Pituitary origin of persistently elevated human chorionic gonadotropin in a patient with gonadal failure

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Objective: To report a case of persistently elevated low levels of hCG to increase awareness of pituitary origin of persistently elevated hCG in patients with gonadal failure.
Design: Case report and literature review.
Setting: Large university-affiliated infertility practice.
Patient(s): A 16-year-old patient with primary amenorrhea, normal secondary sex characteristics, ovarian failure, and a 46,XY karyotype. Her past medical history was significant for focal segmental glomerulosclerosis, leading to a diagnosis of Frasier syndrome.
Intervention(s): At age 31 years, she desired pregnancy by oocyte donation and was found to have persistently elevated low levels of hCG (>35 mIU/mL).
Main Outcome Measure(s): Pituitary hCG.
Result(s): Both serum free β-hCG and hyperglycosylated hCG were undetectable. Total serum hCG diluted appropriately was not blocked by blocking agent and was detected in the urine. Subsequent treatment with exogenous E_2, in preparation of a donor oocyte cycle, suppressed her hCG levels (down to 8 mIU/mL). These results indicated a pituitary source of the serum hCG.
Conclusion(s): This report reinforces the need to consider pituitary hCG as the origin of persistently elevated hCG levels in patients with gonadal failure. Although levels of hCG <14 mIU/mL have been considered normal in postmenopausal women, our case suggests that patients with gonadal failure at younger ages might have a higher pituitary output of hCG. (Fertil Steril® 2013;99:293–6. ©2013 by American Society for Reproductive Medicine.)
Key Words: Pituitary, hCG, Frasier syndrome, gonadal dysgenesis, ovarian failure

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Human chorionic gonadotropin is a glycoprotein hormone composed of two dissimilar subunits designated α and β, with 15 different isoforms (1). Of these 15 variants, 5 are natural synthetic products made by the placenta in pregnancy or by nontrophoblastic malignancies: regular intact dimer (hCG), hyperglycosylated hCG (hCG-H), free β-hCG-H, free α-hCG, and O-glycosylated free α-hCG. The other 10 variants are dissociated or degraded products, from macrophage cleavage and cleavage by proteases in the circulation and the kidney: free β-hCG, nicked hCG, nicked hCG-H, nicked free β-hCG, nicked free β-hCG-H, and free β-hCG core fragment. All of the nicked isoforms are missing the carboxyl terminus. Normally produced by the syncytiotrophoblastic cells of the placenta, hCG is commonly used as a marker for pregnancy detection and monitoring (1). Serum concentrations of hCG also have clinical use as tumor markers for trophoblastic diseases, germ cell tumors, and other malignancies (1, 2). Regular hCG is made by fused villous syncytiotrophoblast cells and hCG-H is made by extravillous cytotrophoblast cells, gestational trophoblastic disease, and testicular germ cell tumors. (1, 2). Free β-hCG-H is made by placental

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site trophoblastic tumors, and nontrophoblastic malignancies, the latter of which also makes free β-hCG.

In addition to its synthesis during normal pregnancy, trophoblastic disease, or cancer, a small amount of hCG is normally produced by the pituitary gland in conjunction with the structurally similar glycoprotein hormones LH, FSH, and TSH (1, 3–5). The highest blood hCG concentration in nonpregnant premenopausal women have been reported to be 4.6 IU/L, consistent with the conventional hCG cutoff of 5.0 IU/L (6). The highest hCG concentration in postmenopausal women have been reported to be 13.1 IU/L and it has been suggested that in postmenopausal women, hCG concentrations of less than 14.0 IU/L should be considered normal (6).

Women presenting for infertility treatment usually receive a serum hCG test to rule out pregnancy before any procedure, but persistently elevated hCG results can lead to delays in the procedure to unveil the cause of these elevations, especially in those who have no potential to get pregnant without any intervention. We present a case of a patient with Frasier syndrome (gonadal dysgenesis with nephrotic syndrome) and a history of bilateral gonadectomy who presented for oocyte donation as therapy for her infertility and was found to have elevated serum hCG levels beyond ranges reported in postmenopausal women.

