven by a number of studies. However, the exact mechanism of this phenomenon is still unknown. The first study reported by Cole et al. showed that choriocarcinoma cells mainly produce H-hCG, and this is a factor that induces invasion in choriocarcinoma[4]. It seems that H-hCG expresses protease enzymes, thereby facilitating invasion. This invasion can be controlled in a complete molar pregnancy or partial mole, or it may be uncontrolled in GTN[5]. In complete and partial moles, regular hCG is the main form of hCG because the syncytiotrophoblast cells are the main cells in benign moles. However, a small amount of H-hCG is also produced by the extra-villous cytotrophoblasts. In GTN, H-hCG makes up a high percentage of hCG because cytotrophoblastic cells account for a high percentage of cells in these invasive tumors[6]. The hCG tumor marker plays an important role in the diagnosis and treatment of patients with GTN, especially in patients receiving chemotherapy. Unfortunately, beta-hCG (B-hCG) may not be helpful in all cases. H-hCG marker, which allows for distinguishing active GTN from quiescence GTN, is very important in therapeutic planning in these patients[7]. An increase in the percentage of hCG-H indicates the presence of active disease. Physicians usually wait until hCG rises rapidly or until the diagnosis is confirmed by other methods. The purpose of the present study was to help physicians avoid unnecessary treatment of GTN and begin the treatment of patients with neoplasia as soon as possible. Cases of quiescence GTN do not need chemotherapy, while it is necessary to treat active GTN[8]. Since few studies have been conducted in this field worldwide, and no similar study has been conducted in our country (Iran), the present study aimed to investigate B-hCG/H-hCG ratio in GTN patients.

MATERIALS AND METHODS

This was a cross-sectional study in 22 GTN patients who were referred to an oncology clinic of an academic hospital of Mashhad University of Medical Science in Iran between December 2017 and May 2018. Inclusion criteria were plateau level of B-hCG (during 4 weeks) or persistent low level of HCG. After ruling out other etiologies and a history of medical illness (such as liver and kidney diseases and hypertension); patients with no contraindications for chemotherapy were eligible for the study. Exclusion criteria included patient's refusal to continue cooperation after initiation of the study; inability to follow-up the patient; confirmed metastasis or evidence of GTN recurrence in subsequent

studies. H-hCG was measured with Zelbio kit, which is an ELIZA kit (Germany) with reported accuracy of more than 99%[9]; then the ratio of H-hCG/total hCG was evaluated. If the proportion was more than 20%, active GTN was diagnosed, and if it was less than 20%, quiescent GTN was the diagnosis. In patients with active GTN, interventional procedures included a change in dose intensity or chemotherapeutic agents, or a surgery was proposed. Only serial follow-up was recommended in patients with quiescent GTN. Patients' status was followed during therapy and until normal level of hCG was reached. Descriptive statistical methods included central indices, distribution and frequency distribution in appropriate tables and charts, and were analyzed with version 23 of SPSS software.

RESULTS

In this study, 22 GTN patients were evaluated. The mean age of patients was 31.36 ± 8.01 years and the mean body mass index was 20.7 ± 2.1. The most frequent diagnosis was hydatidiform mole, which was reported in 14 (64%) patients, while partial mole was confirmed in 18.2% (4 patients). Placental site trophoblastic tumor accounted for 13.6% (3 patients). The lowest frequency was related to choriocarcinoma, which occurred in only one patient (4.5%). In total, chemotherapy was administered in approximately 18 (82%) patients (Tab. 1). The most common chemotherapy regimen was methotrexate (MTX) – 72% (13 patients), followed by a combination of MTX and Actinomycin (3 patients) – 17%, and methotrexate and EMA-Co (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine) in 1.2% (2 patients).

The time interval between the onset of chemotherapy until plateau or persistent low level of hCG was 11.26 ± 4.03 weeks with a range between 4 and 18 weeks. The time interval between the plateau hCG level and testing H-hCG was 5.27 ± 2.76 weeks, with a range between 2 and 13 weeks. The reason for the prolongation of this range was the lack of timely participation in the tests. The mean B-hCG level was 36.6 mIU/mL with a range between 5.20 and 212.00 mIU/mL. The mean H-hCG/total hCG ratio was 6.24%, ranging from 0.6 to 49.30%. This ratio was less than 20% in 82% (n = 18) of cases; the therapeutic process was intended only as continuous follow-up. Among these patients, 14 (77.8%) had spontaneously normalized levels of B-hCG during 6 months of follow-up. Two patients underwent chemotherapy due to an increase in B-hCG. Other patients are still under follow-up without disease progression (Tab. 2). Among 4 patients whose H-hCG/total hCG ratio was more than 20%, hysterectomy was recommended to one patient due to multiparity and disease limited to the uterus. The dose of methotrexate was increased in one patient. In the other 2 patients, chemotherapy regimen was changed to EMA-CO, and a decrease in B-hCG level to normal was observed in all of them.

