Archives of Clinical Trials

Original Article

Risk of ovarian hyperstimulation syndrome in infertile patients with PCOS treated by HP HMG

Manar Tareq Mohammed, Hamza Elmahaishi, Narges R Ben Halim, Elmahaishi MS

Lamis IVF center - Misurata/Libya

Correspondence

Manar Tareq Mohammed & Elmahaishi MS

Lamis IVF center - Misurata/Libya

Email: Manartareq92@gmail.com & elmahaishi@elmahaishi.com

- Received Date: 02 Dec 2022
- Accepted Date: 06 Dec 2022
- Publication Date: 15 Dec 2022

Abstract

Polycystic ovarian syndrome (PCOS) is the commonest endocrinopathy affecting women in reproductive age group. The prevalence may vary from 8.7% to 17% depending on clinical criteria used. PCOS in women having IVF presents multiple challenges ranging from a poor to an exaggerated response, poor fertilization, poor blastocyst conversion and ovarian hyperstimulation syndrome (OHSS). OHSS is at increased risk in PCOS patients receiving fertility treatments varying from mild to severe cases which can be life threatening.

Aim of the study: The presence of OHSS in infertile PCOS patients who followed non-pituitary down regulation protocol by using HP HMG injections.

Materials and methods: The study type was case series study. It was done in Lamis IVF center - Misurata / Libya during the period 1- 9 -2021 to 31- 8 -2022. 118 infertile patients with PCOS were randomly selected for the study. All patients were selected started ovulation induction with non-pituitary down regulation protocol using highly purified HMG injections.

Results: The age of the patients ranges between 18 and 45 years with a mean age of 30 years. The mean number of retrieved oocytes was 19.33 ± 10. The study also showed that the mean number of mature oocytes picked up was 9.41 ± 5.5 with mean success of 77.6%. Hyperstimulation syndrome was reported only in one case (prevalence of 0.8%) which was mild (needed no admission). Regarding the embryo, the mean number of transfers was 2.36 ± 0.6 with two cases showed no fertilization and 82 cases were associated with poor sperm.

Conclusion: In our study OHSS in PCOS patients treated by highly purified HMG injections developed in only one case which was mild (needed no admission).

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by menstrual irregularities, chronic anovulation, hirsutism, androgenic alopecia, and acne. At diagnosis, patients can with different manifestations according to the disease phenotype, patient's age, and lifestyle. However, most patients pursue medical care because of the clinical symptoms of PCOS, such as hyperandrogenism, menstrual irregularities and infertility. Recent studies have shown that PCOS is associated with 80% of anovulatory infertility; however, the precise mechanism of PCOS-induced anovulation is still undetermined. The treatment strategies of PCOS are symptomatic depending mainly on the desired goals and clinical benefits. Life style intervention is still the first line treatment option for overweight females seeking pregnancy. In addition, there are many pharmacological agents that could be added to induce ovulation such as metformin, and clomiphene citrate [1] & injectable human gonadotrophin.

According to the Rotterdam consensus [2], PCOS is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/ or an ovarian volume >10 mL in at least one ovary).

Abnormality of the hypothalamic-pituitary-ovarian or adrenal axis has been imposed in the pathophysiology of polycystic ovarian disease. A disturbance in the secretion pattern of the gonadotrophin- releasing hormone (GnRH) results in the relative increase in luteinizing hormone (LH) to follicle stimulating hormone (FSH) release [3]. Ovarian estrogen is responsible for causing an abnormal feedback mechanism that caused an increase in LH release [4]. Usually, in healthy women, the ratio between LH and FSH usually lies between 1 and 2. In polycystic ovary disease women, this ratio becomes reversed, and it might reach as high as 2 or 3 [5].

PCOS women having IVF presents multiple challenges ranging from a poor to an exaggerated

Citation: Mohammed MT, Elmahaishi H, Halim NRB, Elmahaishi MS. Risk of ovarian hyperstimulation syndrome in infertile patients with PCOS treated by HP HMG. Arch Clin Trials. 2022;2(4):1-5.

response, poor egg to follicle ratio, poor fertilization, poor blastocyst conversion and ovarian hyperstimulation syndrome (OHSS) [6].

OHSS is a serious complication of ovulation induction that usually occurs after gonadotropin stimulation, followed by human chorionic gonadotropin administration, for infertility treatment [7].

The hallmark of OHSS is an increase in the permeability of the capillaries, resulting in a fluid shift form the intravascular space to the extravascular compartments. Vascular endothelial growth factor (VEGF) plays a critical role in the pathogenesis of OHSS by increasing vascular permeability. VEGF is secreted by the granulosa cells, and human chorionic gonadotropin (hCG) stimulates its secretion. Severe OHSS is associated with higher levels of VEGF [8].

