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FSH-secreting pituitary adenoma: Do not miss this diagnosis in cases of spontaneous ovarian hyperstimulation syndrome!

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Abstract

Gonadotropin producing pituitary adenoma with spontaneous ovarian hyperstimulation syndrome (OHSS) is an extremely rare diagnosis in reproductive-age women. To our knowledge, only 32 cases reports of spontaneous OHSS are described in the literature. This disease is relatively unknown by gynaecologists and can lead to iatrogenic ovarian surgery and a delay in diagnosis. We report an atypical case of follicle-stimulating hormone (FSH)-secreting pituitary adenoma with spontaneous OHSS in a 25-year-old infertile woman with menstrual disturbances and abdominal pains. Transvaginal ultra sound revealed enlarged ovaries with multiple cysts, for which a gynaecologist scheduled an operative laparoscopy for "atypical bilateral ovarian tumours". In hormonal analysis, oestradiol and prolactin levels were elevated and serum FSH level was normal, whereas luteinizing hormone (LH) was suppressed. Pituitary Magnetic Resonance Imaging revealed a macroadenoma extending to the right cavernous sinus. The patient underwent an emergency transsphenoidal pituitary surgery after a surgery for synchronous bilateral ovarian torsion. After pituitary surgery, the ovarian size and all hormone values were normalized. The patient then resumed regular menstrual cycles, conceived and delivered a normal child. Gonadotroph adenoma is a disease that must be known by gynaecologists to properly diagnose and treat women presenting spontaneous OHSS. Timely diagnosis may prevent unnecessary and potentially damaging pelvic surgical procedures.

Keywords

FSH; pituitary adenoma; spontaneous ovarian hyperstimulation syndrome

Abbreviations

FSH: follicle-stimulating hormone; LH: luteinizing hormone; OHSS: ovarian hyperstimulation syndrome; E2: oestradiol; PRL: prolactin; IGF-1: insulin-like growth factor-1; ACTH: adrenocorticotrophin; TSH: thyrotropin; T4: thyroxine; T3: triiodothyronine; MRI: magnetic resonance imaging

Introduction

Gonadotroph adenomas are the most common histological subtype of pituitary adenomas, accounting for 43 to 64% of clinically non-functioning pituitary adenomas [1–3] and for 25 to 35% of all pituitary adenomas [1,3–5]. These tumours are often difficult to diagnose because they inefficiently produce gonado tropins that do not induce a specific clinical syndrome [6]. Gonadotroph adenomas are usually revealed by symptoms due to local mass effects such as visual disturbances, headaches and hypopituitarism [7]. Gonadotroph adenomas are overall difficult to diagnose in post-menopausal women because of the physiological increase in serum concentrations of gonadotropins [8]. Therefore, gonadotroph adenomas are often diagnosed as non-functioning pituitary adenomas [9].

Interestingly, patients with follicle-stimulating hormone (FSH)-secreting gonadotroph adenomas have been reported to present with symptoms of gonadotropin oversecretion and with clinical manifestations such as precocious puberty, menstrual disorder, difficulties in conceiving and spontaneous ovarian hyperstimulation syndrome [10,11]. The endocrine profile of these reported cases generally showed elevated serum oestradiol (E2) levels, normal to slightly increased FSH levels, suppressed luteinizing hormone (LH) levels and elevated α-subunit levels [1,11].

Ovarian hyperstimulation syndrome (OHSS) with enlargement of the ovaries and multiple ovarian cysts mostly occurs in adult women as an iatrogenic complication of assisted reproductive techniques due to gonadotropin therapy for controlled ovarian stimulation [13]. Spontaneous OHSS have rarely been described with primary hypothyroidism, bilateral granulosa cell tumours or gestational trophoblastic disease [14–18]. Mutations of the FSH receptor have also been reported as causes of spontaneous OHSS [19–21].

Although spontaneous OHSS has been described to be induced by FSH-secreting pituitary adenoma and is well known by endocrinologists, this diagnosis is often unknown by gynaecologists and could lead to a diagnosis delay. The aim of our case was to describe an unusual management by gynecologists of a spontaneous OHSS. The patient gave written consent for us to describe and publish her medical history.

