

Thyroid dysfunction during severe ovarian hyperstimulation syndrome. A case report

Zaburzenia czynności tarczycy podczas ciężkiego zespołu hiperstymulacji jajników. Opis przypadku

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Abstract

Thyroid disorders, both in women who wish to conceive and in gravidas, has become a topic of much interest to numerous researchers. Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening condition among women undergoing controlled ovarian hyperstimulation (COH).

We present a case of thyroid dysfunction in severe OHSS in a patient diagnosed with subclinical hypothyroidism before COH. The dose of L-thyroxine (L-T4) was increased before the procedure in order to reach TSH levels below 2.5mU/L, and from day 1 of the stimulation the dose of L-T4 was increased by 33%. The patient remained clinically and biochemically euthyroid until day 8 after the embriotransfer (ET). Then, the woman developed severe OHSS, with fluid in the pleural and peritoneal cavity and laboratory evidence of severe OHSS. Laboratory thyroid function tests revealed overt hypothyroidism. L-T4 dose was not increased due to serious clinical condition of the patient. Iodine supplementation was initiated instead. After the symptoms subsided, a period of clinical and laboratory euthyroid state was observed, followed by gestational hyperthyroidism. The L-T4 dose was reduced and iodine supplementation was temporarily ceased. The thyroid function stabilized, while maintaining the L-T4 and iodine supplementation, at 20 weeks of gestation. The patient gave birth by a caesarean section at 37 weeks of gestation and returned to the pre-pregnancy dose of L-T4. To the best of our knowledge, this has been the first report about a patient with thyroid dysfunction in severe OHSS in the Polish literature.

On the basis of the presented case and a review of the literature on thyroid dysfunction in women undergoing COH and OHSS, we conclude that clinical signs and biochemical parameters need to be taken into consideration while making therapeutic decision in women with thyroid dysfunction in the course of OHSS. Also, further studies are necessary to elucidate the matter.

Key words: **thyroid function / controlled ovarian hyperstimulation /
in vitro fertilization / ovarian hyperstimulation syndrome /**

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Streszczenie

Zaburzenia czynności tarczycy u kobiet planujących ciążę i podczas ciąży są przedmiotem rosnącego zainteresowania. Zespół hiperstymulacji jajników (OHSS) jest chorobą potencjalnie zagrażającą życiu kobiety poddanej procedurze kontrolowanej hiperstymulacji jajników (COH).

W pracy przedstawiono przypadek zaburzeń czynności tarczycy podczas ciężkiego OHSS u pacjentki z rozpoznaną przed COH subkliniczną niedoczynnością tarczycy. Przed przystąpieniem do procedury zwiększono dawkę L-tyroksyny (L-T4) aby uzyskać stężenie TSH poniżej 2.5mU/L, a od pierwszego dnia stymulacji zwiększono dawkę L-T4 o 33%. Pacjentka pozostawała w klinicznej i biochemicznej eutyreozy do 8 dnia po wykonanym embriotransferze. Wówczas wystąpiły objawy ciężkiego OHSS z obecnością płynu w jamie opłucnowej i laboratoryjnymi wykładnikami ciężkiego OHSS. Wykonane badania czynności tarczycy pozwoliły na rozpoznanie jawnej niedoczynności tarczycy. Ze względu na ciężki kliniczny stan pacjentki nie zwiększono substytucji L-T4 lecz dołączono suplementację jodem. Po ustąpieniu objawów ciężkiego OHSS nastąpił okres klinicznego i laboratoryjnego wyrównania czynności tarczycy, po którym u pacjentki wystąpiła ciążowa nadczynność tarczycy związana z ciążą bliźniaczą. Dawkę L-T4 zredukowano i czasowo zaprzestano suplementacji jodem. Po 20 tygodniu ciąży czynność tarczycy ustabilizowała się przy zachowaniu substytucji L-T4 i jodem. Pacjentka urodziła drogą cięcia cesarskiego w 37 tygodniu ciąży. Po porodzie zredukowano dawkę L-T4 do stosowanej przed ciążą. Pacjentka z zaburzeniami czynności tarczycy podczas ciężkiego OHSS została opisana po raz pierwszy w polskiej literaturze.

Na podstawie przypadku oraz dokonanego przeglądu literatury dotyczącej zaburzeń czynności tarczycy u kobiet poddanych procedurze COH i OHSS sformułowano wnioski dotyczące uwzględniania zarówno objawów klinicznych jak i parametrów biochemicznych w podejmowaniu decyzji terapeutycznych oraz o konieczności dalszych badań w przedmiocie zaburzeń czynności tarczycy w przebiegu OHSS.

