ORIGINAL RESEARCH PAPER

Volume-7 | Issue-10 | October-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A CASE OF HYPOGONADOTROPIC HYPOGONADISM: A VARIANT WITH HIGHER RISK OF OHSS.

Gynaecology

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ABSTRACT

OHSS, though a rare complication of ovarian stimulation, but if not detected early and adequately managed can lead to life threatening consequences.

Objective: To report a case of a variant of hypogonadotropic hypogonadism with severe OHSS and to discuss the risk factors and strategies of prevention.

Case report: Here, we present a case of hypogonadotropic hypogonadism with polycystic ovarian morphology. She was a thin built woman with eight years of infertility. Her AMH value was on a higher side and on ovulation induction. She developed severe late onset OHSS on day 11 of the HCG trigger which was successfully managed.

Conclusion: While doing ovulation induction in patients with hypogonadotropic hypogonadism, it should be kept in mind that there exists a variant with polycystic ovarian morphology (PCOM), who might show hyper-response to gonadotropin stimulation. These are the patients who are at high risk of OHSS and need more frequent monitoring. Serum AMH and polycystic morphology on stimulation can help suspect OHSS at an early stage. Luteal coasting or use of progesterone's in place of HCG for luteal phase support can help in decreasing the risk of severe OHSS.

KEYWORDS

OHSS, PCOS, Hypogonadism, AMH, HCG

INTRODUCTION:

OHSS (ovarian hyper-stimulation syndrome) is a rare but serious complication following ovarian induction and controlled ovarian stimulation. The incidence of moderate OHSS being 3-6% and that of severe OHSS is 0.1-3%[1] in all cycles.

OHSS presents with a spectrum of symptoms ranging from mild abdominal pain to third space fluid collection to hepatic and renal dysfunction and thromboembolism[1]. So, early detection and treatment will help limit the disease thus decreasing the morbidity and mortality associated with it.

Hypogonagotropic hypogonadism is classified as WHO type 2 anovulation[2]. The incidence of severe OHSS in these patients is 0.6%[3]. The low risk of OHSS in these patients is thought to be due to impairment of hypothalmic-pituitary function. These patients usually develop one or two follicles with gonadotropin stimulation.

However, a variant of hypogonadotropic hypogonadism has also been identified which behave in a similar manner like poly-cystic ovarian syndrome. Although, on baseline ultrasound ovaries may not be seen but on stimulation with gonadotropins, hyper-response due to PCOS may get unmasked[4]. They develop multiple follicles and enlarged ovaries[3]. This hyper-response increases the risk of OHSS. Definitely, the hormonal profile of these patients is very different from those of PCOS. They have lower FSH, LH and estradiol value as compared to PCOS[3].

However, the number of small antral follicles are not affected in these patients. So AMH value in patients with hypogonadotropic hypogonadism is generally not affected[5]. But this variant of hypogonadotropic hypogonadism with polycystic ovarian morphology have comparatively higher AMH value. AMH (anti-mullerian hormone) is a useful marker in these patients for prediction of OHSS in these patients[5].

Other risk factors for OHSS in these patients are young age and low BMI[6]. HCG (Human Chorionic Gonadotropin) plays the major role in the pathogenesis of OHSS by increasing various pro-angiogenic factors like VEGF (vascular endothelial growth factor), pro-renin, renin, angiotensin 2 and various interleukins[7]. These factors increase vascular permeability causing fluid to shift from intravascular to extravascular compartment resulting in ascites, pleural and pericardial effusion and edema in the dependent parts[8]. So, the factors which increase HCG like pregnancy, multiple stimulated follicles (>20 in ART and >6 in OI), HCG for ovulation trigger or luteal phase support increase the risk of OHSS[7].

Also, a higher dose of gonadotropins required for ovarian stimulation in patients with hypogonadotropic hypogonadism and inability to use GnRH agonist[9] for triggering ovulation adds to the risk of OHSS in these patients.

Based on the time of onset, OHSS is divided into early onset and late onset. Early onset OHSS develops within 3-7 days of the HCG trigger[10]. It depends on ovarian stimulation protocol and is precipitated by higher gonadotropin dose for simulation, higher peak estradiol levels and exogenous HCG for triggering ovulation. Late-onset OHSS usually develops more than 10 days after the HCG trigger. It is due to the endogenous rise in HCG due to ongoing pregnancy[10].

Here we present a case of hypogonadotropic hypogonadism in the background of polycystic ovarian morphology (PCOM) who developed OHSS which was aggravated by new onset of pregnancy.

CASE REPORT:

A 27-year women presented with the history of primary infertility for 8 years. She was thin built with a BMI of 21.23 kg/m2. She had a history of primary amenorrhea and use of combined oral contraceptive pills for the resumption of her menstruation. On detailed evaluation, diagnosis of hypogonadotropic hypogonadism and male factor infertility was made. Her baseline AMH value was 3.5 ng/ml and on baseline transvaginal scan (TVS), ovaries were barely visible. We planned her for gonadotropin stimulation followed by donor intrauterine insemination (IUI).