Variable		Number (%)
Diagnosis	Hydatiform mole	14 (63.6)
	Partial mole	4 (18.2)
	Placental site trophoblastic tumor	3 (13.6)
	Choriocarcinoma	1 (4.5)
Chemotherapy	No	4 (18.2)
	Yes	18 (81.8)

Tab. 1. The clinical features of the study group

DISCUSSION

The purpose of the present study was to help physicians avoid unnecessary treatment in patients suffering from GTN and begin the treatment in patients with neoplasia as soon as possible. The results of this study indicate that H-hCG level can be used to distinguish an active GTN from the quiescence one. Cases of quiescent GTN do not need chemotherapy, while it is necessary to treat the active GTN group. According to studies, the continuous level of hCG begins to change, and hCG rapidly increases within 6 months to 10 years after it reaches the plateau level in 10–25% of patients with quiescence GTN. In many of these patients, the subsequent follow-up confirms the presence of a tumor with pathology of choriocarcinoma or other GTN cases. In fact, quiescence gestational trophoblastic disease is a pre-malignant syndrome which can become malignant in a number of patients. As noted, a single measurement of H-hCG is sufficient to confirm active GTN. This process allows to initiate treatment as early as possible or it may indicate a delay in treatment until hCG-H is present in the blood[7,8]. Previous studies also approve using H-hCG as a diagnostic tool. In his review study, Cole reported that a total of 100% of trophoblastic malignancies produced hyperglycosylated hCG markers in serum and urine and that no benign disease cases are positive for this malignancy promoter. They also indicated that hyperglycosylated hCG and its free β-subunit exist in all human cancers and promote malignancy[10]. Another, more recent study showed that the hCG β-subunit produced by cancers promotes malignancy, enhances cancer cell growth, cancer cell invasion and blockage of apoptosis in cancers. A study of 42 choriocarcinoma cases showed that percentage hyperglycosylated hCG exactly correlates with weekly doubling rate of cancer[11]. Another study was designed to answer the following two questions: Can H-hCG be a reliable marker for the diagnosis of active neoplasia in pregnancy or choriocarcinoma? And can H-hCG help in differentiating quiescent gestational trophoblastic disease from active neoplasia? The study patients were 82 GTN cases; choriocarcinoma, previous hydatidiform mole under chemotherapy and low real positive hCG level. The results of the present study were consistent with the previous study. There was no significant difference in total hCG value between women with quiescence GTN and active cases ($p > 0.05$). However, H-hCG was significantly higher in active cases ($p < 0.000001$). Indeed, hCG was able to differentiate this phenomenon with a 5% false positive ratio, while H-hCG could differentiate 100%

Patient's code	H-hCG/total hCG ratio	Therapeutic plans	Final situation
001	More than 20%	Follow-up	Monthly follow-up
002	Less than 20%	Follow-up	Zero concentration/ended Follow-up
003	Less than 20%	No referral	–
004	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
005	Less than 20%	Follow-up	Zero concentration/ended Follow-up
006	Less than 20%	Follow-up	Zero concentration/weekly Follow-up
007	Less than 20%	Follow-up	Zero concentration/ended Follow-up
008	More than 20%	Follow-up	Zero concentration/ended Follow-up
009	Less than 20%	Follow-up	Zero concentration/ended Follow-up
010	Less than 20%	Follow-up	Zero concentration/ended Follow-up
011	More than 20%	Follow-up	Zero concentration/ended Follow-up
012	Less than 20%	Follow-up	Zero concentration/ended Follow-up
013	Less than 20%	Follow-up/an increased beta/hysterectomy/ an increased concentration/PET scan	Under follow-up
014	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
015	Less than 20%	Follow-up/an increased concentration	Under chemotherapy
016	More than 20%	Chemotherapy/a decreased concentration	Ended Follow-up
017	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
018	Less than 20%	Follow-up	Zero concentration/monthly Follow-up
019	Less than 20%	Follow-up/an increased concentration/an increased dose of methotrexate/an increased concentration again/a recommended hysterectomy	No referral
020	Less than 20%	Two zero concentrations	Zero concentration/weekly Follow-up
021	Less than 20%	One zero concentration	Zero concentration/weekly Follow-up
022	Less than 20%	Follow-up	Zero concentration/monthly Follow-up

Tab. 2. The results of follow-up in the study group

active GTN with the same false positive ratio[12]. Active disease was diagnosed half to 11 months earlier than the rapid increase in hCG using HCG-H in 23 patients in the present study. In the remaining 11 patients, H-hCG increased during clinical diagnosis of GTN tumor. Consistently, in 2009, Muller and Cole reported their experience of the US hCG Reference Laboratory Service between 1999 and 2009, on 133 cases of quiescent GTN, 35 cases of active disease and 30 cases of low level hCG. All cases of patients with low level of hCG (hCG-H less than 40%) were resistant to chemotherapy. The Center recommends that chemotherapy should not be used in patients with low level of hCG unless the hCG level is above 3,000 IU/mL[5].

All told, hCG and hyperglycosylated hCG free β-subunit promote the production of invasive enzymes collagenases and metalloproteinases, promote cell growth, and block cellular apoptosis, or have all malignancy properties[13].

We hope to make an antibody against hCG-H that would block tumorigenesis to prevent disease progression in GTN patients in the future.

LIMITATIONS

Small sample, which reduces the power of the study to generalize the results, is one of the limitations of our study.

 DOI: 10.15557/CGO.2020.0007

The limited duration of the study, which makes it unlikely that patients will ultimately be followed for months or years, is also a limitation. Another limitation of this study was the inability to perform long-term follow-up in all patients as they were not residents of Mashhad.

CONCLUSION

The data in this study suggests using H-hCG as a tumor marker in patients with persistent low level of B-hCG, which is useful to distinguish between quiescence gestational trophoblastic neoplasia, which does not need treatment, and active gestational trophoblastic neoplasia. However, further studies with larger sample size are needed to confirm and generalize the above findings. In addition, it is also useful to choose the best treatment option for patients. However, further studies with larger sample size are recommended.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication

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DOI: 10.15557/CGO.2020.0007 CURR GYNECOL ONCOL 2020, 18 (2), p. e34–e38