CASE REPORT

Pregnancy, malignancy or mother nature? Persistence of high hCG levels in a perimenopausal woman

Ayşe Y Demir,¹ Ruben EA Musson,² Willem A Schöls,³ Jitze M Duk³¹Laboratory for Clinical Chemistry and Haematology, Meander Medical Center, Amersfoort, The Netherlands²Laboratory for Clinical Chemistry and Haematology, University Medical Center Utrecht, Utrecht, The Netherlands³Department of Gynaecology and Obstetrics, Meander Medical Center, Amersfoort, The Netherlands**Correspondence to**
Dr Ayşe Y Demir,
ay.demir@meandermc.nl

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SUMMARY

Despite the fact that a small percentage of perimenopausal women have mild elevations in human chorionic gonadotrophin (hCG) concentrations (<14 IU/L) besides high levels of gonadotrophins, a considerable number of clinicians are not aware of this phenomenon. We report a case of a 53-year-old woman with an unusually high hCG concentration (>40 IU/L) given her menopausal state. Although a pregnancy or a malignancy was unlikely on the basis of stable hCG levels, elevated gonadotrophins and a negative transvaginal ultrasound, her physicians were uncertain and chose an expectant approach by repeated testing. Ultimately, after consulting the laboratory, analytical interference was ruled out and pituitary origin of unusual high hCG level could be confirmed after conduction of a suppression test by oestrogen–progesterone hormone replacement therapy. Until that time, the patient had undergone a vast amount of laboratory tests and gynaecology consultations, resulting in an enormous amount of confusion, anxiety and overdiagnosis.

BACKGROUND

Slightly elevated serum human chorionic gonadotrophin (hCG) up to 14 IU/L is a normal laboratory finding in nearly 10% of women above 55 years of age. If, in addition, follicle-stimulating hormone (FSH) is >20 IU/L, pregnancy can usually be ruled out in perimenopausal and postmenopausal women. However, hCG concentrations that are inappropriately elevated >14 IU/L raise concerns of pregnancy or a hCG-producing malignancy, although analytical interference, assay variation or pituitary origin can still be sensible explanations. We present a case of 53-year-old patient with an unusually high hCG concentration (>40 IU/L) for her menopausal state, who underwent a considerable amount of laboratory tests and gynaecology consultations, resulting in confusion, anxiety and overdiagnosis. Being aware of normal pituitary secretion of hCG in perimenopausal and postmenopausal women, ruling out false positive laboratory results and conducting a suppression test as first steps in the early phase of the diagnostic process can avoid unnecessary evaluation and anxiety.

CASE PRESENTATION

A 53-year-old woman was referred to our obstetrical outpatient clinic by a primary care midwife with the suspicion of a molar pregnancy on ultrasonography examination. The patient reported

that she had had no menstruation for 4 months and had been experiencing menstrual irregularities for several months prior to the last episode. She thought she was menopausal and was having unprotected intercourse since then, but regularly performed home pregnancy tests (threshold for detecting urine hCG is 20 IU/L). When the results were repeatedly positive, she was seen by the midwife. She had no complaints related to menopause and no abdominal pain.

INVESTIGATIONS

Basic gynaecological examination revealed no abnormalities. Transvaginal ultrasonography (TVU) demonstrated neither physiological or molar pregnancy nor any other pathology, except for a 16 mm sized follicle in the left ovary. Laboratory investigations revealed elevated gonadotrophins (FSH 66 IU/L and LH 38 IU/L) and an elevated total beta-hCG (intact hCG and free beta-hCG: 43 IU/L) that were analysed on a routine immunochemistry analyser (Architect i2000SR, Abbott B.V., Hoofddorp, The Netherlands).

DIFFERENTIAL DIAGNOSIS

Differentials of inappropriately elevated hCG concentration in this case were:

- ▶ Pregnancy
- ▶ Malignancy, that is, trophoblastic disease, germ cell tumour or any other malignancy.
- ▶ Laboratory origin, that is, false positive test results due to analytical interference or assay variation.
- ▶ Pituitary origin.