The other suggested factors that may act directly or indirectly on the development or severity of OHSS are angiotensin II, insulin-like growth factor, epidermal growth factor, transforming growth factor alpha and beta, basic fibroblast growth factor, platelet-derived growth factor, interleukin-1B, and interleukin-6 [9,10].

The main event in the pathogenesis of OHSS is ovarian enlargement, secretion of vasoactive substances, ascites, and hypovolemia resulting from an acute extravasation of fluid into the interstitial space [8,11].

The clinical treatment of OHSS depends on its severity, complications, and absence or presence of pregnancy [12,13]. The treatment involves dealing with electrolytic imbalance, hemodynamic changes, liver dysfunction, pulmonary manifestations, hypoglobulinemia, febrile morbidity, thromboembolic events, adnexal torsion, and neurological manifestations [8,14]

The symptoms of OHSS are not specific and there are no diagnostic tests for the condition. Hence, care must be taken to exclude other serious conditions that may present in a similar manner but require very different management. Careful assessment by an experienced clinician may be needed, along with full blood count, serum electrolytes and osmolality, pelvic ultrasound scan and, in selected cases, abdominal imaging. The combination of elevated hematocrit and reduced serum osmolality and sodium is indicative of OHSS [15].

It should be remembered that OHSS by itself is not commonly associated with severe pain, pyrexia or signs of peritonism. The presence of these features should lead to a thorough clinical review and investigation to rule out other diagnoses. Important differential diagnoses include pelvic infection, pelvic abscess, appendicitis, ovarian torsion or cyst rupture, bowel perforation [16] and ectopic pregnancy. OHSS should not, therefore, be the 'default diagnosis' for women presenting with abdominal pain during fertility treatment.

The diagnosis of OHSS is made on clinical grounds (Tables 1 and 2).

Regarding severity of OHSS , it's classified in Table 3.

Several schemes have been developed for classifying the severity of OHSS [17,18] with no clear agreement between investigators .The scheme in Table 3 is based on the classification of OHSS severity proposed in the previous edition of the RCOG guideline combined with useful features from previous classifications.

Aim of the study

Is to estimate the risk of ovarian hyperstimulation syndrome in infertile PCOS patients who received HP HMG injections going for ICSI.

Materials and methods

The study type was case series study. It was done in Lamis IVF center in Misurata / Libya during the period 1st September2021 to 30th September 2022. 118 infertile patients with PCOS were randomly selected for the study 21.5% (total ICSI cases at the same period were 548 patients).

Table 1. *Relavent history from a women suspected to be suffering from OHSS*

History
Time of onset of symptoms relative to trigger Medication used for trigger (hCG or GnRH agonist) Number of follicles on final monitoring scan Number of eggs collected Were embryos replaced and how many? Polycystic ovary syndrome diagnosis?
Symptoms
Abdominal bloating Abdominal discomfort/pain, need for analgesia Nausea and vomiting Breathlessness, inability to lie flat or talk in full sentences Reduced urine output Leg swelling Vulval swelling Associated comorbidities such as thrombosis

Table 2. *Examination and investigation of women with suspected OHSS*

Examination
General: assess for dehydration, oedema (pedal, vulval and sacral); record heart rate, respiratory rate, blood pressure, body weight **Abdominal:** assess for ascites, palpable mass, peritonism; measure girth **Respiratory:** assess for pleural effusion, pneumonia, pulmonary oedema
Investigations
Full blood count Haematocrit (haemoconcentration) C-reactive protein (severity) Urea and electrolytes (hyponatraemia and hyperkalaemia) Serum osmolality (hypo-osmolality) Liver function tests (elevated enzymes and reduced albumin) Co-agulation profile (elevated fibrinogen and reduced antithrombin) hCG (to determine outcome of treatment cycle) if appropriate Ultrasound scan: ovarian size, pelvic and abdominal free fluid. Consider ovarian Doppler if torsion suspected
Other tests that may be indicated
Arterial blood gases D-dimers Electrocardiogram (ECG)/echocardiogram Chest X-ray Computerised tomography pulmonary angiogram (CTPA) or venti-lation/perfusion (V/Q) scan

