Ovarian Cyst Regression With Levothyroxine In Spontaneous Ovarian Hyper Stimulation Syndrome Associated With Hypothyroidism.

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Abstracts: Spontaneous ovarian hyperstimulation syndrome (sOHSS) can occur following hypothyroidism. Ultrasonography facilitates diagnosis and monitoring of this syndrome. We describe complete regression of ovarian changes in two hypothyroid patients with sOHSS after treatment with levothyroxine (l-T4). [Nayak V NJIRM 2014; 5(5) :88-93]

Key Words: Spontaneous Ovarian Hyperstimulation syndrome (OHSS), Hypothyroidism.

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Introduction: Ovarian Hyper stimulation (OHSS) is a rare but well-known iatrogenic complication of ovarian stimulation occurring during fertility therapy.This syndrome is characterized by ovarian enlargement due to multiple ovarian cysts and an acute fluid shift into the extravascular space.

In extremely rare cases, this syndrome can occur without any iatrogenic induction of ovulation. In this case, it is called spontaneous OHSS (sOHSS), which has often been reported in association with pregnancy, FSH-secreting adenoma, or exceptionally TSH-secreting macro adenoma.

Clinical signs and symptoms of OHSS include abdominal pain, distension with massive ovarian enlargement, nausea and vomiting. It may cause severe morbidities like ascites, dyspnoea, adnexal mass, electrolyte imbalance, haemoconcentration and acute renal failure.

Here, we are discussing two unusual cases of spontaneous OHSS , both associated with hypothyroidism. Our first case, a natural conception was associated with spontaneous OHSS with hypothyroidism. And the second case is ofa nonpregnant woman, presented withspontaneous OHSS with hypothyroidism, & after t/t with levothyroxine, complete resolution of OHSSoccurred in both patients.

Case:

1. 25yrs old, G2P0A1 presented with H/o 3 months of Amenorrhoea with c/o abdominal pain and Per Vaginal Bleeding since 6 hrs. It was a spontaneous conception with no h/o any treatment taken for infertility. Pelvic ultrasonography revealed findings s/o incomplete abortion with massive ovarian enlargement in both the ovaries (OHSS like picture). On further investigation she had a haematocrit- 14.5, PCV-26.6%, ESR-13mm/hour,TSH->150 microgram and CA 125-99, to rule out molar pregnancy, BHCG wasdone levels - Beta-HCG-16.4 IU/ml

2. A 26 year old P2L2 came with severe pain in lower abdomen, vomiting, constipation since 2 days. Her LMP was 15 days back. Her USG showed typical picture of OHSS.

Table 1: Investigation of the Both the Patients Were

	T3	T4	TSH	Sr. Estradiol	CA-125	B-hCG
Case 1	0.28 ng/ml	0.5 ug/dl	>150 uIU/ml	350 pg/ml	20 U/ml	16.4 IU/ml
Case 2	0.45 ng/ml	0.6 ug/dl	>100u IU/ml	386 pg/ml	39 U/ml	2 IU/ml

After the diagnosis of sOHSS, both the patient were closely monitored, proper hydration was maintained & were started on Tab Thyronorm 100 microgram OD. After which they responded completely with complete resolution of the ovarian masses and regression of the cysts over 3 mths. Both the patients had a un eventful recovery and conceived spontaneously subsequently.

Result: Conservative medical treatment with levothyroxine, adequate hydration and analgesics showed regression of the cysts in both ovaries by 12 weeks. Serial ultrasoundsrevealed complete regression in the cyst and patient became euthyroid by 12-14 weeks.

Discussion: The etiopathogenesis of spontaneous ovarian hyper stimulation is unclear. It was suggested that Polycystic Ovarian Syndrome, Twins, Molar pregnancy in which the endogenous hCG levels were higher than normal, mutation in FSH receptors could be risk factors in spontaneous ovarian hyper stimulation. Hypothyroidism is another important risk factor.[1,2,3,8]

OHSS is a rare but well-known iatrogenic complication of ovarian stimulation occurring during fertility therapy. In extremely rare cases, this syndrome can occur without any iatrogenic induction of ovulation. In this case, it is called spontaneous OHSS, which has often been reported in association with pregnancy, FSH-secreting adenoma, or exceptionally TSH-secreting macro adenoma.[1,2,5]

Only a few cases of sOHSS have been described in the literature.[17,19] The pathogenesis of sOHSS remains unclear. It has been postulated that it might involve the activation of some mediators and vasoactive substances such as histamine, serotonin, prostaglandins, interleukins, estrogens, prolactin, the ovarian renin-angiotensin system, and vascular endothelial growth factor (VEGF).[6,7] Today, there is growing evidence suggesting a key role of VEGF, presumably of a follicular origin, in the pathogenesis of OHSS.[4,5]
Under this model, exogenous gonadotropins or other substances with gonadotropin-like activity can activate the mediators, leading to increased vascular permeability, extravascular fluid accumulation, haemoconcentration, deep vein thrombosis, and other complications observed in OHSS.

