Ovarian and intellectual hyperstimulation

While reluctantly doing their math homework, many children ask: "I am never going to use this in my life, what's the point in learning this?" A few years later, as working adults, this turns into: "I wish I had paid more attention in math class."

A similar phenomenon occurs in the training and practice of Reproductive Endocrinology and Infertility (REI) specialists: fellows may complain about the "RE" part of our profession during their formative years but later appreciate the familiarity with former Board examination learning objectives such as "mechanism of hormone action" or "clinical pharmacology of hormones." Not infrequently, we come across cases that stimulate our intellects and remind us of the complex underlying endocrine framework that forms the foundation of our work.

In this issue of *F&S Reports*, Souza et al. (1) report one such case: a 32-year-old primigravida diagnosed with spontaneous ovarian hyperstimulation syndrome (OHSS) in the context of profound hypothyroidism. The pregnancy was naturally conceived, and the patient reported a long-standing history suggestive of hypothyroidism, including dry skin and constipation. Her medical history was significant for anemia, which was treated with iron supplementation. She was found to be profoundly hypothyroid (thyroid-stimulating hormone [TSH] = 100 mIU/L) and anemic (hemoglobin = 6.7 g/dL), with a mildly elevated cancer antigen 125 (CA-125; 56 IU/mL). Her ovaries were enlarged and appeared hyperstimulated on ultrasound evaluation; a magnetic resonance imaging examination at 18 weeks confirmed the multifollicular appearance of the ovaries. Aggressive thyroid hormone replacement with normalization of TSH led to regression of the follicular cysts. In the third trimester, the patient developed preeclampsia and delivered a healthy infant at 37 weeks via cesarean section. Complete ovarian cyst regression was noted 8 months postpartum.

In 1960, Judson Van Wyk and Melvin Grumbach (2) first reported a "syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism."

They described the clinical course of three girls with features of isosexual precocious puberty in the setting of hypothyroidism, whose "abnormal signs disappeared promptly when the hypothyroid state was alleviated." Polycystic ovaries may develop in this condition, now known as the "Van Wyk and Grumbach syndrome" (3). In medicine, when a variety of etiologies are proposed for a condition, it usually means that we simply do not know the exact mechanism yet. Theories to explain the pathogenesis of the Van Wyk and Grumbach syndrome include a concomitant overproduction of gonadotropins resulting from nonspecific thyroid feedback or glycoprotein synthesis overlap, as well as a potential direct action of TSH on follicle-stimulating hormone (FSH) receptors (3). The glycoproteins FSH, luteinizing hormone, human chorionic gonadotropin (hCG), and TSH all share the same α-subunit, but individual noncovalently linked β-subunits and different glycosylation patterns confer distinct receptor specificity and biologic activity (4). However, there is significant cross-reactivity, demonstrated by our ability to use hCG to trigger final oocyte maturation, and the occurrence of potentially life-threatening thyroid storm induced by hCG-producing molar pregnancies.

In the case report by Sousa et al. (1), a diagnosis of Van Wyk and Grumbach syndrome was considered but rejected given that the patient did not have precocious puberty. Spontaneous ovarian hyperstimulation in the setting of profound hypothyroidism could be viewed as an adult variation of the syndrome. However, the patient did not have the vascular features of full-blown OHSS, and it is questionable whether the mere presence of multiple hormonally inactive follicular cysts in the ovaries merits the term "ovarian hyperstimulation." Conceivably, pathophysiologic mechanisms akin to those in Van Wyk/Grumbach gradually produced the multifollicular enlargement of the ovaries over time. In this theory, the observed follicles may have been hormonally active during initial development and then remained as "burnt out" follicular cysts on cessation of steroid hormone secretion. Even though estradiol (E2) concentrations before pregnancy are unavailable, a persistent E2 elevation can be ruled out on the basis that the patient conceived spontaneously, which is remarkable given the profound hypothyroid state and the appearance of the ovaries.

It remains unclear whether the observed multifollicular development was due to a direct action of TSH on FSH receptors, or concomitant elevation of gonadotropins, as the investigators did not have information on the FSH levels before pregnancy. If a markedly elevated TSH level was directly responsible for the clinical findings, it might have acted in synergy with a mutated FSH receptor. Activating mutations of the FSH receptor gene located on chromosome 2 have been demonstrated to increase responsiveness to FSH and confer the ability to nonspecifically respond to other tropic hormones, including TSH (5). However, this is speculative as testing for FSH receptor mutations was unavailable in the reported case.

The investigators do not mention whether the patient had regular periods before pregnancy or how long it took her to get pregnant. The fact that she conceived a singleton pregnancy suggests monofollicular ovulation in the context of multifollicular ovaries. Her profound anemia is a well-known multifactorial feature of long-standing hypothyroidism. The lack of hemoconcentration or other vascular features of clinical OHSS reinforces the notion that the follicles were hormonally inactive and largely devoid of luteinized granulosa cells. Moreover, while iatrogenic OHSS and the described spontaneous ovarian hyperstimulation may share similarities, they appear to be different disease entities regarding phenotype and clinical course. Do the observed ovarian follicles persist for prolonged periods, or is there a constant turnover, even though they appear to be hormonally inactive? The observed recession on thyroid replacement therapy suggests that either there is a constant turnover that ends when the TSH is normal or that TSH is required for the persistence of lingering follicular cysts.

Future studies in pregnant or nonpregnant patients with this condition will be essential in further exploring its

pathogenesis. Investigators reporting additional cases should seek to include a detailed hormonal assessment during the development and maintenance of ovarian follicles, including FSH and E2 levels; sequencing of the FSH receptor gene; and ideally tissue biopsy of the follicular cysts before regression. In vitro studies of harvested granulosa cells could shed more definitive light on the pathophysiologic mechanism.

The investigators of this case report raised more questions than they answered. However, by reporting this patient with ovarian hyperstimulation in the setting of profound hypothyroidism, they stimulated our intellect and set the stage for further research into the etiology of the described condition.

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