Case Report

In November 2013, under a context of infertility, a 25-year-old nulligravid woman complained to her gynaecologist about irregular menstruation since 2011 and abdominal pain that persisted beyond 6 months. Her menarche occurred at the age of 14 years, and she had regular menstrual cycles of 28 days until 2011. On the first evaluation, her serum prolactin concentration was found to be mildly elevated [42 ng/ml; normal range: 4.8–23.4 ng/ml), and trans abdominal ultrasonography revealed enlarged ovaries with multiple cysts without ascites. On the basis of a clinical history of oligomenorrhea and ultrasound examination, her gynaecologist diagnosed her with polycystic ovarian syndrome. Subsequently, the patient was placed on a cyclic oestrogen and progestin therapy for 2 months (ethinylestradiol 0.03 mg, drospirenone 3 mg per os), and she was prescribed gonadotropin releasing hormone agonist (leuprorelin acetate 3.75 mg IM) for pituitary desensitization. However, the cystic ovaries were not resolved at control ultrasound. Her gynaecologist scheduled laparoscopic exploration for “atypical bilateral ovarian tumours”. In October 2014, before surgery, the patient was referred to the Department

of Endocrinology to evaluate her endocrine profile after the discovery of an increased serum levels of prolactin (80 pg/mL). At that time, she also reported headaches, a sensation of fullness in the lower abdomen and weight gain of 5 kg in 5 months. During the evaluation, no galactorrhoea, signs of hirsutismor visual disturbances were observed. The patient weighed 58 kg and was 155 cm tall. She was normotensive. The patient's history of cystic ovaries was not reported to the endocrinologists at first, and she did not complain about them.

A detailed hormonal evaluation showed elevated serum oestradiol (E2) (3248 pg/ml; normal range for follicular phase: 13–166 pg/ml) and prolactin (PRL) (80 pg/ml; normal range: 4.8–23.4 ng/ml) levels, suppressed LH level (<0.1 mUI/ml; normal range for follicular phase: 2.4–12.6 mUI/ml) and normal FSH level (12 mUI/ml; normal range for follicular phase: 3.5–12.5 mUI/ml). The patient's serum testosterone was 647 pg/ml (normal range: 100–600 pg/ml) and -subunit was 1.2 mUI/ml (normal range <0.6 mUI/ml). Pregnancy test was negative. Basal levels of insulin-like growth factor-1 (IGF-1), adrenocorticotrophin (ACTH), cortisol, thyrotropin (TSH), thyroxine (T4) and triiodothyronine (T3) were normal (Table 1). Neither a metoclopramide hydrochloride (10 mg i.v.) nor luteinizing hormone-releasing hormone (LHRH) stimulation test induced a pituitary response (Table 2). A pituitary Magnetic Resonance Imaging (MRI) showed an 18 x 22 x 21 mm pituitary macroadenoma invading the right cavernous sinus but without optic chiasm compression (**Figure 1**). The visual field examination was normal. The suspected diagnosis was a non-functioning pituitary macroadenoma with hyperprolactinemia due to disconnexion. A dopaminergic agonist (cabergoline 0.25 mg weekly) was prescribed, and transsphenoidal surgery was scheduled.

While waiting for her adenoma surgical resection, the patient was admitted in December 2014 to the Department of Obstetrics and Gynecology because of acute abdominal pain and vomiting. Ultrasonography and pelvic MRI showed bilateral multicystic enlargement of the ovaries, and these results indicated a right ovarian torsion (**Figure 1**). Laparoscopic exploration revealed synchronous bilateral ovarian torsion, which was successfully managed by laparoscopic detorsion. In view of the endocrine profile, clinical images and diagnostic imaging, the patient's diagnosis was modified to spontaneous OHSS caused by an FSH-secreting pituitary macroadenoma, and an emergency transsphenoidal tumour resection was performed. Immunohistochemical staining of the pituitary tumour was moderately positive for FSH (40%) and negative for -sub unit, LH, growth hormone, PRL, ACTH and TSH. The Ki-67 proliferative index, which measures the growth fraction of tumour cells, was low (2%), and the over expression of p53 protein was not detected in any cell. Four days after pituitary surgery, the serum FSH level decreased to 1.4 mUI/ml, while the LH level increased to 0.6 mUI/ml. E2 and PRL levels were normalized (**Table 1**). The large bilateral ovarian cysts spontaneously decreased to a normal size. A pituitary MRI conducted 3 months after surgery showed no residual tumour. The patient resumed normal menses, and she spontaneously conceived during the following year. In February 2016, she delivered a healthy male baby weighing 2600 g by vaginal delivery at 38 weeks of gestation.