The exact mechanism by which sOHSS might occur in the context of hypothyroidism also remains unclear.sOHSS with may occur due to excessive hCG that is associated with the syndrome. It is known that even recurrent spontaneous ovarian hyper stimulation syndrome can occur with hypothyroidism.

HCG is a member of the family of glycoprotein hormones that also includes Follicular stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH). These 4 hormones have 2 subunits:[1,2,9]

- a common alpha subunit
- a beta subunit that is specific to each molecule.

Their subunits, albeit distinct, share greater than 40% amino acid homology. In addition, the receptors for the glycoprotein hormones have related structures. LH and hCG both bind to the LH receptor, whereas TSH and FSH under normal circumstances bind to separate TSH and FSH receptors, respectively.[14,15]

The hypothesis is that once the hormone binds to its receptor, it stabilizes the conformation of the receptor's extracellular portion, initiating downstream signalling events. There is a significant increase in the capillary permeability, extravascular fluid accumulation, haemo -concentration and elevated plasma concentration of von Willebrand factor, all known complications of OHSS. Elevated levels of this cytokine were found both in the serum and in the ascitic fluid of patients with severe OHSS. There is massive transudation of protein-rich fluid (mainly albumin) from the vascular space especially into the peritoneal and pleural cavities. It has been reported that the intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation inducing agents.

However it has been also reported that the serum concentrations of VEGF does not predict the course of the disease.Various mechanisms have been proposed for spontaneous ovarian hyper stimulation syndrome.

The etio-pathogenesis of spontaneous OHSS is less clear. Some authors suggested that polycystic ovary syndrome (PCOS) could also be a risk factor for spontaneous OHSS.However some cases developed this condition without underlying PCOS.[3,8]

OHSS also has been observed in women with normal or lower than normal hCG concentration. Thus, it is postulated that high concentrations of hCG are not responsible for every case of OHSS.

Different mechanisms have been proposed by DE-LEENER et all [9] for the classification of spontaneous ovarian hyper stimulation syndrome into three types, based on clinical presentation and FSH

Receptor Mutation:
(1) Due FSH receptor mutation, [9,2,20]
(2) sOHSS secondary to high levels of hCG. This type is probably the most frequent one.
(3) Associated with hypothyroidism,taking into account that TSH has weak FSH activity (This is the likely mechanism in our cases).[9,2,17,19]

Although there are no clear predictive risk factors for the development of OHSS, young age, polycystic ovarian syndrome, asthenic habitus, luteal supplementation of hCG, protocols with GnRH , a high level of serum estradiol, multiple follicles and ovarian necklace sign were reported as the possible risk factors. The exact mechanism by which ovarian hyper stimulation syndrome might occur in hypothyroid patients is not understood clearly.[17]

A possible explanation was suggested by Rotmensch and Scommegna, on the basis of preferential formation of estriol via the 16-hydroxylation pathway instead of the normal 2-hydroxylation that has been demonstrated in hypothyroid patients.Excessive gonadotropin release, due to decreased feedback regulation caused by substitution of estradiol by the less potent estriol, would result in excessive ovarian stimulation.[10,17]

In a recent report, a pregnant woman with spontaneous ovarian hyper stimulation syndrome, uncontrolled hypothyroidism, elevated human chorionic gonadotrophin (hCG), deep vein thrombosis, and Rh isoimmunization was reported by Edwards- Silva et al.[13]

Cardoso et al, described a case of consistent regression of large bilateral ovarian cysts in a hypothyroid patient after the institution of thyroid hormone replacement therapy, suggesting the causal relationship between primary hypothyroidism and spontaneous ovarian hyper stimulation syndrome.[11]

Nappi et al. presented a case of untreated hypothyroidism associated with spontaneous ovarian hyper stimulation syndrome. In their patient, thyroid replacement therapy and fluid administration also led to prompt resolution of the spontaneous ovarian hyper stimulation syndrome.[12]

The main radiological findings in OHSS are multiple cystic enlargements of both ovaries (> 5 cm) associated with fluid accumulation in the peritoneum, pleura, or pericardium. However, these findings are not very specific to this particular disorder because some other conditions (including ovarian cystic neoplasm as serous or mucinoustumours) often display similar characteristics. Therefore, to improve the differential diagnosis based on imaging findings, radiologists should search for the classic soap-bubble or wheel-spoke appearance of the ovarian cystic mass, which results from multiple, enlarged follicles arranged peripherally around a central stroma.