MATERIALS AND METHODS

The patient was a 31-year-old woman with primary gonadal failure. She had a disorder of sexual differentiation caused by Frasier syndrome and desired to have an oocyte donor IVF-ET cycle. At age 16 years, she presented with primary amenorrhea. At that time, she reported thelarche at age 11 years and pubarche at age 13 years. There was no evidence of an eating disorder or excessive exercise, and she was virginal. Her height was 153.5 cm (10th percentile), weight was 50 kg (25th percentile), and body mass index (BMI) was 21.2 (56th percentile for age). On examination of her sexual maturity rating, her breasts were Tanner stage 5 and pubic hair was Tanner stage 4. Pelvic examination revealed normal female external genitalia. Of note, the patient had a history of progressive proteinuria, up to 5 g of protein per 24-hour urine collection. A kidney biopsy performed revealed focal segmental glomerulosclerosis. She was medically managed with improvement of her renal function (normal blood urea nitrogen and creatinine) and protenuria around 2.5 g per 24 hours.

On further work-up, her FSH was >170 mIU/mL and E_2 was <20 pg/mL. A pelvic ultrasound revealed a normal uterus and did not visualize the gonads. A karyotype performed came back as 46,XY. The patient was advised to have removal of her gonads due to the risk of malignant transformation. She underwent bilateral laparoscopic gonadectomy, which visualized a normal uterus, normal fallopian tubes, a 2.5 × 3 cm left gonad and a 3 × 4 cm right gonad. The pathology of the gonads revealed bilateral gonadoblastomas with areas of dysgerminomas, which likely accounted for the presence of her breast tissue as they secrete E_2. A postoperative computed tomography (CT) scan of the abdomen and pelvis was negative for adenopathy or metastasis. Ovarian cancer markers, including CA-125, lactate dehydrogenase (LDH), inhibin B, and α-fetoprotein (AFP), were all normal. Postoperatively, she was started on oral contraceptives (OC) as hormone replacement. A final diagnosis of Frasier syndrome was established, which is a disorder of sexual differentiation and is notable for having both 46,XY female and focal segmental glomerulosclerosis.

At age 31 years the patient desired pregnancy and presented for oocyte donation using her husband's sperm. She was on hormone replacement therapy (HT) with an OC pill. On baseline blood testing, she was found to have persistently elevated hCG levels ranging from 11–35 mIU/mL. Other laboratory values revealed FSH >170 mIU/mL, LH 140 mIU/mL, and E_2 <20 pg/mL. A transvaginal ultrasound revealed copious free fluid in the cul-de-sac. To rule out a recurrent or metastasizing dysgerminoma as the reason for her elevated hCG, tumor markers (including AFP, inhibin B, LDH) and a positron emission tomography/CT scan of the whole body were performed and were normal. To rule out a pituitary adenoma as a reason for the elevated hCG, a magnetic resonance imaging (MRI) of the brain was performed and was also normal. A plan to drain the fluid from the pelvis by ultrasound-guided culdocentesis was anticipated for further testing, but the fluid regressed spontaneously on the day of the scheduled procedure. Other potential causes of the pelvic ascites, such as renal (findings of stable blood urea nitrogen, creatinine, and urine protein), cardiac (findings of normal cardiac function), rheumatologic (findings of normal antinuclear antibodies [ANA], C3, C4, anti-ribonucleoprotein antibody [anti-RNP], and antidouble-stranded DNA antibodies), and infectious causes (findings of normal purified protein derivative [PPD] tuberculosis skin test and negative Strongyloides antibodies) were considered and additionally ruled out. The study was Institutional Review Board approval exempt.

RESULTS

A request to the USA hCG Reference Service was made for consultation. Blood and urine samples were sent. The results are shown in Table 1. Total serum hCG diluted 1:2 appropriately, hCG was not blocked by blocking agent and hCG was detected in the urine using a quantitative urine hCG test on the Siemens Immulite-1 hCG (15 mIU/mL) indicating that this is not a false positive (phantom) hCG, caused by a heterophyllic antibody reaction (1). The undetectable levels of free

TABLE 1

Blood and urine hormonal testing by USA hCG Reference Service.

Test		Significance
Serum total hCG (mIU/mL)	39	Elevated
Urine total hCG (mIU/mL)	16	Not phantom hCG
Serum total hCG diluted 1:2		Not phantom hCG
Serum total hCG not blocked by blocking agent		Not phantom hCG
Serum FSH (mIU/mL)	>170	Menopausal levels
Serum free β-hCG (mIU/mL)	<0.54	Not cancer
Serum hyperglycosylated hCG (mIU/mL)	<0.05	Not gestational trophoblastic disease

Merhi. Pituitary hCG. Fertil Steril 2013.