INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of controlled ovarian stimulation (COS) usually occurring during the luteal phase or during the early part of pregnancy ***(Avecillas et al.,*** ٢٠٠٤).

The incidence of OHSS has a wide variation between different centers. This is partly because of different definitions for the grades of severity and partly because of the adoption of different criteria for prevention. It has been estimated to be ***20% - 33%*** for ***mild*** cases, ***3% - 6%*** for ***moderate*** cases and ***0.1% - 0.2%*** for ***severe*** cases ***(Rizk,*** ٢٠٠٦).

However as regard the incidence among those who are under assisted reproductive technology (ART) it was found to range from ***0.5% - 5.0% (Alvarez et al , 2007).***

This syndrome was first described in ١٩٤٣ as "*syndrome d'hyper-luteinisation massive des ovaries"* when early forms of gonadotropins were used to induce ovulation. The first fatal case of OHSS was described in ١٩٥١ with oliguric renal failure as primary complication which led to death ***(Rydbergel, 1943).*** It was unclear why the syndrome develops, and the pathophysiology was poorly understood ***(Villasante et al., 2007).***

However recently vascular endothelial growth factor (VEGF) has been found to be an important mediator of OHSS, where it stimulates new blood vessel development and vascular hyperpermeability by acting through VEGF receptor ٢ (VEGFR-٢) on the endothelial cells. However, the signal pathway of hCG-induced VEGF secretion is still unclear and deserves further investigation ***(Chen et al.,*** ٢٠٠٨).

The risk factors associated with the development of ovarian hyperstimulation syndrome (OHSS) are; *young age* (Mean age ٣٠,٢ ± ٣,٥ years) ***(Delvigne & Rozenberg, 2002),*** *low body mass index* (asthenic-habitus), *higher or repeated doses of exogenous hCG* ***(Budev et al.,2005),*** *polycystic ovary syndrome, history of atopy or allergy, serum vascular endothelial growth factor* (>٢٠٠ pg/ml), *high serum estradiol* (>٣٠٠٠ pg/ml - ٤٠٠٠ pg/ml), *previous episode of OHSS, increased number of developing follicles* (١٠ follicles of ٤-١٠ mm in each ovary) (Vloeberghs et al., ٢٠٠٩).

Ovarian hyperstimulation syndrome is a clinical diagnosis where the symptoms may include abdominal pain and distension, ascites, gastrointestinal problems, respiratory compromise, oliguria, hemoconcentration and thromboembolism ***(Schorge et al., 2008).***

Classification has been settled due to the wide range of clinical features. This classification categorizes patients according to mild, moderate and severe disease. In *mild* disease, patient often report mild abdominal distention, soreness, nausea, and vomiting. Ovarian enlargement can be ٥ cm -١٢ cm. Moderate disease is marked by the presence of abdominal ascites on ultrasound examination.While *Severe* disease is diagnosed when there are clinical signs of tense ascites, hydrothorax, shortness of breath, hemoconcentration, hypercoagulability and any complications of OHSS such as renal failure, thromboembolism or acute respiratory distress syndrome (ARDS) ***(Burney et al., 2007).***

A distinction between early and late onset OHSS has been described, with *early* OHSS, has an onset set within ٩ days of oocyte retrieval. In contrast, *late* OHSS has onset more than ٩ days after oocyte retrieval. Late OHSS has not been associated with measures of follicular response, but with multiple gestations. Early and late OHSS may even reflect somewhat distinct pathophysiologic mechanisms. It has been proposed that early OHSS may result from ovarian stimulation by the exogenous hCG given to trigger ovulation, whereas late OHSS may be more closely linked to the endogenous hCG produced when pregnancy ensures ***(Mathur et al., 2000).***

Several methods were tried to prevent OHSS, however the syndrome is unlikely to be eliminated completely by dose individualization because of the narrow margin between the dose needed for multifollicular development and the dose that induces hyperresponse ***(Aboulghar & Mansour, 2003).***

Among preventive measures considered to lower the risk of OHSS includes; delaying the administration of hCG until estradiol levels plateau or decrease, using a lower dose of hCG in high-risk patients, using exogenous progesterone during the luteal phase instead of hCG and using ٢٥٪ albumin during oocyte retrieval ***(The Practice Committee of the American Society for Reproductive Medicine, 2004).***

Other preventive measures include cryopreservation and coasting but it was found that cryopreservation of all embryos for transfer in later cycle was not effective in prevention of OHSS ***(Aboulghar & Mansour, 2003).*** However coasting (withholding FSH and delaying hCG until serum E٢ decreases to a safe level) is currently the most commonly used method for prevention of OHSS, and it reduces markedly the incidence of OHSS; although prolonged coasting is associated with lower pregnancy rates ***(Mansour et al., 2005).***

AIM OF THE WORK

The aim of this study is to point out the modern trends in the prevention and management of ovarian hyperstimulation syndrome.

