CASE REPORT

Postmenopausal pregnancy? Evaluation of elevated hCG in a 59-year-old woman

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SUMMARY

Slightly elevated serum human chorionic gonadotropin (hCG) can be a normal finding in postmenopausal women. We report a case of a 59-year-old woman with a history of abnormal uterine bleeding who presented with a concern for pregnancy after developing nausea and vomiting a few weeks after unprotected intercourse. Although pregnancy was extremely unlikely, hCG was obtained in order to reassure the patient since she reported that her mother conceived at the age of 60. Serum hCG was positive, prompting concern for malignancy versus pregnancy. Stable serum hCG levels, elevated follicle-stimulating hormone and negative transvaginal ultrasound ruled out both malignancy and pregnancy. Positive serum pregnancy test and hCG elevation was attributed to normal postmenopausal state.

BACKGROUND

Various disease processes result in elevated human chorionic gonadotropin (hCG) which can alarm both the patient and the healthcare provider. The birth rate for women over the age of 50 has increased since 1997 with Hamilton *et al*[1] reporting 743 births for this population in the 2014 Centers for Disease Control and Prevention *National Vital Statistics Reports*, higher than the 677 reported in 2013. The patient's history of unprotected sexual intercourse, combined with her family history of women with viable pregnancies in their late 50s, led to the ordering of pregnancy testing that was unexpectedly positive. This prompted two important questions: Was our patient indeed pregnant? Or did she have a malignancy in the setting of abnormal uterine bleeding? We, along with our colleagues, were unaware of the physiological increase in pituitary secretion of hCG in some postmenopausal women. Collectively, we rarely order hCG in women over the age of 50 years; however, it is important for primary care providers to know how to accurately interpret the results in the few instances that hCG is measured in this population.

CASE PRESENTATION

A 59-year-old woman with thalassaemia, iron deficiency anaemia, bipolar disorder and irritable bowel syndrome (IBS) presented to primary care clinic with concern that she may be pregnant. She had unprotected intercourse 3 weeks prior to presentation and 2 weeks later developed daily nausea and emesis. She denied abdominal pain, fevers, chills, headaches or diarrhoea worse than her baseline IBS with diarrhoea. She reported 'menstrual cycles' every 3–4 months lasting 2–3 days, each with spotting between cycles. Last episode was 3 months ago. Evaluation by gynaecology for abnormal uterine bleeding several months prior was notable for benign endometrial biopsy. She was told that she was postmenopausal; however, she did not believe her gynaecologist as she continued to have cyclic vaginal bleeding. In addition, she recalled that her mother conceived her at age 59 and an aunt conceived at age 60.

On examination, she was mildly obese. Abdomen was soft with mild, diffuse tenderness to palpation. No uterus was palpated. There was no evidence of abnormal hair growth or virilisation.

INVESTIGATIONS

- Urine pregnancy test
- Serum qualitative pregnancy test
- Serum quantitative hCG
- Follicle-stimulating hormone (FSH)
- Transvaginal ultrasound
- Gynaecology consult

DIFFERENTIAL DIAGNOSIS

- Normal pregnancy
- Ovarian germ cell tumour
- Gestational trophoblastic neoplasia
- Ectopic production of hCG from non-trophoblastic tumours (cervical, colon, lung)
- False-positive pregnancy test

OUTCOME AND FOLLOW-UP

Urine pregnancy test was negative. Given her family history of pregnancies at advanced maternal age, recent unprotected intercourse and the desire to reassure the patient, a qualitative serum pregnancy test was also obtained. The qualitative serum pregnancy test returned positive. Subsequent quantitative serum hCG was 7.11 IU/L (non-pregnant <5 IU/L).

Gynaecology was consulted and recommended FSH, repeat quantitative hCG and a transvaginal ultrasound to rule out malignancy. FSH was 89.1 IU/L, repeat quantitative hCG was 7.19 IU/L and transvaginal ultrasound showed enlarged fibroid uterus, normal left ovary, incompletely visualised right ovary and normal endometrial thickness. Note that endometrial biopsy from several months prior was normal.

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Given repeat hCG remained <10 IU/L and ultrasound was negative for a mass or intrauterine pregnancy, her elevated hCG was attributed to a postmenopausal state and no further workup was pursued. Her nausea and vomiting resolved and was attributed to viral gastroenteritis. She had a negative routine screening colonoscopy as well. She continues to follow closely with gynaecology to monitor postmenopausal bleeding without a clear source.

DISCUSSION

In postmenopausal women, hCG is produced alongside the structurally similar luteinizing hormone (LH)/FSH by the anterior pituitary, and it has 50% of the biological activity of hCG produced in pregnant women.[2] As levels of oestrogen/progesterone decrease in the postmenopausal state, FSH increases since low levels of sex hormones are insufficient to provide the necessary negative feedback on the hypothalamic–pituitary–ovarian axis.[3] Snyder *et al*[4] found that serum hCG concentrations increased with age in 720 non-pregnant women. Levels in women >55 years were higher (<2.0 to 13.1 IU/L) compared with non-pregnant women 18–40 years (<2.0 to 4.6 IU/L) and 41–55 years (<2.0 to 7.7 IU/L). In women aged >55 years, 16 out of 240 (6.7%) had serum hCG >5 IU/L. Similarly, Patel *et al*[5] found that 56 out of 666 women >55 years old had hCG level >5 IU/L yielding a prevalence of 8.4% in their study.

