Acute Ovarian Torsion and Primary Hypothyroidism

abstract

A 12-year-old girl presented with acute abdominal pain due to an acute ovarian torsion. She required an oophorectomy. Clinical and laboratory assessment confirmed severe primary hypothyroidism. In this report, we review this rare complication of untreated primary hypothyroidism and the physiologic mechanisms proposed to explain this phenomenon. Pediatrics 2013;132:e233–e238

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ABBREVIATIONS
FSH—follicle stimulating hormone
LH—luteinizing hormone
NL—normal limits
TSH—thyroid stimulating hormone

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Primary hypothyroidism is frequently seen in children, with a prevalence of ~2.5%, and autoimmune thyroiditis the most common cause of acquired hypothyroidism. Hypothyroidism can have deleterious effects on linear growth and pubertal timing, causing characteristic and easily recognizable changes on the growth chart. Primary hypothyroidism has been noted to cause ovarian enlargement and precocious puberty, described as early as 1905. Decades later, Van Wyk and Grumbach proposed that this phenomenon may be secondary to overlap in pituitary hormonal feedback. More recently, the promiscuity of the gonadotropin receptors, especially the follicle stimulating hormone (FSH) receptor has been described, likely due to the homologous binding domains that are shared between the glycoprotein hormone receptors, FSH receptor, luteinizing hormone (LH) receptor, and thyroid stimulating hormone (TSH) receptor.

Previous reports have shown that the bilateral ovarian enlargement seen in hypothyroidism resolves with levothyroxine replacement. However, the devastating complication of ovarian torsion leading to infarction is rare and, to our knowledge, has been reported only once before in a child, in a case from India. We describe a case of a 12-year-old girl with delayed diagnosis of hypothyroidism that ultimately resulted in ovarian torsion and loss of 1 ovary. We draw attention to the importance of accurate growth charts as diagnostic clues to hypothyroidism and review the pathophysiology with evidence for a primary role for TSH in ovarian hyperstimulation.

PATIENT PRESENTATION

A 12-year, 8-month old girl presented to the emergency department with acute abdominal pain. Her vital signs (temperature 35.5°F, heart rate 63 beats per minute, blood pressure 119/81 mm Hg) were discordant with her distress. Her general appearance was notable for short stature, obesity, and coarse facial features. Her abdomen was distended with diffuse tenderness without appreciable masses. She had Tanner stage 2 breast development without other secondary sexual characteristics. Her skin was dry with a distinctly doughy texture. Deep tendon reflexes showed a slowed relaxation phase. Her thyroid gland was not clinically enlarged.

An ultrasound of her abdomen (Fig 1) was performed and revealed massive cystic bilateral ovarian enlargement (right: 11.7 × 6.5 × 10.5 cm; left 9.9 × 5.4 × 9.1 cm). Absence of blood flow to the right ovary was seen. Radiographic suspicion for ovarian torsion led to emergent laparotomy. Her right ovary and fallopian tube were found to be infarcted and were removed. The histology of both ovaries was consistent with benign follicular cysts.

Thyroid function was evaluated given a high level of clinical suspicion at presentation for primary hypothyroidism. TSH was elevated at 903 μIU/mL (normal limits [NL]: 0.36–5.8), total thyroxine was undetectable at <1 μg/dL (NL 4.9–10), as was total triiodothyronine at <17 ng/dL (NL: 80–200). Thyroid autoantibodies showed an antithyroglobulin antibody titer of 485 IU/mL (NL: 0–40), and thyroid peroxidase antibodies were <10 IU/mL (NL: 0–35). Her bone age was significantly delayed at 7 years, 10 months. The patient was diagnosed with primary hypothyroidism with secondary ovarian enlargement leading to acute ovarian torsion.

Review of her medical record revealed minimal linear growth between age 8 and 12 years (Fig 2). Her height z score at presentation was −4.4. Beginning at 10 years of age, she had irregular vaginal spotting (Fig 3). Breast development began before age 10 years, without evidence adrenarche. She had constipation, cold intolerance, weight gain, and hair thinning. She had difficulties at school secondary to extreme...
FIGURE 2
Growth chart reproduction illustrating height and weight measurements. Hypothyroidism likely occurred around age 8 years. Circles illustrate raw height and weight data; triangle is height for adjusted bone age of 7 years, 10 months.
fatigue. She was started on daily levothyroxine, and 8 weeks after her surgery, she was euthyroid with a normal TSH (1.45 μIU/mL) and total thyroxine (6.8 μg/dL). Her luteinizing hormone (ultrasensitive assay) was prepubertal (0.04 mIU/mL [NL: 0.04–10.8]) at her initial presentation but rose to the pubertal range (2.73 mIU/mL) after 2 months on levothyroxine. Subsequent laboratory evaluation after initiation of levothyroxine revealed a pubertal estradiol (25 pg/mL [NL: 5–370]), FSH of 5.7 mIU/mL (NL: 0–15), and elevated prolactin level (36 ng/mL [NL 3–18]).

On a pelvic ultrasound performed 10 weeks after initiation of levothyroxine, her left ovary had returned to normal size (3.5 × 3.9 × 1.9 cm). Her weight had decreased by 7.5 kg. Her symptoms of fatigue, cold intolerance, and skin changes resolved. Linear growth in the first year after initiation of levothyroxine therapy was 10.3 cm, and her mean growth velocity for the 2 years after diagnosis was 8.85 cm per year. As expected, bone age also rapidly advanced in the first 12 to 18 months. Given this, along with the patient’s reluctance to undergo adjunctive growth-promoting therapies, she attained a final height of 145 cm, significantly below the midparental height of 162 cm.

