Persistent Elevated β HCG in a Non Pregnant Patient with Chronic Renal Insufficiency. A rare case Leading a Misdiagnosis of Ectopic Pregnancy

Kronik Böbrek Yetmezliği olan gebe olmayan hastada sürekli hCG Yüksekliği: Hatalı ektopik gebelik tanısına yol açan nadir bir durum

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ÖZET

Giriş: Beta-hCG tüm hücrelerden küçük miktarlarda salgılanır ancak büyük oranda böbrekten atılır ve seviyesi diyaliz hastalarında gebelik olmadan da yüksek bulunabilir.

Olgu sunumu: 27 yaşında sağlıklı multipar kadın hasta yüksek beta hCG düzeyi ile acil servise başvurdu. Son dönem böbrek yetmezliği vardı. Beta-hCG seviyesi 180 mIU/mL olarak bulundu. Referans aralığa göre 2-3 hafta gebelik ile uyumlu idi. Diyaliz öncesi ve sonrası ölçümlerde fark yoktu. Ölçüm Beckman Coulter System (USA) analizöründe yapıldı. Heterofil antikor ihtimaline karşı farklı sistemlerde ve dilüsyonla ölçüm tekrarlandı. Üç sistemde de benzer sonuçlar alındı. hCG düzeyi 17 gün yatış süresi boyunca 90,76± 5,54 (ortalama±SD). Hiç bir radyodiagnostik inceleme de intra veya extrauterin gebelik için tanı koydurmadı. Biz hCG düzeyinin diyalizde etkilendiğine karar verdik.

Sonuç: Kronik böbrek yetmezliği olan hastalarda gebelik olmasa bile hCG düzeylerinin yüksek bulunabileceğini ve yanlışlıkla intra veya extra uterin gebeliğe işaret edebileceğini düşündük. Diyaliz hastalarında serum beta hCG düzeylerinin güvenilir olmadığı ve seri beta hCG ölçümlerinin önemli olacağı sonucuna vardık.

Anahtar Sözcükler: hCG, hemodiyaliz

ABSTRACT

Background: Beta-human chorionic gonadotropin (beta-hCG) is secreted in small amounts by all cells and since the hormone is largely excreted by the kidneys, its levels can be elevated in non-pregnant-dialysis patients.

Case presentation: A 27-year-old healthy multigravid woman was seen in our emergency department with a history of a higher β -hCG level. She had end-stage renal disease. Beta-hCG level was 180 mIU/mL. It was fitted for 2-3 weeks pregnancy according to reference interval.There were no differences

between pre and post dialysis hCG levels. The analysis were performed using Beckman Coulter System (USA). In case of heterophile antibody the analysis repeated with dilution on different analysers. We found almost same β hCG results from three systems. Her β hCG levels were 90,76± 5,54 mIU/mL (mean ± SD) during 17 days lenght of stay at hospital. None of the radiodiagnostic tests either diagnosed a intrauterine or extrauterine pregnancy. We decided that this hCG levels were affected from dialysis.

Conclusions: We conclude that elevated β hCG values can be found in non pregnant women on chronic hemodialysis, erroneously indicating an early pregnancy or an extrauterine pregnancy. Since serum β hCG levels are not reliable in dialysis patients, the diagnosis should be confirmed by measuring serial β hCG levels.

Key words: hCG, hemodialysis

INTRODUCTION

Human chorionic gonadotropin (hCG) is a heterodimeric hormone consists of an α (14.5 kD) and, β (22.2 kD) subunit. The α -subunit of hCG is the same as in other pituitary hormones –luteinizing hormone, follicle stimulating hormone, and thyroid stimulating hormone–whereas the β -subunit is unique and provides specific biological functions for each hormone. HCG is produced in small amounts by the pituitary gland and other organs, such as testis, liver, colon, and in much larger amounts by placental trophoblast and malignancies such as hydatidiform mole, choriocarcinoma, and germ cell tumors (1). HCG is secreted in small amounts by all cells and since the hormone is largely excreted by the kidneys, its level can be elevated in dialysis patients even if without pregnancy (2). Pregnancy is infrequent in women undergoing renal replacement therapy (RRT) and may lead to serious maternal and fetal complications in this patient population"

Although rates of conception have increased for women on hemodialysis (HD), overall conception rates for women on renal RRT remain low. Pregnancy is infrequent but has a complicated course in women on dialysis. The diagnosis of pregnancy in women on dialysis is complicated by major difficulties. Firstly, the pregnancy may be missed because rates of conception in dialysis patients are almost negligible.

