Case Report

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A 14-year-old girl with premature ovarian insufficiency but with a positive pregnancy test

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Abstract

Objectives: Childhood cancer survivors are at risk for premature ovarian insufficiency, especially after treatment with alkylating agents. The objective of this report is to highlight a case in which this phenomenon caused a false-positive pregnancy test.

Case presentation: A workup was performed in a 14-year-old girl with a positive pregnancy test. She was diagnosed with stage IV neuroblastoma of the left adrenal gland at the age of 4 years. She received extensive treatment, including alkylating agents, and had been diagnosed with premature ovarian insufficiency. An LH/hCG suppression test was performed using high dose 17 bèta-estradiol: hCG levels normalized.

Conclusions: The pregnancy test was false-positive due to production of low amounts of hCG by the pituitary gland as a result of high LH concentrations following premature ovarian insufficiency. It may be helpful to perform the LH/hCG suppression test to prove pituitary origin of the hCG overproduction.

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Introduction

Female childhood cancer survivors are at increased risk of premature ovarian insufficiency (POI); on average, the chance had been estimated to be around 8 % [1, 2]. Recent data suggest an even higher incidence at age 40 years: 14.9–18.6 % [3]. Above average risk is seen in survivors who have been treated with alkylating agents or radiotherapy to a field including the ovaries [3, 4]. Surveillance for gonadal failure in pre- and peripubertal girls has been recommended by yearly clinical assessment (growth and puberty) in combination with determination of the follicle stimulating hormone (FSH) concentration from age 12 and up [5].

Pregnancy tests are usually urinary or blood tests detecting human chorionic gonadotropin (hCG). hCG is a glycoprotein that consists of an alpha and a beta subunit. The hCG alpha unit is structurally similar to the alpha unit of luteinizing hormone (LH), FSH, and thyroid stimulating hormone (TSH), and the beta unit is unique to hCG. hCG is mainly produced by the syncytiotrophoblast after conception. The function of hCG is to inhibit involution of the corpus luteum. In addition, hCG stimulates trophoblast differentiation and spiral artery genesis [6]. Small amounts of hCG are produced by the liver, colon, and pituitary.

Elevated hCG in urine or plasma can have several causes, including the following:

- Pregnancy
- Interfering antibodies (for example, antianimal antibodies, or heterophile antibodies, an overarching term)
- Gestational trophoblastic disease (mole pregnancy)
- Malignancy; germ cell tumors, in particular seminoma, choriocarcinoma, teratoma with elements of choriocarcinoma, and islet cell tumor
- Pituitary overproduction

Elevated hCG outside of pregnancy has been described in postmenopausal women [7]. It has been shown that the production of hCG is stimulated by gonadotropins and suppressed by sex steroids [8]. Multiple studies have confirmed the presence of hCG and free beta-subunit of hCG in the human pituitary [6, 9].

In case of pituitary overproduction of LH, also an excess of the alpha subunit (similar in LH and hCG) is produced. The hCG and LH beta subunits genes are located closely together on the same chromosome and are similar in DNA sequence due to evolutionary relatedness. For these reasons, hCG beta subunit production is also slightly up-regulated when LH beta unit production is up-regulated, which is the case after menopause [6]. In this way, in case of increased pituitary LH concentrations, which are found after menopause, both hCG alpha and beta units are up-regulated and complete hCG is formed and secreted. In a study of pre-, peri-, and postmenopausal women, it was indeed found that hCG concentrations increased with age [10]. It was proposed that the upper limit of the reference range for hCG should be 8 IU/L in perimenopausal women and 14 IU/L in postmenopausal women. The levels are, however, assay dependent. It has been suggested that pregnancy may be considered unlikely in women with an hCG concentration <14 IU/L in combination with FSH >20 IU/L [10]. It is not known whether these cutoffs are applicable to children with POI, although these values may provide some guidance.

To render a pituitary origin of elevated hCG likely, caused by high levels of LH due to premature ovarian insufficiency, a 2-week course of estrogen treatment may be trialed. If hCG concentration falls with increasing estrogen concentrations, this may be interpreted as being caused by negative feedback on the hypothalamic–pituitary level and thus make pituitary origin likely [7].