Discussion

A pathophysiological classification system of spontaneous OHSS has been suggested by Panagiotopoulou et al. [22] based on hypersecretion and similarities in the beta-subunit of the four, oestradiol, prolactin and alpha-subunit levels should be the first-line of investigation. The

glycoprotein hormones (hCG, TSH, FSH and LH) and/or mutation in the FSH receptor. This classification entails four types of spontaneous OHSS: type I corresponds to the mutated FSH receptor with normal FSH, hCG and, TSH levels; type II corresponds to cases with secondary to high hCG levels (gestational trophoblastic disease for example), type III is related to hypothyroidism with high TSH levels; type IV includes gonadotroph adenomas secreting FSH or LH [22]. Therefore, to improve the aetiological diagnosis and management of spontaneous OHSS, a detailed hormonal evaluation of hCG, TSH, FSH, LHendocrinological pattern of most reported cases of spontaneous OHSS induced by gonadotroph adenoma demonstrated normal or elevated FSH levels, suppressed LH levels, elevated oestradiol levels, increased alpha-subunit levels and supranormal concentrations of prolactin. Our patient exhibited the typical profile, which should be an indication for pituitary imaging. Screening for FSH receptor mutations should be performed in the second line of investigation.

In our case, despite the non-elevated level of FSH, we could confirm the connection between spontaneous OHSS and gonadotroph adenoma because of the clinical improvement after tumour resection and FSH-positive immunohistochemical staining of the pituitary tumour. In a number of reports, it has been confirmed that functioning gonadotroph adenomas produce intact and biologically active FSH with an increased bioactivity to immunoreactivity ratio [23–25]. This may explain why "physiological" levels of FSH are nevertheless adequate to cause an ovarian hyperstimulation syndrome that is resolved after tumour removal.

To our knowledge, only 32 cases of spontaneous OHSS associated with gonadotroph adenomas have been reported in the literature. Halupczok et al. [11] have summarized the clinical and biological characteristics of those 32 patients. Among them, 17 patients have undergone at least one pelvic surgery with an exploratory laparotomy, a transvaginal cyst aspiration, a cystectomy, an oophorectomy or a hysterectomy. In our case, laparoscopic exploration was scheduled by her gynaecologist and was fortunately cancelled due to the endocrinologist assessment. This case underlines the importance for gynaecologists to recognize this unusual diagnosis in order to avoid iatrogenic ovarian surgery.

The most common clinical manifestations of FSH-secreting gonadotroph adenomas with OHSS are menstrual disorders with secondary amenorrhea, oligomenorrhea and irregular menses. Other presenting symptoms include abdominal or pelvic pain, abdominal distension and increased girth and infertility. Metrorrhagia, menometrorrhagia, galactorrhoea and precocious puberty are also described to be warning signs. Neurological symptoms due to the local mass effects are determined by the size of the pituitary adenoma and are thus less common than gynaecological complaints. Therefore, the gynaecologist appears to be the first person in contact with the patient and should be aware of this unusual diagnosis. In our case, the diagnosis delay was up to two years. In summary, spontaneous OHSS is a rare entity, relatively unknown to gynaecologists, that must be recognized because it could lead to an iatrogenic ovarian surgery. To this end, dialogue between gynaecologists and endocrinologists must be encouraged.

Conflicts of interest

The authors have no conflicts of interest. No benefits of any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.

Figures

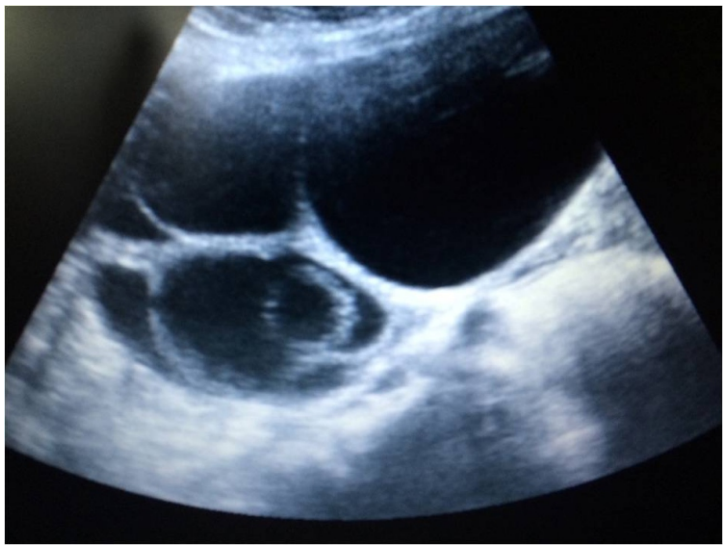

Figure 1*:* Spontaneous ovarian hyperstimulation syndrome: transvaginal sonographic image of enlarged ovarian cysts

