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POSSIBLE PREDISPOSING AND PREDICTABLE FACTORS FOR THE DEVELOPMENT OF OVARIAN HYPER STIMULATION SYNDROME (OHSS) IN WOMEN WITH POLYCYCTIC OVARY SYNDROME (PCOS) WHOM UNDERGONE INTRACYTOPLASMIC SPERM INJECTION (ICSI)

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a serious, iatrogenic problem which complicates ovulation induction/controlled ovarian stimulation (COS) during any assisted cycle. It usually occurs due to hCG which administered following exogenous gonadotropin stimulation for triggering final oocyte maturation. Women with polycystic ovary syndrome (PCOS) are at high risk but not all PCOS women develop OHSS. It can be effectively prevented and treated when diagnosed early. The study aims to know the possible factors which predispose the women with PCOS to develop OHSS and what are the predictors of its' development during COS/ICSI cycle to be avoided if possible, in the future by careful pre-cycle evaluation and intra-cycle monitoring of the predisposed women. The study included 53 females who seek ICSI treatment for infertility due to PCOS. They were followed up retrospectively and divided according to the development of OHSS into two groups. Group I (n=10): females who developed OHSS and group II (n=43): females who did not develop OHSS following COS/ICSI program. Assessment of demographic data, body mass index(BMI), cycle day 2 hormonal profile, TVUS for endometrial thickness(ET), the total dose of gonadotropins, duration of stimulation cycles, type of oocyte maturation trigger, estrogen and ET at the day of trigger and a total number of retrieved oocytes was done to know possible predisposing and predictable causes for developing OHSS. The study showed women who developed OHSS were insignificantly younger with a higher BMI than those who did not, p-value= 0.24 and 0.08 respectively. Cycle day 2 estrogen, LH, prolactin and ET were higher, total dose and duration of the stimulation cycle were less, most of them were triggered by GnRH agonist, having a higher level of estrogen and thicker ET at the day of trigger and produced higher number of oocytes. Conclusion: Despite being a significant, proved risk factor for OHSS, not all women with polycystic ovaries develop OHSS during COS/ICSI. Young age group women, those with a high BMI and who had high cycle day 2 E2, LH and Prolactin are more liable to develop OHSS. Women with PCOS who produced a high number of oocytes and had high serum E2 level on the day of oocyte maturation trigger are more likely to develop OHSS.

INTRODUCTION

One of the most common endocrine problem in reproductive age group females is polycystic ovarian syndrome (PCOS). More than 80% of cases of anovulatory infertility are usually due to it with a large number of women fail to get a pregnancy spontaneously and need assisted reproduction [1]. The syndrome is characterized by hormonal dysfunction with hyperestrogenemia, excess androgen and high LH in relation to FSH [2] which are responsible for the presentation, symptoms severity, type of treatment and response to the treatment [3]. Assisted reproductive techniques (COS and ICSI) are considered the best treatment modality for women who fail to respond to the conventional treatment measures with an acceptable outcome but not free from complications [4].

Multiple factors determine the reproductive functions of the females with this syndrome; weight and body mass index are the important ones and nearly 35% of those females are overweight and obese [5]. An important correlation has existed between obesity, symptom severity and response to treatment measures [6]. Controlled ovarian stimulation and assisted reproduction outcomes are negatively affected with multiple factors; elevated LH, intra-follicular and serum androgen levels excess and hyperestrogenemia [7, 8].

Ovarian hyperstimulation syndrome is one of the most serious and important complications of assisted reproduction [9] with different clinical presentations and ultrasonic features. Women with special conditions are usually at high risk; PCOS women, young age group, low BMI, those stimulated by GnRH agonist protocol, those triggered by hCG and those with high E2 level [10, 11, 12, 13]. However, not all PCOS women developed OHSS during assisted reproduction [14]. So, this study aims to determine the factors which predispose those women to OHSS, the predictable factors for its development and how can we help us to avoid OHSS development in the next cycle.

MATERIALS AND METHODS

The study was a retrospective cohort and the data were collected from the Fertility Center, Al- Sadr Medical City, Al- Najaf AL-Ashraf, in Iraq.

Fifty three sub-fertile females with PCOS were recruited and included in the study. The sample size was determined according to the prevalence of OHSS in any ICSI cycle (0.1-5%). They had been diagnosed with PCOS according to Rotterdam criteria [15]. The age was less than 35 years old (as with increased women age, the cycle is at a higher rate of cancellation due to older women showed poor response to ovarian stimulation) and their male partners had either normal or mild-moderate impairment in semen parameters (according to World Health Organization criteria in 2010 [16].