Case presentation

A 14-year-old girl presented at the emergency department at a regional hospital with acute abdominal pain. As part of the routine workup for abdominal pain in a female adolescent, a pregnancy test was performed.

Medical history

The girl had an extensive medical history. She was diagnosed with stage IV neuroblastoma of the left adrenal gland at the age of 4 years, for which she was treated according to the Dutch Childhood Oncology Group (DCOG) NBL 2009 protocol [11]. Therapy included chemotherapy, surgical removal, local radiotherapy (primary site and para-aortal lymph nodes, 21.6 Gy in 12 fractions), two courses of I-131 meta-iodobenzylguanidine (MIBG, 7,400 and 5,550 MBq, respectively), autologous stem cell transplantation, isotretinoine, and immunotherapy (dinutuximab with IL2 and GMCSF). Chemotherapy consisted of carboplatin (1,500 mg/m^2), cisplatin (487.5 mg/m^2), doxorubicin (178.1 mg/m^2), decarbazine (3,000 mg/m^2), vincristine (6 mg), ifosfamide (22,500 mg/m^2), melphalan (187.5 mg/m^2), vindesine (8.9 mg/m^2), etoposide (1,200 mg/m^2), and etoposide phosphate (937.5 mg/m^2). From age 5, she was in complete remission.

During follow-up, at age 12, gonadal status was evaluated. She had short stature (−2.7 standard deviations) and was prepubertal (Tanner stage B1P1A1). Luteinizing hormone – LH – (47 IU/L) and follicle stimulating hormone – FSH – (130 IU/L) levels were found to be elevated, together with an undetectable level of anti-Müllerian hormone (AMH), on which the diagnosis POI was based (see Table 1). Turner syndrome was excluded (46 XX karyotype). Her POI was considered a complication of the alkylating chemotherapy (especially Melphalan). She started on 17-beta-estradiol 0.5 mg per day orally to induce puberty. Both the girl and the parents were counseled that infertility was to be expected.

Diagnostic assessment

Surprisingly, the urine pregnancy test, testing for presence of human chorionic gonadotropin (hCG), came back positive. To confirm the presence of an elevated concentration of hCG, it was measured in blood, which confirmed hCG elevation (8.1 IU/L, reference <7.01 IU/L).

The girl was diagnosed with acute appendicitis, based on an ultrasound and laboratory results. Surgery was performed, after ultrasonography of the uterus and abdomen did not confirm pregnancy. The appendicitis was pathologically confirmed. The girl and her parents were confused and

Table 1: Laboratory investigations.

	Primary workup	Before estradiol 2 mg per day for 2 weeks	After estradiol 2 mg per day for 2 weeks
LH, IU/L	54	60	17
FSH, IU/L	130	140	60
Estradiol, pmol/L	138	98	262
AMH, ug/L	<0.03		
hCG, IU/L, ref 0–3	8	6	<2

LH, luteinizing hormone; FSH, follicle stimulating hormone; AMH, anti-Müllerian hormone; hCG, human chorionic gonadotropin.

upset that they had been counseled previously for infertility, while the pregnancy test seemed to indicate otherwise. After recovery from surgery for her appendicitis, she was re-evaluated biochemically at our pediatric endocrinology outpatient clinic. Re-evaluation confirmed persistently elevated LH (54 IU/L), FSH (130 IU/L), and hCG (8 IU/L, reference 0–3 IU/L) concentrations, while anti-Müllerian hormone was still not detectable (<0.03 ug/L), see Table 1. We concluded that the diagnosis of POI was correct and confirmed that the girl was expected to be infertile.

Considering the medical history of the patient, extra attention was given to the possibility of a second neoplasm. The combination of germinoma and neuroblastoma has been reported previously [12].