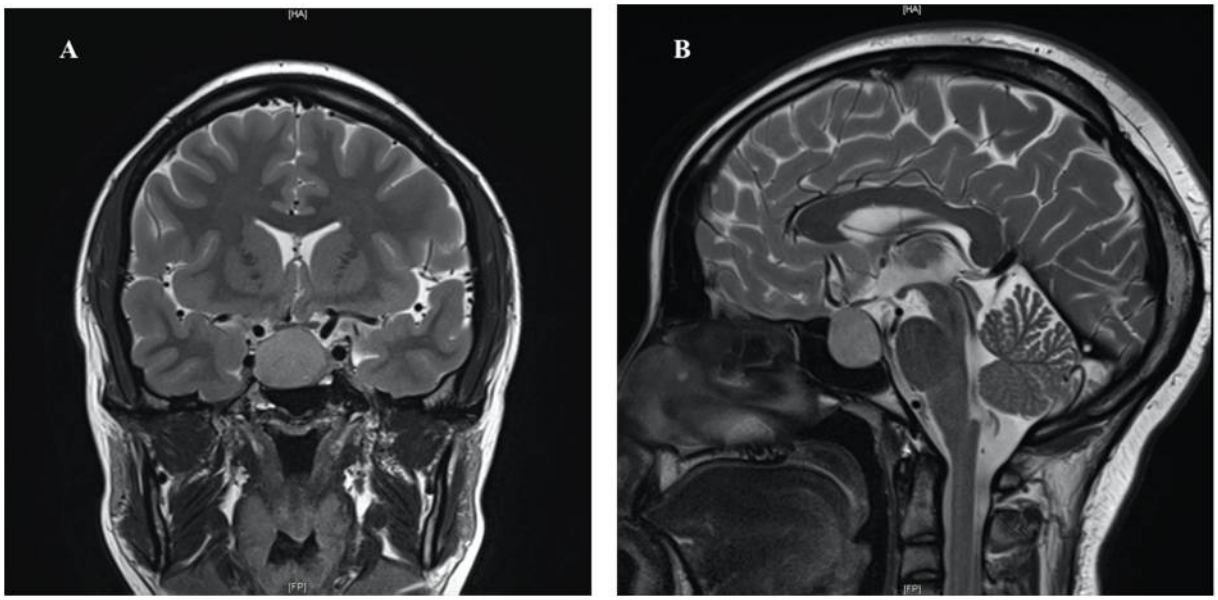

Figure 2: FSH-secreting pituitary adenoma. T2-weighted coronal (A) and sagittal (B) MRI revealing an intra-sellar tumor measuring 18 x 22 x 21 mm.