All participants with their partners were assessed by history, physical examination, BMI and fertility investigations (cycle day 2 hormones E2, LH, FSH, prolactin, endometrial thickness by trans-vaginal ultrasound (TVUS) and male seminal fluid analysis). All were treated by ICSI and subjected to COS with GnRH antagonist; Cetrotide 0.25 mg*1 s.c and gonadotropins; Gonal-F 75IU*2 for 7-10 days and followed up strictly by serial TVUS and E2 level (the role of GnRH antagonist to suppress the pituitary release of FSH & LH to prevent spontaneous ovulation by endogenous LH surge and allow the ovaries to be stimulated by exogenous FSH). Oocytes maturation trigger was done when they produced a suitable number of oocytes (at least 7-14 follicles of a size of ≥16 mm) by either GnRH agonist; Decapeptyle 0,1mg*2 or hCG; Pregnyl 5000iu*2 s.c depending upon the gynecologists' protocol and drugs' availability in the center.

Then, the participants divided into two groups according to developing OHSS or not: group I included women who developed OHSS and group II included those who did not. The diagnosis of OHSS was done depending on certain criteria depends on clinical presentation and ultrasound features [17] and only those who develop moderate-sever hyperstimulation syndrome who necessitate cycle cancellation and freeze all embryos were included (no embryo transfer cycle). Women older than 35 years old, without PCOS, with endometriosis, with uterine fibroid, with unexplained infertility, with mild OHSS, previous history of OHSS, or previously failed ICSI were excluded from the study.

For the analysis of the data, SPSS (24.0) was used. Depending on the type of the data; continuous mean ±SD was calculated or categorical; the percentage was calculated with a comparison by t-test or Chi-square respectively depending on the p-value of ≤0.05.

RESULTS

Table 1 illustrate the means of age, BMI and cycle day 2 baseline investigations of both studied groups. The women who developed OHSS were insignificantly younger, p-value=0.24 with higher BMI, p-value=0.08. Regarding the hormonal profile and ET, they had insignificantly higher LH, prolactin and ET, p-value= 0.36,0.86,0.12 and 0.46 respectively except E2 which was significantly higher 56.8±24.8 vs 37.7±20.1, p-value-0.01.

Table 2 shows the total dose and duration of gonadotropin stimulation and E2 & ET on the day of HCG trigger. There was no significant difference among them except E2 on the day of trigger, which was significantly higher in the women with OHSS, p-value=0.01.

Table 3 shows the type of ovulation trigger and the total number of retrieved oocytes following COS in both groups. Regarding the women with OHSS group, 9 out of 10 were triggered by GnRH agonist while only 1 was triggered by hCG with a significant difference, p-value=0.001 and

they produced a significantly higher number of oocytes, p-value 0.001.

Table 1. A comparison between both groups regarding age, BMI, hormonal profile and ET.

Parameter	G-I (N=10) Mean ±SD	G-I(n=43) Mean ±SD	P-value
Age (years)	26.7±4.3	28.3±3.2	0.24
BMI (kg/m²)	31.11±5.6	28.4 ±4.1	0.08
E2 (pg/ml)	56.8±24.8	37.7±20.1	0.01
LH (iu/l)	5.6±3.4	4.5±3.4	0.36
FSH (iu/l)	4.8 ±1.0	4.9 ±1.5	0.86
Prolactin (ng/dl)	30.6±18.0	24.3±9.5	0.12
ET (mm)	4.0±1.2	3.7±0.9	0.46

Table 2. Total dose, duration of gonadotropins, E2 and ET at day of trigger comparison between both groups

Parameter	G-I Mean ±SD	G-II Mean ±SD	P-value
Total dose (iu)	1515.0 ±472.4	1697.6± 644.8	0.40
Duration (days)	9.4 ±1.2	10.0± 1.7	0.31
E2 (pg/ml)	10278.1±2353 2.7	1773.8±926.1	0.02
ET (mm)	10.6±3.1	9.5±2.3	0.23

Table 3. A comparison between both groups regarding the type of ovulation trigger and the number of produced oocytes

Ovulation trigger	G-I Mean ±SD	G-II Mean ±SD	Total	P-value
GnRH agonist	9	16	25	
hCG	1	27	28	
Total	10	43	53	
To. No. of oocytes	24.7 ±4.2	9.2±5.1		0.001

DISCUSSION

Any COS/ICSI cycle aims to stimulate the ovaries to produce an adequate number of best quality oocytes to be inseminated to get a sufficient number of good quality embryos to be transferred to the uterus to get a successful pregnancy without complications [18]. One of the most common complications is OHSS. The establishment OHSS-freecycle could be done by careful evaluation of the sub-fertile couples, payment of a special attention to the possible risk factors, optimization of COS and considering some preventative measures [19].