DISCUSSION

Hypothyroidism is not typically viewed as either a surgical emergency or an acutely life-threatening condition. We report a case of a child with acute ovarian torsion, resulting in ovarian infarction necessitating oophorectomy as a direct consequence of severe undiagnosed hypothyroidism. To our knowledge, this specific outcome has not been reported in the United States before. Several reports have been published detailing the constellation of precocious puberty, large bilateral multicystic ovaries, and premature menarche in the context of severe hypothyroidism. However, the devastating complication of ovarian loss as in this case is rare, reported only once previously, in India.9 Ovarian removal has been performed in several cases of ovarian hypertrophy without ovarian torsion, often due to the severity of the presentation, without hypothyroidism being known or clear evidence to support the procedure.11 In most situations, oophorectomy can be avoided if the diagnosis of hypothyroidism is considered. Where bilateral ovarian enlargement exists, hypothyroidism must be definitively excluded because strong evidence exists that the ovaries return to normal with simple levothyroxine replacement.12,13 However, when left untreated or unrecognized, ovarian torsion can occur.

In 1960, Van Wyk and Grumbach proposed a lack of negative feedback to the pituitary in children with profound hypothyroidism, leading to elevated gonadotropins concurrent with TSH, resulting in manifestations of atypical precocious puberty.4 However, subsequent cases have revealed that gonadotropins are not routinely elevated.8,13–15 Indeed, in our case, LH was prepubertal despite a history of thelarche and intermittent vaginal bleeding. Given that integrity of the hypothalamic-pituitary-gonadal axis is known to be dependent on normal thyroid function, this would be expected. Thus, our case supports the notion that classic gonadotropin-dependent (and LH-dominant) central precocious puberty is not likely to explain the Van Wyk and Grumbach syndrome. Rather, it is more probable that homology between the glycoprotein hormones and their receptors explains ovarian stimulation.

Both the TSH and FSH receptors are part of the glycoprotein family of hormone receptors, all of which have a binding region located in the extracellular domain. The backbone of this domain is nearly identical for the FSH and TSH receptors.16 At normal levels, TSH binding to the FSH receptor produces minimal biologic effect, but at high concentrations of TSH, as found in profound hypothyroidism, the biologic activity may be sufficient to cause ovarian stimulation, follicle formation, and estrogen secretion. This process is independent from the gonadotropin releasing hormone–FSH axis, which does not undergo feedback inhibition.17 Affinity of the FSH receptor for TSH would also explain the typical presentation for boys with pubertal changes in the context of hypothyroidism. Testosterone levels are not

FIGURE 3
Pelvic ultrasound of the uterus with a thick endometrium (14.7 mm) demonstrating estrogen effect.
elevated, with minimal virilization, but testicular enlargement is seen, likely as a result of FSH receptor stimulation. Conversely, pubertal changes from LH receptor activation lead to Leydig cell stimulation and testosterone secretion without significantly enlarged testes. The pubertal changes and ovarian enlargement seen in this case, as in others, support this hypothesis that TSH, at high levels, binds to the FSH receptor.

Our patient’s lack of growth would have provoked additional investigation; however, she had been lost to primary care follow-up at around age 7 years. The characteristic growth pattern of acquired hypothyroidism consists of a plateau in height gain with either unaffected weight or relative weight gain. When severe, final adult height is known to be affected despite appropriate treatment of the hypothyroidism once it is detected, as in this case. Other modalities to promote linear growth as an adjunct to thyroid hormone replacement, such as growth hormone, gonadotropin-releasing hormone analogs, or aromatase inhibitors, have not been shown to affect height recovery.18

Leaving final height aside, the usefulness of a growth chart in avoiding such a devastating outcome as ovarian loss cannot be understated. The diagnosis of acquired hypothyroidism in childhood is often delayed. In a retrospective review of 21 children with profound hypothyroidism, mean bone age at the time of diagnosis of hypothyroidism was 4.1 standard deviations below the mean.18 Unfortunately, this appears to have changed little since reports from the 1980s.19 Because skeletal age progresses little, or not at all, after the onset of hypothyroidism, bone age at diagnosis times the likely onset of the hypothyroidism. In our patient, despite a chronologic age of 12-years, 8-months, bone age was delayed by almost 5 years. This could be prevented with appropriate annual growth assessment and targeted investigation in the presence of slow linear growth. Clearly, a delayed diagnosis of hypothyroidism can be shown to cause ovarian infarction along with adverse final height outcome, among other sequelae.

In summary, acute ovarian torsion in children can be caused by unrecognized primary hypothyroidism. The mechanism of pubertal symptoms and ovarian enlargement is not consistent with classic central precocious puberty but rather displays, in stark clinical context, the homology evident in the glycoprotein family of hormone receptors. Of utmost importance is that hypothyroidism should be considered in any child with precocious puberty with discordant supportive findings, such as growth failure or delayed bone age. More children may be at risk for acute ovarian torsion than previously recognized, and vigilance must be maintained to avoid this catastrophic presentation of a common childhood condition.

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