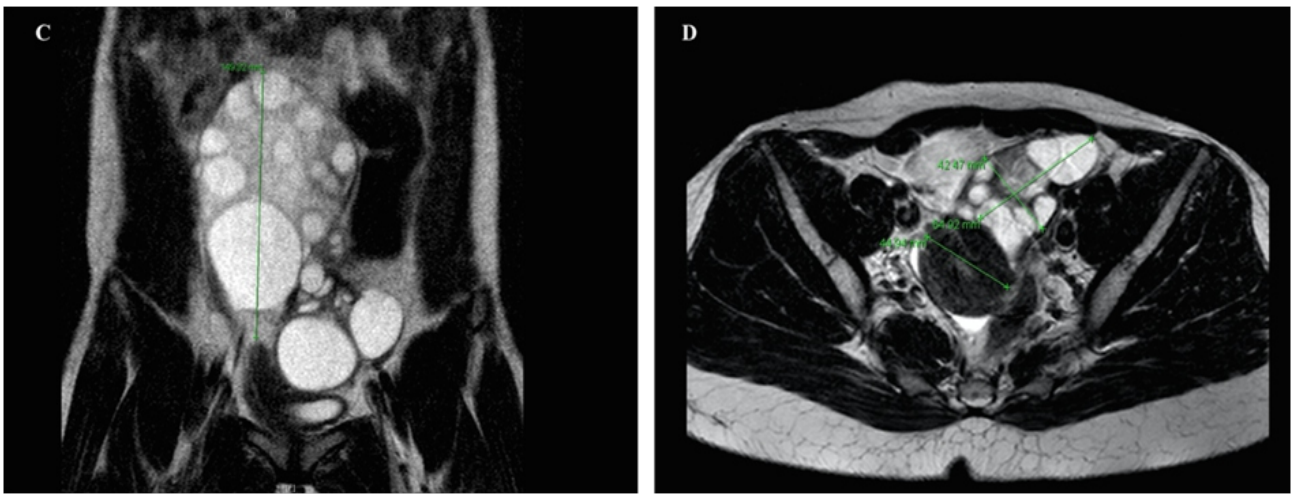

Figure 3: Spontaneous OHSS and FSH-secreting pituitary adenoma. T2-weighted pelvic MRI with (C) sagittal and (D) axial sections showed multicystic enlargement of bilateral ovaries.(left ovary: 65 x 42 x 66 mm, right ovary: 150 x 100 x 60 mm)

Tables

Table 1: Spontaneous OHSS and FSH-secreting pituitary adenoma. Hormone levels before and after transsphenoidal surgery.

Hormones	2 months before surgery	4 days after surgery	3 months after surgery	Reference range
FSH (mIU/ml)	12	1.4	11.7	fp: 3.5-12.5 mc: 4.7-21.5 lp: 1.7-7.7
LH (mIU/ml)	< 0.1	0.6	17.5	fp: 2.4-12.6 mc: 14.2-95.6 lp: 1-11.4
E2 (pg/ml)	3248	98	162	fp: 13-166 mc: 86-499 lp: 44-211
Progesterone (ng/ml)	-	0.3	1.26	fp : 0.18–1.47 mc : 0.75–2.95 lp : 1.66–27
α-Subunit (mIU/ml)	1.2	-	1	<0.6
PRL (ng/ml)	80	5.6	7	4.8–23.4
Testosterone (pg/ml)	647	-	386	100–600
DHEA-S (ng/ml)	1566	-	-	354-4053
Δ4-Androstenedione (ng/ml)	1.3	-	-	0.1–2.99
TSH (mIU/l)	5	2.01	2.67	0.27-4.2
Ft4 (pmol/l)	13	14.3	13.2	12-22
Ft3 (pmol/l)	4	4.18	4.27	3.1-6.8
IGF-1 (ng/ml)	151	154	181	47-200
ACTH 8h (pg/ml)	38	55	46	
Cortisol (nmol/l) 8am	473	437	217	>300

Table 2: Spontaneous OHSS and FSH-secreting pituitary adenoma. LHRH stimulation test results.

LHRH Stimulation Test		0 min	30 min	60 min
	FSH (mIU/ml)	11.5	14.4	13.9
	LH (mIU/ml)	0.1	1	0.7

References

1. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe H-J, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol. Jan 2 2007; 156 (2): 203–16.

2. Yamada S, Ohyama K, Taguchi M, Takeshita A, Morita K, Takano K, et al. A study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas. Neurosurgery. Sep 6 2007; 1 (3): 580-584; discussion 584-585.

3. Rishi A, Sharma MC, Sarkar C, Jain D, Singh M, Mahapatra AK, et al. A clinicopathological and immunohistochemical study of clinically non-faunctioning pituitary adenomas: A single institutional experience. Neurol India. Jun 5 2010 ; 58 (3): 418–23.

4. Wade AN, Baccon J, Grady MS, Judy KD, O'Rourke DM, Snyder PJ. Clinically silent somatotroph adenomas are common. Eur J Endocrinol Eur Fed Endocr Soc. Jul16 2011; 5 (1): 39–44.

5. Ho DM, Hsu CY, Ting LT, Chiang H. The clinicopathological characteristics of gonadotroph cell adenoma: a study of 118 cases. Hum Pathol. Aug;28 1997; (8): 905–11.

6. Katznelson L, Alexander JM, Klibanski A. Clinical review 45: Clinically nonfunctioning pituitary adenomas. J Clin Endocrinol Metab. May;7 1993; 6 (5) :1089–94.

7. Young WF, Scheithauer BW, Kovacs KT, Horvath E, Davis DH, Randall RV. Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. Mayo Clin Proc. 1996 Jul;71 (7): 649–56.

8. Daneshdoost L, Gennarelli TA, Bashey HM, Savino PJ, Sergott RC, Bosley TM, et al. Recognition of gonadotroph adenomas in women. N Engl J Med. 1991 Feb 28; 324 (9) 589–94.

