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Olgu Sunumu / *Case Report*

Slightly High Serum hCG Due to Chronic Kidney Disease

Kronik Böbrek Hastalığına Bağlı Olan Serum hCG Yüksekliği

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ABSTRACT

Aim: A number of recent reports have investigated the origin of false-positive hCG results. This case report demonstrates a slightly high true positive hCG in a young female patient with chronic kidney disease.

Materials and Methods: The patient's serum hCG value was measured with 4 immunoassay systems. Dilution and (polyethylene glycol) PEG 6000 precipitation were performed.

Results:hCG results were found slightly high in the 4 immunoassay method. The recovery ratio was calculated as 0,98 for the dilution result and 0,54 for PEG result on Immulite. Dilution and PEG 6000 precipitation studies were not supported heterophile antibody presence.

Conclusion: Further work-up showed that the unexpected positive hCG result was secondary to Chronic Kidney Disease (CKD). It should be considered that HCG may be elevated in CKD patients like our case.

***Key Words**: hCG, immunoassay, polyethylene glycol(PEG)*

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ÖZET

Amaç: Son zamanlarda yayınlanan bazı makaleler yanlış pozitif human koryonik gonadotropin (hCG) sonuçlarının kaynağını araştırmıştır. Bu olgu, kronik böbrek hastalığı (KBH) olan genç bir kadın hastada hafif yüksek gerçek pozitif bir hCG sonucunu göstermektedir.

Gereç ve Yöntem: Hastanın serum hCG değeri 4 immunoassay sistemi ile ölçüldü. Daha sonraki aşamada dilüsyon ve PEG 6000 ile çöktürme gerçekleştirildi.

Bulgular: 4 immunoassay yöntemi ilede hCG sonuçları bir miktar yüksek bulundu. Immulite ile geri kazanım oranı dilüsyon sonucu için 0,98, PEG sonucu için 0,54 olarak hesaplandı. Dilüsyon ve PEG 6000 ile çöktürme çalışmaları, heterofil antikorların varlığını desteklemedi.

Sonuç: Sonuçların hepsi birlikte değerlendirildiğinde beklenmeyen pozitif hCG sonucunun KBH'na sekonder olduğu gösterildi. Bizim vakamız gibi KBH hastalarında HCG yüksekliği olabileceği göz önünde bulundurulmalıdır.

Anahtar Sözcükler: hCG, immunoassay, polietilen glikol(PEG)

INTRODUCTION

Human chorionic gonadotropin (hCG) is a glycoprotein hormone composed of alpha (α) and beta (β) subunits. The α subunit is similar to those of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH)(1,2). Those hormones are related by α subunits with identical amino acid sequences (3). The β-subunit of hCG discriminates from other pituitary glycoprotein hormones, which confers unique immunological and biological functions (1).β-subunit is encoded by six allelic genes and consists of 145 amino acids. α and β subunits are singly synthesized and modified in the endoplasmic reticulum (4). It's known that 30% of hCG being yielded is excreted by the kidney and another component is metabolized by it (5).

hCG has five different bioactive variants which contain hyperglycosylated hCG, hyperglycosylated hCGβ, and sulfated hCG (6,7). Also, hCG is produced by the pituitary gland in very small amounts which consist of its own β subunit (8). Automated laboratory tests do not distinguish between hCG variants.

The results obtained from hCG specimens are used in the assessment of pregnancy, ectopic pregnancy, threatened abortion, recent termination of pregnancy, trophoblastic disease, and germ cell tumors, etc. Phantom hCG attributes to constant mild elevations of hCG, causing physicians to mistreat patients when neither hCG nor pregnancy or tumors are present (9,10).

Various commercial hCG tests are available in the market to use diagnosis, maintenance, and monitoring of pregnancy, pregnancy-related diseases, and tumors.

In this report, we present the case of a woman of childbearing age with chronic renal disease who had secondary amenorrhea for 18 months.

CASE REPORT

An 18-year-old woman applied to the outpatient clinic with a complaint of amenorrhea in September 2021. The clinician performed a physical examination and ultrasound for her. Then he requested a serum hCG test from the laboratory. The hCG test was analyzed on an Advia Centaur XP immunoassay analyzer and the result was reported as 10.8 mIU/mL. Then, the patient was called to the outpatient clinic two days later for hCG level follow-up. The result of serum hCG value on that day was reported as 11.8 mIU/mL on Advia Centaur XP Siemens.

Due to discrepancies between clinical and laboratory findings, laboratory consultation was requested by the gynecologist.

To further investigate this inconsistency, the sample was measured with another immunoassay system to exclude device-

induced variation and the result was 66,7mIU/mL on Immulite 2000. The inconsistent results between the two analyzers created confusion. Upon this, the patient's hCG test was measured with Access, and Alinity auto analyzers in another two laboratories in the same city, and the results obtained were 25,74 mIU/mL and 15,3 mIU/mL respectively. All measurements were performed on the same day.

Also, the serum of the patient was pretreated with PEG 6000 (CAS-No:25322-68-3; Merck Ltd.) to remove interfering antibodies and hCG was measured at 17,9 mIU/mL on Immulite 2000. A dilution (1:2) study was performed with assay buffer and the hCG result was 33 mIU/mL on Immulite 2000. The recovery ratio was calculated as 0,98 for the dilution result and 0,54 for the PEG result.

MATERIALS and METHODS

At our center, PEG 6000 is routinely used to precipitate heterophilic antibodies in immunoassays.