DEFINITION AND RISK FACTORS

Ovarian hyperstimulation syndrome (OHSS) is a syndrome characterized by ovarian enlargement and shift of fluid from the intravascular space to the extravascular space. This leads to accumulation of fluid in the peritoneal, pleural and rarely, the pericardial cavities, resulting in intravascular fluid depletion and haemoconcentration ***(Rizk & Nawar, 2004).***

It is the most concerning complication of controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART) ***(Busso et al., 2010).*** It was thought that this syndrome is a medical complication that is both completely iatrogenic and unique to the treatment of infertility ***(Burney et al., 2007).*** But, it can rarely occur spontaneously without COH ***(Akbay et al., 2010).***

The incidence of both forms of OHSS has a wide variation between different centers. This is partly because of different definitions for the grades of severity and partly because of the adoption of different criteria for prevention. It has been estimated to be ٢٠٪-٣٣٪ for ***mild*** cases, ٣٪-٦٪ for ***moderate*** cases, and ٠,١٪-٠,٢٪ for ***severe*** cases ***(Rizk,*** ٢٠٠٦). However as regard the incidence among those who are under assisted reproductive techniques (ART) it was found to range from ٠,٥٪ - ٥,٠٪ ***(Alvarez et al., 2007).***

Risk factors:

I- Spontaneous ovarian hyperstimulation syndrome (OHSS):

Among the risk factors for spontaneous OHSS that has been reported are; ***multiple pregnancies*** and ***hydatidiform moles*** which are known to be associated with abnormally high values of hCG. Although a case of spontaneous OHSS has been reported in a case of missed abortion with very low hCG levels ***(Aali & Narooi, 2008).***

Also ***hypothyroidism*** was reported as another risk factor, as it was thought that the thyroid stimulating hormone (TSH) has a weak follicle stimulating hormone (FSH) like activity on follicle stimulating hormone receptors (FSH-R) with subsequent gonadal stimulation ***(Anasti et al., 1995; Silva & Racine, 2008)***.

In hypothyroidism, there is preferential formation of estriol which is a weaker suppressor of gonadotropin release than estradiol resulting in relative increase in the pituitary gonadotropins release ***(Larsen et al., 1998)***. Alternatively, low levels of thyroid hormone might activate the release of FSH and LH besides the targeted activation of TSH release ***(Grumbach & Styne, 1998).***

Only three cases of spontaneous OHSS have been reported in non-pregnant women with ***primary hypo-***

thyroidism in which regression of OHSS was obvious with the initiation of thyroxin replacement therapy ***(Taher et al.,*** ٢٠٠٤).

Also, ***follicle stimulating hormone secreting pituitary adenoma*** was noticed and that made us scope the need to view the ovary as a part of the hypothalamic-pituitary-gonadal-axis not as an isolated organ ***(Roberts et al., 2005).***

The recent identification of the ***follicle stimulating hormone receptor (FSH-R) gene mutation*** is considered as another risk factor which causes ***familial gestational spontaneous ovarian hyperstimulation syndrome (FGSOHS)*** what was attributed in the past under the topic of unknown etiology ***(Meduri et al., 2008)***.

II- Iatrogenic ovarian hyperstimulation syndrome (OHSS):

Among the risk factors for iatrogenic ovarian hyperstimulation syndrome:

١-Age:

It is commonly observed that women suffering from OHSS are significantly younger ***(Rizk, 2006).*** It was noted that young women (<٣٥ years) were included in the high risk group while older women (>٣٥ years) were included in the low risk group ***(Levine & Navot, 2009).*** Possible explanations are that the ovaries of younger women have a higher density of gonadotropin receptors making them more responsive to gonadotropins, or that they have a larger number of follicles that are able to respond to gonadotropin ***(Delvigne & Rozenberg, 2002).***

٢-Body mass index (BMI):

It was found that patients with OHSS had a significantly lower mean body weight than did a control population **(*Navot et al., 1988)***. However, later it has been concluded that BMI or total body weight does not influence markedly the response to COH ***(Delvigne et al., 1993)***. There is still controversy about the inclusion of a low BMI (Asthenic habitus) in the list of variables influencing the incidence of OHSS ***(Budev et al., 2005)***.