Table 3. *Proposed RCOG classification of severity of OHSS*

Category	Features
Mild OHSS	Abdominal bloating
	Mild abdominal pain
	Ovarian size usually < 8 cm
Moderate OHSS	Moderate abdominal pain
	Nausea vomiting
	Ultrasound evidence of ascites
	Ovarian size usually 8-12 cm^3
Severe OHSS	Clinical ascites (= hydrothorax)
	Oliguria (<300 ml/day or < 30 ml/hour)
	Haematocrit > 0.45
	Hyponatraemia (sodium <135 mmol/l)
	Hypo-osmolality (osmolality < 282 mOsm/kg)
	Hyperkalaemia (potassium > 5 mmol/l)
	Hypoproteinaemia (serum albumin < 35 g/l)
	Ovarian size usually > 12 cm
Critical OHSS	Tense ascites/large hydrothorax
	Haematocrit > 0.55
	White cell count>25 000/ml
	Oliguria/anuria
	Thromboembolism
	Acute respiratory distress syndrome

a Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

The cases selected according to the Rotterdam consensus of polycystic ovarian syndrome.

All the patients were selected; started ovulation induction with Non pituitary down regulation protocol using highly purified HMG injections. Gonadotropin dosing carefully individualized, taking into account the patient's age, body mass, antral follicle count, and previous response to gonadotropins. ovulation follow up done by transvaginal ultrasound & monitor of estradiol level at embryo transfer day.

All embryos transfer were done at morula stage (4th day post oocyte pick up). There's no exclusion criteria according to age, type & cause of infertility (either primary or secondary), previous trials of ICSI, or history of OHSS.

Results

Distribution of cases according to age

From 18 To 22 Years	18	15.30%
From 23 To 27 Years	33	28.00%
From 28 To 32 Years	25	21.20%
From 33 To 37 Years	26	22.00%
From 38 To 42 Years	13	11.00%
From 43 To ≥ 45 Years	3	2.50%
Total	118	100.00%

The mean age of the patients were 30 years, ranges between 18 and 45 years; with 28% at the age group from 23- 27 years, while the age group from 43-45 presents only 2.5%.:

Distribution of cases according to cause of infertility

	Frequency	Percentage
Male Factor	74	62.70%
Female Factor	35	29.70%
Both male & female factor	9	7.60%
Total	118	100.00%

The majority of infertility cases at our study were male factor 62.7%; whereas female factors represent 29.7%, and both male & female factors 7.6%.

82% of the cases were associated with poor sperms.

Distribution of cases according to number of oocytes retrieved for ICSI

No. of oocytes	No. of patients	%
10-20 ovum	79	66.95%
21-30 ovum	26	22%
31-40 ovum	10	8.50%
41- ≥50. ovum.	3	2.50%

The number of oocytes retrieved for ICSI ranges from 10 eggs up to 58 eggs. The mean number of retrieved oocytes was 19.33 ± 10. (number of oocyte retrieved at the study group were 2329 oocytes represents 64.7% of total oocytes retrieved at the same period (total=3598.) No empty follicular syndrome was reported.

Distribution of cases according to number of oocytes retrieved for ICSI

Type of oocytes	MII	MI	GV	DEG.	TOTAL
Total no of oocyte retrieved 2329.	57%	24%	16%	3%	100%

Majority of oocytes retrieved were at metaphase II , while 24% at MI ; 16% & 3% were GV & degenerated respectively.

Hyperstimulation syndrome was reported only in one case (0.8%) which was mild (needed no admission). Regarding the embryo, two cases showed no fertilization & both of them due to poor sperms. (1.7% from PCOS group & 0.4 %from total cases at the same period), and 82 cases were associated with embryo freezing. No cycle cancellation before administration of human chorionic gonadotropin as strategy for the prevention of ovarian hyperstimulation syndrome.

Distribution of cases according to number of oocytes retrieved for ICSI

	E.T.	E. freezing	Total
No. of cases	107 (92.2 %)	9 (7.8%)	116 (100%)
Average No. Of oocytes Picked up	10-58	20-51	
Level of E2 at day of E.T.	2000-4999	5000-7500	

9 patient (7.8%) going for embryo freezing & transfer at the next cycle, this was because of high level of estradiol ≥ 5000 at embryo transfer day.

Discussion

Controlled ovarian stimulation with gonadotrophins is an essential part of in-vitro fertilization treatment. The aim is to produce an optimum number of oocytes to maximize success in the safest possible way. Pituitary downregulation with a gonadotrophin- releasing hormone agonist and stimulation with recombinant follicle- stimulating hormone is used widely. However, there are many different protocols in use with little evidence to determine the optimum regimen [19].