The Advia Centaur Total hCG assay is a two-site sandwich immunoassay using direct chemiluminometric technology. This method utilizes two antibodies that are specific for different epitopes that are present on both the free β-subunit and the β-subunit of intact hCG. Immulite 2000 hCG is a solid-phase, two-site chemiluminescent immunometric assay. Alinity Total βhCG assay is a chemiluminescent microparticle immunoassay. Beckman Access Total β-hCG assay is a paramagnetic particle chemiluminescent immunoassay. Intact hCG and free β-subunit are measurements of this method.

RESULTS

The patient's hospital file is retrospectively analyzed in detail and we realized that the patient was diagnosed with CKD 3 years ago.

The patient hCG test results with different systems are shown in Table 1. Laboratory findings are shown in Table 2. Creatinin and BUN levels demonstrate the patient's CKD. TSH, LH, and FSH levels were in the reference range.

Table 1. hCG Results with Different Immunoassay Systems.
Tablo 1. Farklı İmmunoassay Sistemleri ile hCG Sonuçları.

Date	hCG(IU/L) Siemens	hCG (IU/L) Immulite	hCG (IU/L) Access	hCG (IU/L) Alinity	hCG (IU/L) Dilution(1/2) Immulite	hCG (IU/L) PEG (1/2) Immulite
27.09.2021	11,3	66,7	25,74	15,3	33	17,9
24.09.2021	10,8					

hCG:Rreference range for Siemens 0-6 IU/L, for Immulite 0-5,3 IU/L, for Acess 0-2,9IU/ L and for Alinity 0-2,4IU/L.

Table 2. The Patient's Laboratory Findings.
Tablo 2. Hastanın Laboratuvar Bulguları.

Date	BUN / mg/dL	Kreatinin / mg/dL	TSH / mIU/L	sT4 / ng/dL	LH / IU/L	FSH / IU/L
27.09.2021	41	6,19	1,620		26,27	3,44
24.09.2021			2,479			
06.04.2021			2,132	0,87		
02.04.2021	48	6,82				
22.07.2018	>125	12,78				

BUN:reference range 10-20 mg/dL
Kreatinin :reference range 0,6-1,1 mg/dL
TSH: reference range 0,55-4,78 mIU/L
sT4: reference range 0,85-1,6 ng/dL
LH: reference range 8,7-76,3 IU/L
FSH: reference range 3,4-33,4 IU/L

DISCUSSION

Heterophilic antibodies in human serum can also lead to erroneous hCG test results with interfering antibodies in hCG reagents. To investigate this interference initially, we tested patient serum with 3 different immunoassay systems and obtained results close to each other. These results support the absence of heterophile antibodies in the patient's serum. It is seen that in Table 1 hCG values measured with Immulite and Access are higher than the other two systems. The reason for this is that these two systems use a method in which the alkaline phosphatase enzyme is conjugated with the hCG antibody in the reagent content. Such differences between immunoassay methods are expected with no less frequency. Additionally, altered forms of hCG and the cross-reactivity of materials utilized for hCG calibration in different immunoassays, estimated differences may be due to a deficit of detection of hCG isoforms or bias in calibration between methods (11,12).

Secondly, we performed dilution and PEG 6000 studies and the results did not support the presence of heterophilic antibodies. The recovery ratio of 98 % with dilution study corresponds neat hCG and expected dilution results consistent with each other and inconsistent with the effect being due to a heterophile antibody. The recovery ratio of 54 % with the PEG6000 study remains a grey zone. Additionally, falsely high hCG levels due to heterophile antibodies usually range from 100-500mIU/mL which levels remain too high in our case. As a result, elevated hCG results in our patient may have been truly positive.

Rheumatoid factor (RF)interference can result in a false hCG test measurement. We ruled out this interference with testing our patient serum for RF and it was <20 IU/mL (reference range:0-30 IU/mL).

The new hCG measurement methods do not cross-react with LH, FSH and TSH as did prior assays. Also, as seen in Table 2, the test results of our patient were within the reference range.

At this point, we consider to review the patient's hospital file and found that the patient had been treated for CKD for 3 years.

The importance of CKD as a reason for positive hCG results has not been well studied. It's known that 30 % of hCG in pregnancy is filtered through the glomeruli and the remainder is cleared by metabolism in the kidneys and liver (5). Elevated hCG levels can be obtained in CKD which could be expected with a pregnancy of 3-5 weeks period or incomplete pregnancy (13). Slightly high hCG in CKD may be caused by reduced renal filtration and metabolic clearance (14). In addition, CKD patients have raised production of gonadotropins which can be because of reduced renal clearance as well as uncontrollable production due to regulatory disruptions (13,15).

High hCG levels were found in 5 cases with a mean age of 56,8(46-65) years in routine pretransplant screening. The age of our patient remains quite young compared to the cases in Soni's report (16).

In this case, the fact that the hCG level did not double after two days confirmed the absence of viable pregnancy and supported the hCG elevation due to CKD.

Although measurements of hCG have usually served well in keeping the demands of clinicians, there is a need to adjust cut-off values for CKD patients, as in our case. Also, patients should be informed if they are at risk for persistent mild elevations of hCG results, and this data should be added to the patient's file. It is, therefore, crucial for gynecologists and endocrinologists especially to be aware of this contingency when taking treatment decisions. This case also demonstrates that collaboration between laboratory specialists and clinicians is very important to avoid unnecessary invasive and radiological procedures.

Disclosure statement

No potential conflict of interest was declared by the authors.

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