A case of ovarian enlargement in severe primary hypothyroidism and review of the literature

To the Editor: The association of massive cystic ovarian enlargement with primary hypothyroidism is infrequently reported and not widely recognized in the adult medical or gynecologic literature. At present the exact mechanism leading to ovarian cyst formation in patients with primary hypothyroidism remains uncertain. The clinical findings in patients with severe primary hypothyroidism complicated by massively enlarged ovaries and pituitary can lead to surgery for ovarian cysts or occasionally operation aimed at pituitary adenoma. We report a case of ovarian cyst enlargement associated with severe primary hypothyroidism and review the literature.

A 19-year-old female patient with menarche at the age of 12 years and irregular menstrual cycles presented with 4-year long complaints of generalized pain, swelling in the hands and feet, cold intolerance, decreased activity, excessive sleepiness, short stature, loss of hair and dry skin. She underwent an ultrasound examination for the recent complaint of lower abdominal pain, which revealed large ovaries with multiple cysts. She was scheduled for oophorectomy.

On examination her height was 143.5 cm, bone age lagged by 5 years behind chronological age, the body mass index was 23.3 kg/m^2 with fully developed secondary sexual characteristics, and she had puffy eyes with dry scaly skin. Her laboratory tests showed undetectable free thyroxine (normal, 9.1-23.8 pmol/L), thyroid stimulating hormone (TSH) was 4191.5 mIU/L (normal, 0.47-5.01) with positive antimicrosomal antibodies, prolactin was 38.1 µg/L (normal, 3.8-23.2), and 17-β estradiol was 127.5 pmol/L (normal follicular phase, 110-367). The figure shows the luteinizing hormone (LH) and FSH levels during gonadotropin-releasing hormone (GnRH) stimulation test before and after treatment. Pituitary magnetic resonance imaging (MRI) showed homogenous generalized enlargement of the pituitary gland. A pelvic computed tomography (CT) scan showed multiple bilateral ovarian cysts, the right ovary was 4.5 x 4 cm and the left ovary was 5 x 4 cm. The patient was diagnosed as having primary hypothyroidism with ovarian cystic enlargement. Treatment with thyroxine was initiated under close monitoring and the patient showed marked clinical improvement and normal menses. After six months, a repeat MRI showed a normal pituitary gland and a pelvic CT scan showed complete disappearance of the right ovarian cysts with two cysts remaining in the left ovary.