Polycystic ovary syndrome is considered one of the most common risk factors for the development of OHSS [10]. This related to the fact that the polycystic ovaries contain a large number of small pre- and antral follicles which are highly sensitive to exogenous stimulation with gonadotropins [10]. However, not all PCOS women develop OHSS, this means that some underlying factors might play a role.

Regarding the results of the current study, it had been shown that the incidence of OHSS is 18.8% (10/53) which considered to be high in comparison with the usual results [14, 19] which states an incidence of 6-8% in mild-moderate form and 0.3-1% in the severe form of OHSS in any ICSI cycle. The study showed that the incidence of OHSS was higher in the females of the young age group below 25 years old which was similar to the result of many studies [14, 17, 19). Young age women have a good ovarian reserve which means a suitable number of oocytes to be stimulated with exogenous gonadotropin but with a higher BMI which was inconsistent with the results of most to all the studies which stated that OHSS usually higher in the lean females [14, 17, 19].

The detrimental effect of obesity on ovarian stimulation response may be explained via the effects of certain mediators e.g. leptin and ghrelin [20]. The increased leptin level within follicles leads to inhibition of ovarian steriodogenesis through its antagonizing effect to stimulatory factors (IGF-1, TGF-b, insulin and LH). Also, higher doses of gonadotropin and longer durations of stimulation cycles were needed to stimulate overweight/obese PCOS women than normal-weight women which lead to higher E2 levels and more stimulated follicles and an increased the development of OHSS [21, 22].

The study showed that the women who developed OHSS had a higher cycle day 2 E2, LH and prolactin levels. Similar results were obtained by some studies which showed that beta-hCG and its analogs, estrogen, estradiol, prolactin and progesterone all are implicated in the pathogenesis of OHSS although little was known about their roles [23].

As mentioned previously, all the females were down-regulated by GnRH antagonist protocol as it has been suggested that the suitable protocol for COS in PCOS women is the antagonist as its action is similar to the normal physiology of follicular recruitment, ovarian stimulation occurred with lower doses of exogenous gonadotropin and shorter duration(10) but still, OHSS occurred this means that multiple factors may enhance its development in PCOS women such as young age, high BMI, the type of trigger (hCG), those with higher E2 & prolactin levels and severe form of polycystic ovary syndrome(which is characterized by thick stroma and peripheral distribution of antral follicles). So, further studies on this topic is recommended.

There was no difference regarding the total dose of gonadotropin and the duration of the stimulated cycle in both groups. Regarding the ovulation trigger, the study showed that the females who developed OHSS were were triggered by GnRH agonist. However, it has been suggested that the agonist trigger may decrease the incidence of OHSS development as it takes a shorter duration for increasing LH [24]. So, the higher incidence of OHSS with agonist triggers in this study may be related to the same causes discussed earlier with the antagonist induction protocol. Since, a case

report developed by Raoul & Valeria,2017 showed that patients who triggered by GnRH agonist developed OHSS following COS and they suggested that however, the incidence is relatively uncommon, their occurrence needs further investigations to find a possible underlying cause [25].

The study showed that women who developed OHSS had been produced higher number of oocytes following oocyte retrieval which is consistent with the results of many studies which showed that the women with OHSS had a high number of stimulated follicles and produce a significantly large number of oocytes [14, 19] which is related to the pathophysiology of the syndrome in which the ovaries are highly sensitive to exogenous stimulation [17]. This also can explain the significantly high level of serum E2 level at the day of trigger as more oocytes secrete more E2 which was showed by the study. Many studies were in agreement with this result and showed a significantly high serum E2 level on the day of maturation trigger in women who have OHSS.

From the study's' results, we can conclude that PCOS women despite of being highly sensitive to develop OHSS, not all women with polycystic ovaries developed it which indicates that certain factors may predispose to its development; young age, high body weight and high cycle day 2 serum E2, LH and prolactin and GnRH agonist trigger. Also the study showed that the women who developed OHSS usually produced a large number of oocytes and had a high serum E2 level on the day of oocyte maturation trigger thus they may help in predicting its development and could be used for prevention of its development.

CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

ETHICAL CLEARANCE

A verbal consent was taken from all the included couples.

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