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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.

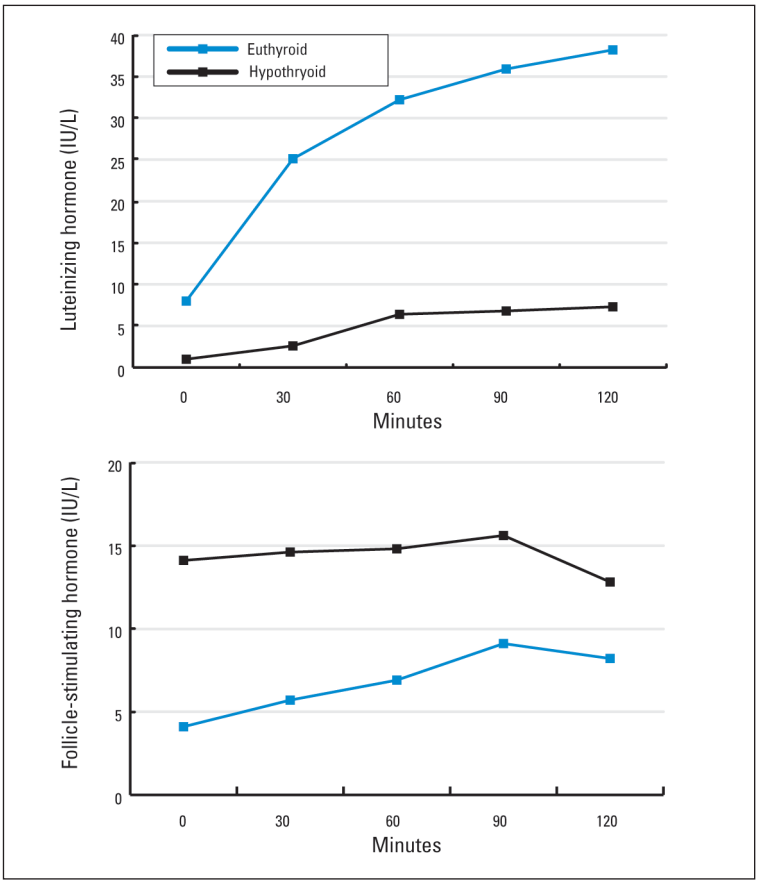

Figure 1. GnRH stimulation test before (hypothyroid) and after thyroxine treatment (euthyroid) (by IV administration of 100 µg with assessment of LH and FSH levels at 0, 30, 60, 90, 120 minutes).

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-

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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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