TREATMENT

Not relevant.

OUTCOME AND FOLLOW-UP

Our patient was complaint free, had no alarming or supporting findings at the TVU and had elevated gonadotrophins that were at a postmenopausal level as expected. Taken together, these findings led us to conclude that a placental origin of the inappropriately high hCG was unlikely, but could not be fully excluded¹ and therefore should be monitored. The hCG levels were checked several times and after 3 months, the inappropriately elevated hCG levels were normalised without any intervention (figure 1).

Eight months after the initial visit, our patient referred again to our outpatient clinic for another

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Figure 1 Several hCG measurements and additional testing at different time points during follow-up. hCG, human chorionic gonadotrophin; hCG-RIA, hCG measured by radioimmunoassay; hCG-Beckman, hCG measured by an alternative method (Beckman); CEA, carcinoembryonic antigen; CA 125, cancer antigen 125; TSH, thyroid stimulating hormone; fT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor-1.

reason: she had a positive result designated as cervical intraepithelial neoplasia (CIN) I during the national cervix carcinoma screening programme. The laboratory investigations were repeated on patient demand in particular and the results were similar to the levels at the first visit. The gonadotropins (FSH and luteinising hormone (LH)) were elevated in concordance with the clinical diagnosis of her menopausal state. Although the inappropriately high hCG caused clinical confusion, an expectant approach was chosen for follow-up of cervical pathology and elevated hCG levels, as there was no strong suspicion for pregnancy or any malignancy. Four months later, the cervical findings had worsened to CIN III and our patient underwent a loop diathermy intervention (LLETZ: large loop excision of the transformation zone).

During this interval, endocrinological investigations were repeated monthly. The persistence of unusually high levels of hCG (figure 1, table 1) resulted in a huge amount of distress of the patient and the clinician, > 25 consults at the outpatient clinic and blood was drawn >10 times for laboratory investigations. Although the level of suspicion was low for malignancy, a set of other oncological biomarkers (CEA, CA 125, alpha-fetoprotein and inhibin B) and pituitary hormones were measured, all of which were within reference range.

Measuring hCG in several dilutions of the same serum sample or with alternative immunoassay methodologies are examples of strategies that can be followed to exclude a false positive hCG result. Dilution experiments with serum from our patient showed a linear response, which made an interference from human anti-animal antibodies and heterophile antibodies unlikely. In addition, the hCG levels we found on our Architect i2000SR platform (Abbott B.V., Hoofddorp, The Netherlands) were confirmed by measurement on a UniCel DxI 800 immunoassay platform

(Beckman Coulter Nederland B.V., Woerden, The Netherlands) and by radioimmunoassay of a Dutch reference laboratory for the measurement of hCG in molar pregnancies (prominently for free beta-hCG and hyperglycosylated hCG). Positive urine hCG tests ruled out a macro-hCG. This led us to conclude that our patient had true high levels of hCG that most likely originated from the pituitary and were not related to pregnancy, trophoblastic disease, germ cell tumour or any other malignancy. Therefore, we decided to prescribe hormone replacement therapy to our patient to confirm the pituitary origin of high hCG. After 2 weeks, blood work demonstrated a reduction of the gonadotropins and hCG to premenopausal levels (figure 1 and table 1).

DISCUSSION

Although qualitative urine and quantitative serum hCG tests in perimenopausal or postmenopausal women are usually negative, several studies have reported that the concentration of hCG in non-pregnant women increases with age and may produce false positive pregnancy tests.²⁻⁷ The concentrations of hCG varied in these studies, depending on the characteristics of the cohort, definition of menopause and the method of measurement, and ranged up to 7.7 and 13.1 IU/L for non-pregnant perimenopausal and postmenopausal women, respectively. Several authors^{7,8} have recommended to round these values to the nearest whole number as the upper limits of normal serum hCG, which will be 8.0 and 14.0 IU/L for non-pregnant perimenopausal and postmenopausal women, respectively. The order of magnitude of hCG concentration in our patient was far above the values that were reported in the literature.⁷⁻⁹ This might be explained by the fact that laboratories use different methodologies to measure total beta-hCG, which result in a large variation between immunoassays of different manufacturers. This phenomenon is clearly visible in the Dutch External Quality Assessment Scheme (Dutch Foundation for Quality Assessment in Medical Laboratories, SKML).