Słowa kluczowe: **czynność tarczycy / stymulacja jajników / zapłodnienie pozaustrojowe / zespół hiperstymulacji jajników /**

Introduction

Thyroid disorders, both in women who wish to conceive and in gravidas, has become a topic of much interest to numerous researchers. Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening condition among women undergoing controlled ovarian hyperstimulation (COH). We present a case of a patient with severe OHSS during COH, previously diagnosed with subclinical hypothyroidism. The literature data on thyroid dysfunction in OHSS are scarce and, to the best of our knowledge, this has been the first report in the Polish literature.

The patient

We present a case of a 34-year-old woman with the diagnosis of secondary infertility. Age at first menarche was 12, with regular 28-day cycles. Her medical history included a laparoscopic salpingotomy due to an ectopic pregnancy, followed by bilateral salpingectomy due to bilateral sactosalpinx. Non-Hashimoto's subclinical hypothyroidism, combined with mild, functional hyperprolactinemia, was diagnosed at the age of 29. The patient had been treated with low doses of L-thyroxine (25 micrograms/day) and cabergoline (0.5mg/week). She had previously received two IVF-ET cycles, but failed to conceive during the two attempts. The patient underwent standard diagnostic workup before COH. Upon examination, the woman was clinically euthyroid, without a palpable goiter. No familial history of thyroid disorders was reported. Thyroid function tests were as follows: TSH-2.64mU/L (N: 0.55-4.78) and FT4-14.4pmol/L (N: 11.5-22.7), antibody titers: thyroid peroxidase (TPO), thyroglobulin (Tg) and TSH receptor (TR) antibody were within the reference range. The dose of L-T4 was increased to 37.5µg/day before COH due to borderline TSH values [3, 4, 5, 6].

Normal results of thyroid function with TSH-0.826mU/L and normal plasma prolactin levels were observed immediately upon commencement of the COH procedure. The classical long agonist protocol of COH, starting with oral contraceptives in the previous cycle with daily dose of 0.1mg triptorelin and 1075 IU of recombinant follicle stimulating hormone (rFSH) during COH, was initiated. Low molecular weight heparin enoxaparin, prednisone, acetylic acid, and folic acid comprised the adjuncts for ovarian stimulation. The dose of L-T4 was increased by 33% (from 37.5µg/day to 50µg/day) from day 1 of the stimulation [1, 2, 8]. rFSH was stopped (coasting) due to high concentrations of estradiol (E2) since day 8 of the stimulation. The final oocyte maturation was performed with 125mcg preparation of recombinant human chorionic gonadotropin (rhCG). Preventive measures for OHSS during COH included: coasting, reduction of the rhCG dose, and cabergoline at a dose of 0.5mg/day since the day of rhCG administration. Albumin infusion and hydroxyethyl starch (HES) were administered on the day of oocyte retrieval. Vaginal micronized progesterone was used for luteal phase support [9]. The patient was monitored after follicular puncture and, in the absence of clinical symptoms of OHSS, embriotransfer (ET) of two blastocysts was performed on day 5. The condition of the patient was satisfactory up to day 8 after ET (27 days from the beginning of the stimulation, 15 days after administration of rhCG), when she presented with abdominal pain, breathlessness and palpitations. Clinical evaluation showed signs of dyspnea, tachycardia and marked abdominal distension. The ultrasound scan revealed an intrauterine twin pregnancy, bilaterally enlarged ovaries – both were 12cm in diameter, marked ascites and pleural effusion. The laboratory findings from day 8 after ET showed hemoconcentration, hyperkalemia, elevated concentrations of

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d-dimers, transaminases and creatinine. The thyroid function results were as follows: TSH-5.127mU/L, fT4-19.33pmol/L and FT3-4.22pmol/L. L-T4 substitution was not increased due to dyspnea and tachycardia, instead iodine supplementation at a dose of 200mg/d was initiated [6]. After the diagnosis of severe OHSS, the patient was hospitalized. The symptomatic treatment consisted of administration of intravenous albumins, diuretics, low molecular weight heparin, acetylsalicylic acid and cabergoline and resulted in improvement of the clinical and biochemical parameters. The patient was discharged home on day 5 of hospitalization. On day 40 after ET the results of the control tests of thyroid function were: TSH-2.365mU/L and fT4-18.67pmol/L. The patient was clinically euthyroid and the dose of L-T4 was unaltered (50µg/day since the beginning of the stimulation). On day 67 after ET the control thyroid tests were: TSH-0.032mU/L and fT4-24.26pmol/L. Hyperthyroidism was diagnosed on the basis of high hCG plasma concentrations, stimulating the thyroid gland in twin pregnancy (gestational hyperthyroidism), and resulting in the need to lower the L-T4 dose to 37.5µg/day and temporary cessation of iodine supplementation [6]. The subsequent thyroid function test results were as follows: TSH-0.056mU/L, fT4-18.15pmol/L, what led to restoration of the previous L-T4 dose and iodine supplementation. Since 20 weeks of gestation the patient remained clinically and biochemically euthyroid. The patient gave birth to two healthy newborns at 37 weeks of gestation by an elective cesarean section. Immediately after the delivery the L-T4 dose was reduced to 25µg/day [6].