She was called on day 1 of her cycle (which was withdrawal after COC intake). She was stimulated with human menopausal gonadotropin (HMG) 150 IU/day for 8 days (day 2-9 of the cycle). Transvaginal scan (TVS) on day 10 revealed 8-10 small antral follicles depicting typical polycystic ovarian morphology but none was more than 10 mm. So, the dose of HMG was increased to 150 mg and 225 mg, alternate day. On day 21 of her cycle, 4 follicles of 18 mm, 3 follicles of 12 mm and 3 follicles of 10 mm were noted. She was given the option of oocyte retrieval and cryopreservation followed by frozen embryo transfer at later date due to multiple follicles and a risk of OHSS. But, this was a precious pregnancy for her and she could not afford IVF (in vitro fertilization). In view of hypogonadotropic hypogonadism, 10,000 IU of Human chorionic gonadotropin (HCG) was given. Her luteal phase was supported with estrogen and progesterone. Also, she received 2

doses of HCG 2000 IU, 72 hours apart, which was withdrawn in view of enlarged ovaries (10 cm3) and multiple follicles noted on TVS done on day 8 of the HCG trigger.

On day 11 of HCG trigger, the patient developed acute onset abdominal pain with distension associated with nausea and vomiting. No history of decreased urine output. On per-abdomen examination, ascites was present. However, her chest was clear. Her hematocrit was 41% and leucocyte count was 16,800. She had hypoalbuminemia (serum albumin- 2.86 g/dl). Her electrolytes, renal function, and liver function tests were within normal limits. No signs of effusion noted on her chest X-ray. Ultrasound revealed enlarged ovaries and free fluid in the abdomen. The diagnosis of severe ovarian hyperstimulation syndrome (OHSS) was made and the patient was admitted. The patient was managed with iv fluids. Strict input-output charting, body weight, and abdominal girth monitoring were done. Her urine output, serum electrolytes, liver and renal function and coagulation profile during the hospital stay were within normal limits. Prophylactic clexane was started. Her urine pregnancy test was positive on day 15 of the trigger. With fluid therapy and high protein diet, her abdominal girth decreased with a decrease in leukocytosis and haemoconcentration (haematocrit-34%) and the patient was discharged in a stable condition on day 18 of the trigger. At present patient is receiving luteal phase support with 2 mg estradiol and 10 mg duphaston and clexane prophylaxis. She is being monitored on the outpatient basis for signs and symptoms of OHSS and we are awaiting her viability scan at 6 weeks hoping this to be a successful pregnancy.

DISCUSSION

Owing to the low FSH and estradiol values, it was initially thought that the patients with hypogonadotropic hypogonadism are at low risk of OHSS. But not everyone is aware of a variant of hypogonadotropic hypogonadism with polycystic ovarian morphology, who are at a higher risk of OHSS. Baseline ultrasound in these patients reveal small and barely visible ovaries but on ovarian stimulation, they develop typical polycystic ovarian morphology (PCOM).

These patients have comparatively higher AMH value which is a positive predictor of OHSS[5]. A study conducted by Lee et al[5], observed AMH as a significant predictor of OHSS. Using the cut-off value of 3.36 ng/ml, AMH had 90.5% sensitivity and 81.3% specificity in predicting OHSS. The patient described here also had AMH value of 3.5 ng/ml which added to the risk of OHSS.

Other risk factors which added to the risk of OHSS in this patient were the young age and low BMI.

The patient had enlarged ovaries on day 7 of the HCG trigger, with symptoms of OHSS occurring from day 11 of the trigger. The reason could be the exogenous HCG given for luteal phase support which was superadded by the endogenous HCG due to ongoing pregnancy. So, this was a case of late-onset OHSS, which is mainly attributed to the endogenous HCG of ongoing pregnancy. Stimulation protocol and HCG for trigger have little role in its development. Identification of the risk factors and frequent monitoring in high-risk patients are effective strategies for prevention of its serious outcome.

Based on the risk factor profile the two options that could be offered to this patient were cycle cancellation[11] or oocyte retrieval followed by cryopreservation and delaying transfer in subsequent cycles which have proven benefit in decreasing the risk of OHSS[6].

This patient refused cycle cancellation because it was a precious pregnancy for her. She had conceived after 8 long years of infertility. Cycle segmentation by oocyte retrieval and later frozen embryo transfer is a safe and effective option for patients who can afford IVF and cost of cryopreservation[12]. Frozen embryo transfer not only decreases the risk of OHSS but also improves endometrial receptivity resulting in better implantation and live birth rate. This patient was not affording for IVF.