Urine pregnancy tests have a threshold of 20 IU/L of hCG, whereas serum pregnancy tests detect much lower levels of hCG (5 IU/L). Serum levels <5 IU/L are consistent with premenopausal, non-pregnant states; levels <14 IU/L are seen in normal postmenopausal women aged >55 years. In perimenopausal women, a non-pregnant state is likely with hCG levels 5–14 IU/L when FSH >20 IU/L.[4]

With the availability of serum tests with such sensitivity, more women may be referred for further evaluation of malignancy or, as in our case, pregnancy. Positive pregnancy tests may also be noted in pathological conditions such as trophoblastic and non-trophoblastic malignancies. Er *et al*[6] report two cases of women with false-positive urine pregnancy tests before being diagnosed with colon and cervical cancer, respectively. Quantitative serum hCG levels were <5 IU/L and the false-positive pregnancy tests were attributed to cross-reactivity of similar hCG subunits. Caution should be exercised when evaluating potential malignant aetiologies. Cole *et al*[7] report six women with history of gestational trophoblastic disease and mean hCG 9.5 IU/L who underwent unnecessary chemotherapy for presumed recurrence of malignancy. They also report three cases that had renal transplant surgery cancelled after a routine hCG level was obtained. These findings demonstrate the potential for significant morbidity with the misinterpretation of physiologic pituitary production of hCG. With the prevalence of positive hCG (defined as hCG level >5 IU/L) among postmenopausal women of approximately 6%–8%, this opens the opportunity for misinterpretation of normal hCG levels by primary physicians.[4 5]

With normal intrauterine pregnancy, hCG levels are >50 IU/L within the first week of conception and double every 48 hours with peak hCG at gestation week 10 (range 27 300–233 000 IU/L)[9] hCG levels >100 000 IU/L are expected in gestational trophoblastic neoplasia, with the understanding that overlap with normal pregnancy levels may exist.[8] Given hCG level overlap in normal pregnancy and gestational trophoblastic disease, ultrasound is often necessary to differentiate.[9] Summary of hCG values is given in table 1.

Table 1 Summary of human chorionic gonadotropin (hCG) values.

Category	hCG levels (IU/L)
Premenopausal (aged 18–40 years), non-pregnant	<5
Perimenopausal (aged 41–55 years), non-pregnant	<8
Postmenopausal (aged >55 years)	<14
Early normal pregnancy	>50
Pregnancy, second–third trimester	27 300–233 000
Gestational trophoblastic neoplasia	>100 000

Learning points

- Serum human chorionic gonadotropin (hCG) <14 IU/L and follicle-stimulating hormone >20 IU/L are consistent with normal menopause.
- In unclear cases of menopause, a 3-week course of oestrogen followed by repeat hCG can confirm intact and normal hypothalamic–pituitary axis in postmenopausal women.
- Suspected cases of malignancy are suggested by elevated free beta-subunit of hCG.

Typically, low hCG levels along with FSH >20 is sufficient to rule out pregnancy in perimenopausal women.[4] However, if further confirmation is desired to confirm normal pituitary production of hCG, a 2–3 week course of oestrogen containing birth control pills can be given followed by a repeat hCG level. hCG of <1 IU/L is consistent with physiologic pituitary production. The decrease in hCG is believed to be a direct result of appropriate negative feedback on the hypothalamic–pituitary–ovarian axis by oestrogen.[7] In cases of suspected malignancy, a free beta-subunit hCG should be measured and, if elevated, followed by appropriate imaging and referral as studies have suggested free beta-hCG is a marker of trophoblastic tumours. LH and FSH in ectopic production of hCG in non-trophoblastic tumours are expectedly low.[8]

Primary internists need to be aware of normal pituitary secretion of hCG in postmenopausal women (<14 IU/L) to avoid unnecessary evaluation and to prevent unnecessary anxiety in postmenopausal women.

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REFERENCES

1 Hamilton Brady E, Martin Joyce A, Osterman Michell JK, *et al*. Births: final data for 2014. *Natl Vital Stat Rep* 2014;64:1–64.
2 Birken S, Maydelman Y, Gawinowicz MA, *et al*. Isolation and characterization of human pituitary chorionic gonadotropin. *Endocrinology* 1996;137:1402–11.
3 Cole LA, Khanlian SA, Muller CY. Detection of perimenopause or postmenopause human chorionic gonadotropin: an unnecessary source of alarm. *Am J Obstet Gynecol* 2008;198:275.e1–275.e7.
4 Snyder JA, Haymond S, Parvin CA, *et al*. Diagnostic considerations in the measurement of human chorionic gonadotropin in aging women. *Clin Chem* 2005;51:1830–5.
5 Patel KK, Qavi AJ, Hock KG, *et al*. Establishing reference intervals for hCG in postmenopausal women. *Clin Biochem* 2017;50:234–7.

6. Er T-K, Jong Y-J, Tsai L-Y, *et al*. Urine pregnancy testing in two women with cancer. *Lab Med* 2007;38:280–1.
7 Cole LA, Yasushi S, Muller Carolyn Y. Letter to the Editor. *N Engl J Med* 2007;356:11 www.nejm.org.
8 Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *The Lancet* 2010;376:717–29.
9 Lima LL, Parente RC, Maestá I, *et al*. Clinical and radiological correlations in patients with gestational trophoblastic disease. *Radiol Bras* 2016;49:241–50.