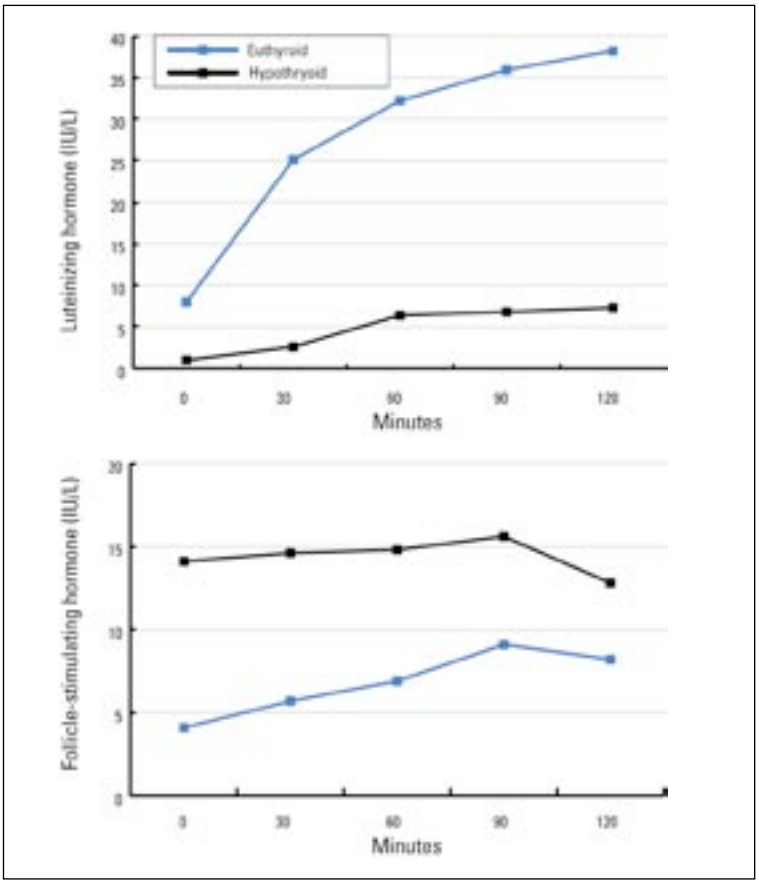

Figure 1. GnRH stimulation test before (hypothyroid) and after thyroxine treatment (euthyroid) (by IV administration of 100 µg with assessment of LH and FSH levels at 0, 30, 60, 90, 120 minutes).

Only 4 cases of massive ovarian enlargement have been reported in nonpregnant women with hypothyroidism (Table 1).[1,2,3,4] These patients were similar to our case, who had severe hypothyroidism of long duration, as evidenced by retarded growth and delayed skel-

etal maturity. They had massively enlarged cystic ovaries, abdominal pain and mild ascites. Pituitary enlargement due to thyrotroph cell hyperplasia in primary hypothyroidism is caused by a decrease in the negative feedback exerted by circulating thyroid hormones. Our case had massive pituitary enlargement that regressed rapidly with thyroxine treatment, while ovarian cysts persisted for several months. We have previously shown that complete resolution of ovarian enlargement may require one year.[4]

Ovarian enlargement in severe primary hypothyroidism is probably due to stimulation of FSH receptors by unusually high levels of TSH, which was proved to have weak FSH-like activity.[5] Other investigators have proposed that patients who have ovarian hyperstimulation syndrome due to hypothyroidism may have a mutation in the FSH receptor that may further increase the sensitivity of the receptor to TSH.[6,7]

Pathological examination of ovarian tissue from a similar case revealed non-luteinized ovarian cysts accompanied by extensive myxedematous infiltration in both ovaries.[3] These pathological features indicate that polycystic ovarian disease may be a misnomer, since the mechanism is probably quite different. Ovarian hyperstimulation could be the result of nonspecific overproduction of all the pituitary hormones by the tumor-like generalized enlargement of the pituitary,[8] which was evident in our patient. However, this mechanism is unlikely since the levels of basal and stimulated gonadotropins in our patients and other patients reported in the literature were within normal limits or suppressed (Table 1). Moreover, with thyroxine treatment and the resolution of ovarian enlargement we noticed an exaggerated response of gonadotropins to GnRH stimulation. Elevated prolactin levels in patients with severe hypothyroidism may be an etiologic factor in ovarian hyperstimulation;[9] however, massive ovarian enlargement is not a recognized feature in prolactinomas with higher levels of prolactin.

Markedly elevated serum levels of estradiol are found in most cases of ovarian hyperstimulation syndrome.[10] Our case and three of the patients described in Table 1 had normal serum estradiol, which has also been found in cases of ovarian enlargement owing to FSH receptor stimulation.[11,12] In conclusion, awareness that ovarian and pituitary enlargement can be caused by severe hypothyroidism will spare patients dangerous and unnecessary operative intervention.

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Table 1. Clinical and hormonal profile of patients with ovarian hyperstimulation and severe primary hypothyroidism reported in literature (nonpregnant cases only), and our case.