Figure 1:

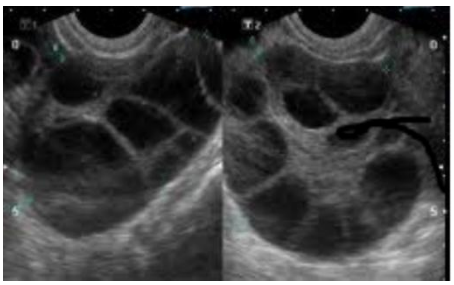

Figure 2: B/L ovaries showing multiple ovarian cysts on ultrasound.

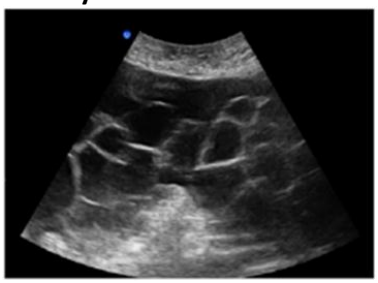

Table 2: Summary of case reports describing patients with OHSS associated with hypothyroidism

Reference	Age (years)	Hypothyroidism	Pregnancy	FSH receptor mutation	Sonographic report	Treatment	Follow-up
Hedayati et al. (3)	15	TSH >100 mIU/l	–	Neg.	Enlarged ovaries with multiple ovarian cysts	Levothyroxine (100 µg)	After 4 months: normal ovary size and regression of cysts
		Ab:Neg.			Rt: 150×75×62		
					Lt: 130×70×68		
	14.5	TSH=72.5 mIU/l	–	NA	Multiple large cysts with rupture of one cyst	Levothyroxine (100 µg	After 4 months: normal
					Rt: 110×65		
					Lt: 118×58		
Akbay et al. (13)	21 (P1)	TSH=8.75 mIU/l	10 weeks	NA	Bilateral multilobulated cystic 130×80 sized ovaries	Levothyroxine (100 µg)	After 3 months of delivery: normal
	Ab:NA	HCG=Nl					
	23 (P2)	TSH=2.16 mIU/l	12 weeks		Bilateral multilobulated cysts	Levothyroxine (100 µg)	After 2 months of delivery: normal
	Ab:NA	HCG=Nl			Rt: 13×70		
					Lt: 110×70		
Dietrich et al. (15)	26 (P1)	Normal	12 weeks	Present (D567N)	Bilateral multicystic ovaries	Conservative	Abortion at 15 weeks
		HCG=118 665			Rt: 140×150		
					Lt: 120×130		
					Enlarged ovaries		
	26 (P2)	TSH=5.51 mIU/l	10 weeks		Rt: 100×100	Levothyroxine (100 µg	Normal delivery at term
	Ab:NA	HCG=147 688			Lt: 100×100		
Lussiana et al. (16)	29	TSH=5.92 mIU/l	22 weeks (with abortion)	Present (with undetermined significance)	Bilateral multiple ovarian cysts	Levothyroxine	After 3 months of abortion: normal ovaries
		Ab:NA			Rt: 200×110		
					Lt: 160×120		
Edwards et al. (9)	30	TSH=41.7 mIU/l	10 weeks	NA	Enlarged mass	Levothyroxine	By 22 weeks of gestation: ovarian regression
		HCG=291 206					
Borna et al. (12)	30	TSH >400 mIU/l	20 weeks	NA	Bilateral multilobulated	Levothyroxine (200 µg)	10 weeks after

					ovarian cysts		delivery: normal ovaries
		HCG=Nl Ab:NA			Rt: 200×160		
					Lt: 160×100		
Sultan et al. (11)	12	TSH=1310 mIU/l	–	Neg.	Large cystic structure	Levothyroxine	After 3 months: resolution of cysts
		Ab:Neg.					
Mousavi et al. (6)	26	TSH >50 mIU/l	–	NA	Bilateral multiseptated ovarian masses	Levothyroxine (100 µg)	After 6 months: normal ovary size
		Ab:NA			Rt: 69×63×96		
					Lt: 66×63×99		
Taher et al. (10)	22	TSH >100 mIU/l	–	NA	Bilateral multilobulated ovarian mass with cystic component	Levothyroxine (100 µg)	After 3 months: marked reduction
		Ab:NA			Rt: 90×120		
					Lt: 60×40		

[i] Ab, antithyroglobulin/antiperoxidase antibody; Neg, negative; NA, not available; P, pregnancy; HCG, human chorionic gonadotropin (IU/l); Nl, normal (according to gestational age); Rt and Lt, right and left ovaries (mm2).

Conclusion: Spontaneous ovarian hyper stimulation syndrome (sOHSS) can occur in women in reproductive age group, with severe hypothyroidism and present with abdominal pain and massively enlarged bilateral ovaries with or without ascites. It is necessary to consider hypothyroidism and other endocrinal disorders in the differential diagnosis of adult patient with multiple ovarian cyst formation in order to prevent inadvertent ovarian surgery. Accurate diagnosis andconservative management with adequate thyroid repletion, maintenance of hydration, serial ultrasounds revealed complete regression in the cyst and patient became euthyroid by 12-14 weeks.

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