To exclude the presence of a germ cell tumor, an abdominal ultrasound was repeated, which revealed no abdominal masses; however, a 1.1 cm lesion in the liver was found. Because hCG can be produced in the liver, this lesion was considered suspicious and an MRI scan of the liver was performed. On this otherwise normal MRI, it was concluded that the lesion was likely benign. It was decided to follow the lesion by ultrasound; the lesion shrunk and was thought to be focal nonsteatosis.

Differential diagnosis

To differentiate between the different possible origins of an elevated hCG, the following considerations were made.

- Urine tests are not subject to interfering antibodies since these molecules are too large to be excreted by the normally functioning kidney. For this reason, interfering antibodies were not thought to be the cause of the elevated hCG level in our patient.
- Pregnancy was deemed highly unlikely given the sexual inactivity of the patient in combination with the high FSH level and low AMH level, a nonincreasing marginally elevated hCG level, and the normal abdominal ultrasounds.
- The relatively low elevation of hCG concentration did not make gestational trophoblastic disease likely.
- Germ cell tumor or pituitary overproduction could both not be formally excluded.

Diagnostic intervention

Under the suspicion of pituitary hCG production caused by an elevated LH concentration due to POI, a hCG suppression test was performed using high dose (2 mg) 17-beta-estradiol daily for 2 weeks. We are not aware of any literature on the dose of estradiol for children for this indication. Since 2 mg estradiol daily is a normal adult dose, we considered this to be a high enough dose for a young person only receiving 0.5 mg at the time to suppress hCG. Other than insomnia, the girl experienced no adverse effects of the high-dose estradiol. After 2 weeks, the concentration of estradiol, LH, FSH, and hCG were measured, see Table 1. The serum estradiol concentration increased from 98 to 262 pmol/L, and the LH and FSH concentrations decreased markedly to 17 and 60 IU/L, respectively, with a simultaneously undetectable hCG concentration (<2 IU/L).

It was concluded that estradiol treatment suppressed LH and hCG production at the level of the pituitary gland and the phenomenon of elevated hCG was considered physiological. Parents and patient could be comforted that there was no new malignant tumor.

Discussion

The laboratory findings in our patient are highly likely due to a premature biochemical menopause caused by destruction of oocytes by alkylating chemotherapy. The low level of estradiol (due to a low dose of 17-beta-estradiol supplementation for the early stage of induction of puberty) did not suppress gonadotropin-releasing hormone at the level of the hypothalamus, as happens in normal pubertal girls. Therefore, LH production was not suppressed but increased, leading to pituitary hCG production. After high-dose estradiol supplementation for 2 weeks, aiming to suppress gonadotropin releasing hormone, subsequently LH, and thereby hCG production in the pituitary gland, the hCG concentration became undetectable [6]. This “suppression test” proved the pituitary origin of the hCG production, and we could refrain from further diagnostic tests. Our case illustrates that also in children diagnosed with POI, pituitary hCG production may be present. Emergency care physicians, pediatricians, (pediatric) oncologists, and endocrinologists may not be aware of this phenomenon, due to the low prevalence of POI in children. This is crucial information, however, for correct interpretation of measurement of urinary or serum hCG concentrations in these young adolescents, possibly in the context of a pregnancy test. In the acute setting, this may lead to a false suspicion of pregnancy, which has medical risks, such as not acknowledging another medical issue causing abdominal pain, or delay or withdrawal of essential medication. In addition, a false-positive pregnancy test has significant psychosocial impact, such as unjustly being asked about sexual activity, the feeling of not having been counseled correctly, or getting false hope for fertility.

Learning points

- Girls with premature ovarian insufficiency can already have a biochemical menopause and thereby an increased pituitary hCG, which may cause a positive urinary pregnancy test.
- Urinary pregnancy tests should be interpreted with caution in girls with (possible) premature ovarian insufficiency, before possible pregnancy is discussed with the girl and her family, because of the psychosocial impact.

What is new?

- A high-dose estradiol "suppression test" can prove the pituitary origin of hCG production in primary ovarian insufficiency in girls (for example in childhood cancer survivors) and prevent unnecessary further diagnostic tests.

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