Inadequate doses of gonadotrophins can lead to a poor response resulting in treatment failure. However, higher doses can lead to a hyper response, resulting in ovarian hyperstimulation syndrome which is potentially life-threatening. Both poor and hyper response are associated with reduced pregnancy rates. Various strategies, such as electively freezing all the embryos, are being introduced to optimize outcomes while ensuring patient safety [19]. Published literature was retrieved through searches of Medline, Embase, and the Cochrane Library from 2011 to 2013 using appropriate controlled vocabulary ([OHSS] ovarian hyperstimulation syndrome and: agonist IVF, antagonist IVF, metformin, HCG, gonadotropin, coasting, freeze all, agonist trigger, progesterone) . Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to February 2013. The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health. Summary Statements:

1. The particular follicle-stimulating hormone formulation used for ovarian stimulation does not affect the incidence of ovarian hyperstimulation syndrome.

2. Coasting may reduce the incidence of severe OHSS also reduces in vitro fertilization pregnancy rates.

3. The use of either luteinizing hormone or human chorionic gonadotropin for final oocyte maturation does not influence the incidence of OHSS .

4. There is no clear published evidence that lowering the human chorionic gonadotropin dose will result in a decrease in the rate of ovarian hyperstimulation syndrome.

5. Avoiding pregnancy by freezing all embryos will prevent severe prolonged ovarian hyperstimulation syndrome in patients at high risk.

6. Pregnancy rates are not affected when using gonadotropin-releasing hormone (GnRH) agonists in GnRH antagonist protocols for final egg maturation when embryos are frozen by vitrification for later transfer [20].

ESHRE 2022 represents a huge analysis of 171 studies and almost 37,000 subjects which shows that Mild OHSS is common in IVF patients, affecting as many as 33%, but rare (1%) in its serious forms. The evidence from this latest meta-analysis showed that in women with predicted normal or high response the use of short GnRH antagonist protocols resulted in little to no difference in live birth rate but a reduction in OHSS of as much as 52% when compared with long GnRH agonist protocols [21].

OHSS is another significant complication of assisted conception treatment, with a prevalence of around 33% in its mild form, and around 1% in severe cases. In its report of IVF activity in 2000, data from ESHRE's EIM Consortium reported an aggregate prevalence (of moderate-to-severe OHSS) of 1.1% in Europe [22].

Young patients with good ovarian reserves are at high risk of OHSS. For these patients, selecting an effective protocol is still a frustrating challenge in IVF/ICSI cycles. The most optimal protocol for high responders should have an acceptable rate of cancellation, obtain moderate healthy mature oocytes and high quality embryos at a reasonable cost and duration of therapy, provide a suitable endometrium for implantation, and have maximal pregnancy and live birth rates [23].

For over 20 years, GnRH agonists have been used to prevent the luteinizing hormone (LH) surge that results from multiple follicular development [24]. However, more and more studies are demonstrating that the GnRH agonist protocol can induce severe OHSS, especially for potentially high responders.

The GnRH antagonist protocol is supposed to reduce OHSS. Many researchers have demonstrated that there are several advantages in antagonist methods, including a shorter duration of Gn and a smaller dose of Gn per cycle [25]. Conflicting evidence still exists regarding the superiority of one protocol over the other [26].

There is still controversy over whether the GnRHant protocol can reduce the incidence of OHSS. A large body of published data shows that the GnRHant protocol can reduce the incidence of mild and moderate OHSS, compared with the GnRHa protocol [27]. However, one meta-analysis including five randomized controlled studies suggested that the incidence of severe OHSS was not associated with the type of analogue [28]. A study published in 2015 where a total of 660 IVF-ET/ICSI cycles were retrospectively identified, they found that in the GnRHa group, 83.53% of cancelled freshly transferred cycles were cancelled because of a high risk of OHSS, which was significantly higher than that in the GnRHant group (43.55%, $P<0.05$). The incidence of moderate and severe OHSS in the GnRHa group was slightly higher than that in the GnRHant group (2.97% VS 1.79%, $P = 0.445$). These results demonstrated that the GnRHant protocol can, to some extent, lower the cancellation rates and the incidence of OHSS [29].

At our study we use highly purified human menopausal gonadotrophin in patient already diagnosed as polycystic ovarian syndrome; we have a good results as mature oocyte's rate, fertilization rate, E.T rate . All obtained with almost no hyperstimulation syndrome.

Although there's Inadequate data on pregnancy outcomes, this protocol results for better oocyte maturity rate (MI, MII) & reduced prevalence of OHSS.

Conclusion

Non pituitary down regulation protocol using highly purified HMG injections are recommended for patients with polycystic ovarian syndrome who considered at risk for ovarian hyperstimulation syndrome.