hCG is a glycoprotein hormone that is generally used as a marker for pregnancy detection and monitoring, as it is synthesised by the syncytiotrophoblastic cells of the placenta. In addition, it is used as an oncological biomarker in trophoblastic diseases, germ cell tumours and other malignancies.¹⁰ hCG is composed of two dissimilar subunits designated as alpha and beta. The alpha subunit is shared among the glycoprotein hormones produced by the pituitary gland, that is, LH, FSH and thyroid-stimulating hormone (TSH). The exact source

Table 1 Several measurements of gonadotrophins and ovarian steroids at different time points during follow-up

Time (months)	FSH (IU/L)	LH (IU/L)	Progesterone (nmol/L)	Estrodiol (nmol/L)
0	66	38	<1	0.15
0.25	48	35	1	0.21
3	3	7	11	0.58
8	77	40	n.a.	0.06
12.5	72	40	0.4	0.09
13	8	12	<1	<0.04

FSH, follicle-stimulating hormone; LH, luteinising hormone.

of hCG in perimenopausal and postmenopausal women with increased serum hCG concentrations is not known. However, the significant correlation between increasing concentrations of pituitary gonadotropins (FSH and LH) and hCG in ageing women suggests that it originates from the pituitary gland in these women.^{4 7 11 12}

In the literature, several reports have described individuals in which false positive hCG results led to unnecessary and harmful interventions, varying from chemotherapy to surgery or both.^{13–15} Possible causes for false-positive hCG results are human antianimal antibodies and heterophile antibodies, which interfere with the immunoassay methodology applied to serum hCG measurements. Iatrogenic causes of these antibodies include vaccination or blood transfusion.^{16 17} Non-iatrogenic causes include placental passage of antibodies and intensive contact with animals. These antibodies are sometimes formed in certain diseases such as celiac disease or immunoglobulin A deficiency.^{18 19} Another cause for false positive hCG results is macro-hCG, a complex composed of hCG molecules bound to immunoglobulins, which results in a prolonged clearance of hCG molecule from the circulation without any clinical significance.²⁰

Pituitary hCG is thought to originate from the anterior pituitary in the perimenopausal and postmenopausal state and it has 50% of the biological activity of hCG produced in pregnant women,¹² as levels of oestrogen and progesterone decreases, hCG increases alongside FSH and LH as a consequence of declining feedback regulation of the hypothalamic–pituitary–ovarian axis.^{4 7 9} There are reports that prescription of oestrogen–progesterone therapy suppresses pituitary hCG and FSH.^{4 9 11} This feedback mechanism was

also demonstrated in a hypogonadal man following an orchiectomy,²¹ in which administration of testosterone normalised mildly elevated hCG concentrations.

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Patient's perspective

Although I was receiving routine controls, I was quite worried and anxious about an unrevealed malignancy. I am very content that my gynaecologist contacted the laboratory doctor, who advised taking anticonceptive medication for a period of time and repeat the testing. Now I know the source of hCG and have peace.

Learning points

- Care providers should be aware of normal pituitary secretion of human chorionic gonadotropin (hCG) in perimenopausal and postmenopausal women.
- If an elevated hCG level in combination with high menopausal follicle-stimulating hormone and luteinising hormone levels is not sufficient to conclude a pituitary source of hCG, suppression of pituitary hCG production with oestrogen–progesterone hormone replacement therapy should be considered without delay.
- Low-threshold consultation with the laboratory should be considered if there is concern about falsely elevated hCG levels during analysis.

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