The patients undergoing ovarian stimulation have supraphysiological levels of estradiol and progesterone which inhibits the natural pulsatile LH (luteinizing hormone) secretion. This can result in asynchrony between embryo development and endometrium resulting in implantation failure. This is even more severe in patients with hypogonadotropic hypogonadism So, they need exogenous luteal phase support in form of HCG or progesterone. HCG, for luteal phase support, has a risk of OHSS so progesterone is the safe option for these patients. Although, this patient received two doses of HCG in the luteal phase, but as soon as enlarged ovaries were noted on the ultrasound, HCG was withdrawn and the patient was continued on estradiol and progesterone.

Another option for OHSS prevention in this patient could be luteal coasting, which requires monitoring estradiol and progesterone levels and administering HCG only when estradiol and progesterone levels are very low[7].

Use of prophylactic aspirin[13] or dopamine agonists like cabergoline in high-risk patients has shown to significantly decrease the risk of OHSS. Aspirin decreases the platelet activation by VEGF which cabergoline directly decreases VEGF levels[6], thus decreasing OHSS risk.

There is a good evidence to support the use of metformin in decreasing the risk of OHSS in patients with PCOS[14]. However, more research is required to prove its beneficial role in patients with hypogonadotropic hypogonadism with PCOS morphology.

Prednisolone, calcium, and albumin are also being studied for OHSS prevention but data to support their use is limited.

A study conducted by Haas et al[15] observed no serious adverse pregnancy outcome like intra-uterine growth restriction, pregnancy-induced hypertension in the pregnancy complicated even by severe OHSS. So, monitoring should be done like any other pregnancy following ovulation induction.

CONCLUSION:

While doing ovulation induction in patients with hypogonadotropic hypogonadism, it should be kept in mind that there exists a variant with polycystic ovarian morphology (PCOM), who might show hyper-response to gonadotropin stimulation. These are the patients who are at high risk of OHSS and need more frequent monitoring. Serum AMH and polycystic morphology on stimulation can help suspect OHSS at an early stage. Luteal coasting or use of progesterone's in place of HCG for luteal phase support can help in decreasing the risk of severe OHSS. Prophylactic aspirin and cabergoline have also shown to beneficial in high-risk patients.

REFERENCES

1. Kumar P, Sait SF, Sharma A, Kumar M. Ovarian hyperstimulation syndrome. J Hum Reprod Sci. 2011;4(2):70-5.
2. Katsikis I, Kita M, Karkanaki A, Prapas N, Panidis D. Anovulation and ovulation induction. Hippokratia. 2006;10(3):120-7.
3. Shoham Z, Conway GS, Patel A, Jacobs HS. Polycystic ovaries in patients with hypogonadotropic hypogonadism: similarity of ovarian response to gonadotropin stimulation in patients with polycystic ovarian syndrome. Fertil Steril. 1992;58(1):37-45.
4. Pandurangi M, Tamizharasi M, Reddy NS. Pregnancy outcome of assisted reproductive technology cycle in patients with hypogonadotropic hypogonadism. J Hum Reprod Sci. 2015;8(3):146-50.
5. Lee TH, Liu CH, Huang CC, Wu YL, Shih YT, Ho HN, et al. Serum anti-Mullerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. Hum Reprod. 2008;23(1):160-7.
6. Practice Committee of the American Society for Reproductive Medicine. Electronic address Aao, Practice Committee of the American Society for Reproductive M. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril. 2016;106(7):1634-47.
7. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet. 2010;27(2-3):121-8.
8. Namavar Jahromi BM, Parsanezhad MM, Shomali ZM, Bakhshai PM, Alborzi MM, Moin Vaziri NMDP, et al. Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management. Iran J Med Sci. 2018;43(3):248-60.
9. Kol S, Solt I. GnRH agonist for triggering final oocyte maturation in patients at risk of ovarian hyperstimulation syndrome: still a controversy? J Assist Reprod Genet. 2008;25(2-3):63-6.
10. Lee KH, Kim SH, Jee BC, Kim YJ, Suh CS, Kim KC, et al. Comparison of clinical characteristics between early and late patterns in hospitalized patients with ovarian hyperstimulation syndrome. Fertil Steril. 2010;93(7):2274-80.
11. Griesinger G, Verweij PJ, Gates D, Devroey P, Gordon K, Stegmann BJ, et al. Prediction of Ovarian Hyperstimulation Syndrome in Patients Treated with Corifollitropin alfa or rFSH in a GnRH Antagonist Protocol. PLoS One. 2016;11(3):e0149615.
12. Mahajan N, Gupta S, Sharma S, Rani K, Naidu P, Arora PR. Early onset ovarian hyperstimulation syndrome despite use of segmentation approach and ovarian hyperstimulation syndrome prophylaxis. J Hum Reprod Sci. 2015;8(4):234-8.
13. Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril. 2010;93(7):2281-4.
14. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, et al. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril. 2011;96(6):1384-90 e4.
15. Haas J, Yinon Y, Meridor K, Orvieto R. Pregnancy outcome in severe OHSS patients following ascitic/plerural fluid drainage. J Ovarian Res. 2014;7:56.