References

1. Rababa'h AM, Matani BR, Yehya A. An update of polycystic ovary syndrome: causes and therapeutics options. Heliyon. 2022;8(10):e11010.

2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19-25.
3. Yen SS. The polycystic ovary syndrome. Clin Endocrinol (Oxf). 1980;12(2):177-207.
4. McKenna TJ. Pathogenesis and treatment of polycystic ovary syndrome. N Engl J Med. 1988;318(9):558-562.
5. Richard SL, Ricardo A. Androgen excess disorders. In: Danforth's Obstetrics and Gynecology; Philadelphia: Lippincott Williams & Wilkins; 2003. pp. 663–672.
6. Thakre N, Homburg R. A review of IVF in PCOS patients at risk of ovarian hyperstimulation syndrome. Expert Rev Endocrinol Metab. 2019;14(5):315-319.
7. Namavar Jahromi B MD, Parsanezhad ME MD, Shomali Z MD, et al. Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management. Iran J Med Sci. 2018;43(3):248-260.
8. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohí J, Simón C. The pathogenesis of ovarian hyperstimulation syndrome: in vivo studies investigating the role of interleukin-1beta, interleukin-6, and vascular endothelial growth factor. Fertil Steril. 1999;71(3):482-489.
9. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril. 2000;73(5):883-896.
10. Naredi N, Talwar P, Sandeep K. VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: Current status. Med J Armed Forces India. 2014;70(1):58-63.
11. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril. 1992;58(2):249-261.
12. Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update. 2003;9(1):77-96.
13. Son WY, Yoon SH, Lee SW, Ko Y, Yoon HG, Lim JH. Blastocyst development and pregnancies after IVF of mature oocytes retrieved from unstimulated patients with PCOS after in-vivo HCG priming. Hum Reprod. 2002;17(1):134-136.
14. Rizk B. Ovarian hyperstimulation syndrome: Epidemiology, pathophysiology, prevention and management. 1 st ed. Cambridge: Cambridge University Press; 2006.
15. Evbuomwan I. The role of osmoregulation in the pathophysiology and management of severe ovarian hyperstimulation syndrome. Hum Fertil (Camb). 2013;16:162–7.
16. Memarzadeh MT. A fatal case of ovarian hyperstimulation syndrome with perforated duodenal ulcer. Hum Reprod. 2010;25:808–9.
17. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril 1978;30:255–68
18. Mathur R, Evbuomwan I, Jenkins J. Prevention and management of ovarian hyperstimulation syndrome. Curr Obstet Gynaecol. 2005;15:132–8
19. Howie R, Kay V. Controlled ovarian stimulation for in-vitro fertilization. Br J Hosp Med (Lond). 2018;79(4):194-199.
20. Corbett S, Shmorgun D, Claman P; Reproductive Endocrinology Infertility Committee; Special Contributor. The prevention of ovarian hyperstimulation syndrome. J Obstet Gynaecol Can. 2014;36(11):1024-1033..
21. Melo P. ESHRE . Reducing the risk of ovarian hyperstimulation syndrome in IVF. Embargo: 10.30 CEST Monday 4 July 2022. Avaialable at: https://www.eshre.eu/ESHRE2022/Media/2022-Press-releases/Melo
22. Controlled ovarian stimulation (COS) protocols for assisted reproduction: a Cochrane systematic review and network meta-analysis. ESHRE . Presentation O-009, Monday 10.30 4 July 2022
23. Weissman A, Farhi J, Royburt M, Nahum H, Glezerman M, Levran D. Prospective evaluation of two stimulation protocols for low responders who were undergoing in vitro fertilization-embryo transfer. Fertil Steril 2003;79(4):886–92.
24. Devroey P, Aboulghar M, Garcia-Velasco J, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Hum Reprod 2009;24(4):764–74.
25. Copperman AB, Benadiva C. Optimal usage of the GnRH antagonists: a review of the literature. Reprod Biol Endocrinol 2013;11:20
26. Orvieto R. GnRH agonist versus GnRH antagonist in ovarian stimulation: has the ongoing debate resolved? Reprod Biomed Online 2014;29(5):647–9.
27. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008;89(1):84–91.
28. Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod 2002;17(4):874–85.
29. Xing W, Lin H, Li Y, Yang D, Wang W, Zhang Q. Is the GnRH Antagonist Protocol Effective at Preventing OHSS for Potentially High Responders Undergoing IVF/ICSI?. PLoS One. 2015;10(10):e0140286.