Discussion

Clinical studies have confirmed a significant impact of COH on the thyroid function [1, 2, 8, 10]. In patients undergoing COH, the thyroid function changes are expressed by significantly elevated values of plasma TSH and drastically decreased plasma fT4 concentrations. It in turn is associated with considerable increase in estradiol (E2) levels, resulting in higher values of thyroid binding globulin (TBG). Also, high E2 levels additionally influence the function of the hypothalamic-pituitary-thyroid axis. Human placental gonadotropin (hCG), administered during COH and appearing in pregnancy after IVF-ET, inhibits TSH secretion. Normal healthy thyroid gland should be able to meet the growing demands without the need of supplementation with exogenous L-T4. Changes in the plasma concentrations of TSH and free T4 can be expected to remain within the normal ranges in patients with normal TSH (<2.5mU/L), without previously diagnosed thyroid diseases and without thyroid antibodies [2]. Studies so far have demonstrated the need to increase L-T4 doses after confirmation of pregnancy, by approximately 30-50%, with significantly growing demand already at 4-6 weeks of gestation, in patients previously treated for hypothyroidism. Even a slight increase in TSH in the reference range was observed to be associated with a higher risk of miscarriage [5, 7, 11]. Regardless, management standards for COH in patients with thyroid disorders, diagnosed before IVF-ET, are yet to be designed [4,8]. In case of pre-existing hypothyroidism, especially with coexisting thyroid antibodies, the demand for exogenous L-T4 COH notably increases during COH [3, 4, 6, 10, 12, 13].

In the case of our patient, the L-T4 dose was increased by 33% (from 37.5µg/day to 50µg/day) since day 1 of the stimulation. The decision was based of the available literature data.

OHSS presents a unique challenge in the course of IVF-ET. The syndrome is characterized by enlarged ovaries and increased permeability of blood vessels, leading to homeostasis disturbances of varying degree. Severe OHSS complicates approximately 0.1-1% of IVF-ET cycles. The available literature reports only isolated cases of OHSS influence on thyroid function and we are not familiar with a case of thyroid dysfunction in severe OHSS, according to Rizk and Aboulghar. In the event of OHSS, the interpretation of thyroid function results presents a considerable challenge due to the following: high levels of E2 resulting in highly elevated concentrations of TBG binding to the administered L-T4, dysregulation of plasma proteins (decreased plasma concentrations of transport proteins involved in the movement of fluids in the third space and intravenous administration of albumin preparations binding the supplemented L-T4), administration of drugs interfering with the binding of L-T4 such as low molecular heparin weight, acetylsalicylic acid and adrenal steroids (prednisone) administered to our patient, as well as dysfunction of liver and kidneys. Fluid, electrolyte and renal imbalance adversely affects iodine metabolism. Furthermore, in the case of embryo implantation, thyroid-stimulating hCG appears and reaches particularly high concentrations in multiple pregnancies. Thus, all clinical decisions ought to take into account the overall condition of the patient and a likely impact of the administered L-T4 preparations on symptom intensity and severity (tachycardia and dyspnea in case of our patient). Also, owing to a transient nature of the disorder, it is essential to account for the fact that the decision to increase the doses of L-T4 during the acute phase of OHSS may lead to a relative excess of thyroid hormones in the event of restored endocrine, fluid, electrolyte and protein balance. We are of the opinion that clinical assessment of patient condition ought to be the decisive factor when introducing L-T4 supplementation, and the decision to alter L-T4 doses laboratory should not be made on the sole basis of laboratory results of thyroid function tests.

Conclusions

L-T4 substitution in OHSS in patients with thyroid dysfunction presents a considerable challenge due to scarcity of data and lack of management standards. L-T4 dose must be individualized. Thus, the need to reach the clinically euthyrotic state and normal laboratory test results, as well as the clinical state of the patient, often serious, need to be taken into consideration. Further studies on thyroid dysfunction, the effects of the therapy on thyroid function and standards of L-T4 substitution in OHSS, ought to be conducted.

Oświadczenie autorów

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