Second, certain clinical manifestations, such as nausea and vomiting, are common in uremia and early pregnancy. Third, the basic pregnancy tests are not reliable in women on dialysis because most marker measured in these tests are excreted through the kidneys and may give false positive results. Therefore, hCG is a useful clinical marker for detecting and monitoring various physiologic and pathologic conditions. Depending on its source or the condition, hCG may be present in serum in different forms such as the intact active dimer, free b-subunit, and various modified forms of the, β -subunit. Several commercial immunoassays are available to measure hCG in serum and urine. They differ with respect to the specificity of reagent antibodies that determine the molecular form(s) of hCG detected by each assay. The configurations of immunometric assays designed as two-site (sandwich) form are susceptible to interferences by heterophile antibodies, which may cause false results and harmful consequences for the patient.

Laboratories have attempted to detect this source of interference in various ways, such as testing the patient's serum by other hCG immunoassays, adding a heterophile antibody that blocks the reagent to the serum and retesting, and by other approaches.

Unexpected finding or persistence of low human chorionic gonadotropin (hCG) levels is not a rare situation. It requires a clinico-biological approach in order to avoid misunderstandings that could lead to inappropriate diagnostic or therapeutic attitudes. Beyond pregnancy, persistent low levels of hCG may be associated with various

benign and malignant conditions, i.e. quiescent gestational trophoblastic disease (QTD), raised pituitary hCG or false positive elevation caused by circulating heterophile antibodies (3).

After interfering heterophile antibodies have been ruled out as the cause of a false-positive serum hCG test, and intrauterin /extrauterin pregnancy and malignancy have been eliminated as common causes of a positive result, a true positive result may also be explained by an uncommon but interesting cause, as described in the present case.

Case presentation: In December 2014, a 27-year-old healthy multigravid woman was seen at our emergency department with a history of an elevated beta-human chorionic gonadotropin (beta-hCG) level. She had end-stage renal disease and had started dialysis 9 years prior to her visit. She had had one pregnancy, which resulted in the vaginal delivery at 37 weeks gestation. On examination, she was pale with a pulse rate of 74 per minute and blood pressure of 110/70 mmHg.

Abdominal examination revealed, lower abdominal tenderness without significant guarding and rigidity. Cervical movements were normal and there was no vaginal bleeding. A transabdominal and transvaginal ultrasound examination demonstrated a normal-looking endometrial thickness and bilateral ovaries.There was minimal free fluid in the culde-sac suggestive of intra peritoneal hemorrhage. Serum beta-human chorionic gonadotropin (beta-hCG) level was 180 mIU/mL. (normal< 5 mIU/mL). Establishing a date of conception was impossible due to irregular menses. It was appropriate for 2-3 weeks pregnancy according to reference interval. There were no differences between pre and post dialysis HCG levels. We thought that the levels were not too high to find differences for our case. Her serum alpha-fetoprotein was negative. We could not check urine hCG levels because she had anuria. In the transvaginal ultrasound scan it was seen that she does not have intrauterin gestational sac. Given that she had hCG levels consistent with 2-3 weeks gestation without sac, she was thought to have extrauterine pregnancy. Beta hCG level were followed with the expectation that it would increase irregularly than normal pregnancy. But our patients all hCG levels were slightly higher during 17 days.

All serum samples for hCG in this patient were tested in the main and emergency laboratory of our hospital by a two-site immunochemiluminometric assay (ICMA) using an automated analyzer, (DXI 800, Beckman Coulter System) (USA). In case of heterophile anticor the analysis was repeated on different vehicles. The same samples were analysed with chemiluminesence assay Immulite 2000 (Siemens, Germany) and electrochemiluminesence immunoassay Cobas e 411 (ECIA; Roche, Mannheim).