9. Katznelson L, Alexander JM, Klibanski A. Clinical review 45: Clinically nonfunctioning pituitary adenomas. J Clin Endocrinol Metab. 1993 May;76(5):1089–94.

10. Chaidarun SS, Klibanski A. Gonadotropinomas. Semin Reprod Med. Nov;20 2002 ; (4): 339–48.

11. Halupczok J, Kluba-Szyszka A, Bidzińska-Speichert B, Knychalski B. Ovarian Hyperstimulation Caused by Gonadotroph Pituitary Adenoma--Review. Adv Clin Exp Med Off Organ Wroclaw Med Univ. Aug 24 2015 : (4): 695–703.

12. Murakami T, Higashitsuji H, Yoshinaga K, Terada Y, Ito K, Ikeda H. Management of ovarian hyperstimulation due to follicle-stimulating hormone-secreting gonadotroph adenoma. BJOG Int J Obstet Gynaecol. Nov 11 2004;1 (11): 1297–300.

13. Kumar P, Sait SF, Sharma A, Kumar M. Ovarian hyperstimulation syndrome. J Hum Reprod Sci. May 2011 ;4 (2): 70–5.

14. Van Voorhis BJ, Neff TW, Syrop CH, Chapler FK. Primary hypothyroidism associated with multicystic ovaries and ovarian torsion in an adult. Obstet Gynecol. May 8 1994 ; 3 (5 Pt 2): 885–7.

15. Hansen KA, Tho SP, Hanly M, Moretuzzo RW, McDonough PG. Massive ovarian enlargement in primary hypothyroidism. Fertil Steril. Jan 6 1997; 7 (1): 169–71.

16. Ilanchezhian S, Mohan SV, Ramachandran R, Babu SR. Spontaneous ovarian hyperstimulation syndrome with primary hypothyroidism: Imaging a rare entity. Radiol Case Rep. 2015; 10 (1): 1050.

17. Segal R, DePetrillo AD, Thomas G. Clinical review of adult granulosa cell tumors of the ovary. Gynecol Oncol. Mar 5 1995; 6 (3): 338–44.

18. Ludwig M, Gembruch U, Bauer O, Diedrich K. Ovarian hyperstimulation syndrome (OHSS) in a spontaneous pregnancy with fetal and placental triploidy: information about the general pathophysiology of OHSS. Hum Reprod. Jan 8 1998;13 (8): 2082–7.

19. Smits G, Olatunbosun O, Delbaere A, Pierson R, Vassart G, Costagliola S. Ovarian hyperstimulation syndrome due to a mutation in the follicle-stimulating hormone receptor. N Engl J Med. Aug 21 2003;349 (8): 760–6.

20. Montanelli L, Delbaere A, Di Carlo C, Nappi C, Smits G, Vassart G, et al. A mutation in the follicle-stimulating hormone receptor as a cause of familial spontaneous ovarian hyperstimulation syndrome. J Clin Endocrinol Metab. Apr 8 2004;9 (4) :1255–8.

21. Delabaere A, Tran X, Jardon K, Pouly J-L, Bourdel N. [Spontaneous ovarian hyperstimulation syndrome in a pregnancy with hypothyroidism]. Gynécologie Obstétrique Fertil. Mar 3 2011; 9 (3): e64-67.

22. Panagiotopoulou N, Byers H, Newman WG, Bhatia K. Spontaneous ovarian hyperstimulation syndrome: case report, pathophysiological classification and diagnostic algorithm. Eur J Obstet Gynecol Reprod Biol. Jul 16 2013; 9 (2): 143–8.

23. Pigny P, Henric B, Lahlou N, Christin S, Mazzuca M, Dewailly D, et al. A gonadotroph adenoma with a high proportion of basic FSH isohormones by chromatofocusing. J Clin Endocrinol Metab. Jun 8 1996;1 (6): 2407–8.

24. Borgato S, Persani L, Romoli R, Cortelazzi D, Spada A, Beck-Peccoz P. Serum FSH bioactivity and inhibin levels in patients with gonadotropin secreting and nonfunctioning pituitary adenomas. J Endocrinol Invest. Jun 2 1998;1 (6): 372–9.

25. Shimon I, Rubinek T, Bar-Hava I, Nass D, Hadani M, Amsterdam A, et al. Ovarian hyperstimulation without elevated serum estradiol associated with pure follicle-stimulating hormone-secreting pituitary adenoma. J Clin Endocrinol Metab. Aug 8 2001; 6 (8): 3635–40.

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