Reference	Age	FSH (IU/L)	LH (IU/L)	Prolactin (µg/L)	Estradiol (pg/mL)	Clinical	Ovary
1	21	19.2	6.2	119	1303	Abdominal pain	Multilobulated, ovarian cysts, rt 10 cm, lt 13.8 cm
2	26	15.7	0.7	36	80	Acute abdomen	Multicystic, rt 14 x 14 cm, lt 11 x 10 cm
3	16	33.6		133.5	104	Pelvic pain	Multicystic enlargement, rt 13 x 10 cm, lt 10 x 9 cm
4	22	9.8	12.6	71.3	150.9	Pelvic pain	Multiloculated ovarian masses, rt 6x4 cm, lt 12 x 9 cm
Our case	19	14.1	1.1	38.1	127	Abdominal pain	Bilateral ovarian cysts, rt 4.5 x 4 cm, lt 5 x 4 cm

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Prevalence of GBV-C/ hepatitis G virus viremia among chronic hepatitis B, chronic hepatitis C and hemodialysis patients in Turkey

To the Editor: The newly discovered hepatitis G virus (HGV) or GBV-C are isolates of the same virus, which is a single-stranded RNA virus of positive polarity with 9362 nucleotides.[1] It can be transmitted via blood transfusion and intravenous drug use, sexually, and from an infected mother to her child.[2] High prevalences of GBV-C/HGV have been found in subjects with frequent parenteral exposure and in groups at high risk of exposure to blood and blood products, including drug abusers, hemodialysis patients, multitransfused individuals and haemophiliacs.[3] Due to shared risk factors, coinfection of GBV-C/HGV with hepatitis B (HBV) or hepatitis C (HCV) viruses in chronically infected patients has been reported at frequencies ranging from 10 to 25%.[4]

Because the prevalence of GBV-C/HGV is unclear in Turkish population, we sought analyze the prevalence of GBV-C/HGV-RNA in the sera of different groups in the Turkish population. Three hundred and ten Turkish serum samples classified into four groups were studied. Sera of 85 hemodialysis patients, 80 chronic hepatitis B patients, 75 chronic hepatitis C patients, and 70 healthy persons (control group) were tested for the presence of GBV-C/HGV-RNA. The control group included apparently healthy individuals who had participated in occupational screening for a randomly selected viral hepatitis marker. Thirty-seven were male and 33 female with a mean age of 42.5±11.8 years (range, 20-65 years). None were positive for anti-HCV or for HBsAg.

RNA was extracted from 150 µl of serum using the Nucleospin Virus Kit (Biogene, Kimbolton, UK). Real-time PCR was performed using primer pairs and a probe located in the 5′ untranslated region (5′UTR) of GBV-C/HGV-RNA using the ABI Prism 7700 Sequence Detector System (Perkin Elmer, Foster City, Calif.). Data were analysed by Fisher' s exact test. A *P* value less than 0.05 was considered significant.

GBV-C/HGV-RNA was detected in 52 of the 310 sera tested with an overall prevalence of 17%. The highest prevalence was encountered among chronic hepatitis B patients (28%) followed by hemodialysis patients (24%), chronic hepatitis C patients (6%), whereas the lowest prevalence rate of 4% was detected among healthy persons (Table 1). HGV was significantly more frequent in chronic hepatitis B patients, hemodialysis patients, and chronic hepatitis C patients than in healthy persons ($P<0.05$).

It has been documented that patients with chronic hepatitis often harbor more than one hepatitis agent.[5] The apparent link between hepatotropic viral infections probably reflects common exposure and transmission patterns rather than a specific interdependence relation. Heringlake et al.[6] reported a striking high prevalence of HGV-RNA among patients with viral hepatitis B, C and D reaching 16%, 20% and 36%, respectively. In our study, the prevalence rate of GBV-C/HGV was 7% in the chronic hepatitis C group. The relative low prevalence of GBV-C/HGV-RNA in this group may be explained by a similar reciprocal replication pattern among patients coinfected with HBV and HCV.[7] This had been proposed by Raimondo et al.,[8] who suggested that while long-lasting persistance of HCV is the rule in chronically infected individuals, clearence of GBV-C/HGV after years of chronic infection is a frequent event.

Table 1. GBV-C/HGV RNA positivity among the four groups.

Group	No. tested	HGV RNA	
		No. positive	%
Chronic hepatitis B patients	80	23	29
Chronic hepatitis C patients	75	5	7
Hemodialysis patients	85	21	25
Healthy controls*	70	3	4
Total	**310**	**52**	**17**

*$P<0.05$ versus other groups.