We found almost the same hCG results with the three systems (148 mIU/mL, 130 mIU/mL, 190 mIU/mL for DXI 800, Cobas e411, Immulite 2000 respectively). All of them were persistently slightly higher during this period. Her hCG level was 90,76± 5,54 (mean ± SD) for all assay for 17 days. The original serum of 08/12/14 was found to have an elevated hCG (180 mIU/mL) and was subsequently tested with serial dilution (1:2 and 1:4) to determine the proportionality of the results. At the end of this study, we excluded the heterophile antibody probability. A transvaginal ultrasound was repeated in 10 days and we have also scanned magnetic resonance imaging for pelvic system. None of the radiodiagnostic tests either diagnosed an intrauterine or extrauterine pregnancy. Her endometrial biopsy was also nonpatognomic. We decided that this elevated hCG levels were caused by dialysis period without an intrauterine or ectopic pregnancy.

DISCUSSION

Human chorionic gonadotropin, a member of the glycoprotein hormone family, is synthesized and secreted by trophoblast cells of the placenta and is a heterodimeric hormone composed of noncovalently linked α and β subunits internally linked by disulfide bonds (2). Elevated hCG in maternal serum and urine are both reliable indicators of pregnancy. Immunometric (sandwich) assays are used for both (4). Although pregnancy in end-stage renal disease (ESRD) patients is infrequent, recent data show that the conception rates are improving overtime. According to data from Registry of Pregnancy in Dialysis Patients (RPDP), conception rate in HD patients in a two-year period (1990-1992) was 1.5% (5).

Pregnancy in dialysis patients is a major challenge to physicians involved in care, given the rarity of occurrence, complications involved and the distressing observation that < 50% of pregnancies in patients receiving conventional dialysis result in surviving infants (6).

Serum beta hCG levels should be interpreted with caution in dialysis patients as levels tend to be slightly elevated even in nonpregnant patients as in our case and can be erroneously interpreted as intact pregnancy in a non-pregnant patient or a non –viable pregnancy in a pregnant patient (7) .

hCG is secreted in small amounts by all cells and since the hormone is largely excreted by the kidneys , its level can be elevated in dialysis patients even if not pregnant (7). Schwarz et al, published their study that beta HCG levels were increased by 10 fold in two of the 19 non pregnant women who were on dialysis with post-dialysis levels being significant higher than pre-dialysis levels (8). But, in our case there were no statistical differences between pre and post dialysis hCG levels.This observation has an important implication in clinical practice when monitoring serial beta hCG levels should be specified when results reported. And also, a laboratory must verify the result with different systems in case of heterophil anticor. We analysed the same sample in three different systems. The results were similar. De Backer B at all reported two non-pregnant patients with low serum hCG. In the first case, hCG levels raised during several years following a spontaneous abortion. The likelihood of heterophilic antibodies interference was ruled out and extensive clinical investigation excluded the presence of a tumour. The diagnosis was QTD. In the second case, elevated hCG came to light as an incidental finding in a women with chronic renal failure and led the clinicians to question the laboratory. The cause was probably an increase in pituitary hCG consecutive to terminal renal failure. These cases illustrate the importance of understanding the biology of the hCG and the causes of its persistent low elevation, which are reviewed in this article. It is essential to demonstrate clinically the presence of a tumour in order to avoid unnecessary and ineffective chemotherapy and/or hysterectomy (3).

Chronic hemodialysis patients have also been shown to have elevated serum levels of the a-subunit of hCG and other pituitary hormones, and pituitary releasing hormones. Several explanations of this phenomenon have been suggested: reduced metabolism and clearance; increased production due to dysregulation; and changes secondary to uremia (9,10). These mechanisms may also account for elevated serum beta hCG levels in such patients To our knowledge, elevated serum hCG has been reported infrequently in hemodialysis patients (10). The incidence of kidney failure treatment in our country has increased in recent years a trend that leads us to surmise that elevated hCG associated with ESRD, such as in our patient, may be more common than generally recognized.

In summary, there are many sources of hCG and reasons for elevated levels, including both benign and pathologic. Due to the molecular heterogeneity of hCG, it is important to know which form(s) are detected by the specific diagnostic assay

used by the laboratory. In patients with elevated hCG levels that are inconsistent with clinical findings, the laboratory should assist the clinician by investigating the unexpected test results by a variety of confirmatory and exclusionary laboratory strategies to avoid harmful mismanagement.

CONCLUSIONS

We conclude that elevated hCG values can be found in non pregnant women on chronic hemodialysis, erroneously indicating an early pregnancy or an extrauterine pregnancy. Since serum beta hCG levels are not reliable in dialysis patients, the diagnosis should be confirmed by measuring serial beta hCG levels.

Consent

The patient described in the case report had given informed consent for the case report to be published.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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