٣-Allergy:

In a previous study, it was found that patients with OHSS had an increased prevalence of atopy (٥٦٪ versus ٢١٪). This hypothesized that general immunological mechanisms may have a role in the development of an inflammatory response in other non-allergy induced situations and that differences in the immunologic sensitivity of patients may be a predictive sign of OHSS ***(Enskog et al., 1999).***

٤-Polycystic ovary syndrome (PCOS):

PCOS is a common endocrinepathy that is associated with menstrual abnormality, such as oligo-ovulation and clinical or biochemical markers of hyper-androgenism. This syndrome is associated with a variety of metabolic abnormalities, such as insulin resistance and lipid disorders ***(Falcone et al., 1990).*** It is believed to be a risk factor in patients with OHSS ***(Delvigne & Rozenberg, 2002; Vloeberghs et al., 2009)***.

٥- Increased number of developing follicles:

The risk of OHSS also rises with the increase in the number of medium-sized developing ovarian follicles (≥١٠ follicles of ٤–١٠ mm in each ovary) (***Vloeberghs et al.,*** ٢٠٠٩) and the number of oocytes (>١٤) retrieved during ART ***(Avecillas et al., 2004).***

٦- Serum estradiol level (E٢):

An increased risk of OHSS has been noted in women who experience a rapid rise in serum estradiol levels or in whom an estradiol concentration ≥ ٢٥٠٠ pg/mL is noted ***(The Practice Committee of the American Society for Reproductive Medicine, 2003&2004).***

٧-Basal serum anti-mullerian hormone (AMH):

Although monitoring the serum E٢ level has been effective in reducing the incidence of OHSS ***(Varma & Patel, 1988; Golan et al., 1989),*** but the relevance of it's use during COS to predict the occurrence of OHSS has been challenged ***(Aboulghar, 2003; Orvieto, 2003).*** As both the serum E٢ level and number of follicles are determined near the completion of COS ***(Lee et al., 2008).***

Also it is not particularly easy to accurately predict OHSS prior to COS for IVF cycles using only age and BMI. So if a reliable marker could be identified in individual's prior menstrual cycles (basal serum hormone level), mild patient friendly protocols for COS that are less aggressive than the present standard long protocol could be utilized to prevent the detrimental effects of OHSS ***(Lee et al., 2008).***

Serum levels of AMH have been reported to be closely related to the ovarian response or ovarian reserve during IVF cycles ***(Penarrubia et al., 2005; Ficicioglu et al., 2006).***

OHSS has been reported to be associated with high serum levels of AMH prior to COS ***(Nakhuda et al., 2006),*** with cut-off value ٣،٣٦ ng\ml ***(Lee et al., 2008).***

٨-***Higher or repeated doses of exogenous human chorionic gonadotropin (hCG):***

It is clear that the incidence of OHSS is related to the stimulation regimen used to stimulate ovulation. Clomiphene citrate is rarely associated with the severe form of OHSS, although a more moderate form can be encountered in about ٨٪ of cycles (Kistner, ١٩٦٥).

A meta-analysis demonstrated no difference in the occurrence of OHSS with the use of urinary-derived gonadotropins or recombinant gonadotropins ***(Van-wely et al., 2003).***

The risk of OHSS is increased significantly with the use of hCG or higher and repeated doses of hCG to induce superovulation and with ART cycles for luteal phase support ***(Avecillas et al., 2004).***

٩-Pregnancy:

Pregnancy not only increases the likelihood of OHSS but also prolongs the duration and severity of OHSS symptoms due to the endogenous hCG ***(Budev et al.,*** ٢٠٠٥).

١٠-Blood group:

No association between ABO blood groups and infertility ***(Solish & Gershowitz, 1969)***. It was thought that there was no association between OHSS and ABO blood groups, but during an evaluation of the clinical course and various blood parameters in OHSS patients, there was an unusual large fraction of patients with blood group A. This observation prompted the investigators to retrospectively investigate the distribution of ABO blood group antigens among OHSS patients, and they found that blood group A was markedly more frequent and blood group O was less frequent in patients OHSS compared to the blood group distribution in all control. This possible association may be considered for an individualized hormone dosing in COH ***(Binder et al., 2008).***

١١-Vascular endothelial growth factor (VEGF):

In a study that compared the free serum VEGF levels in ١٠ patients who developed severe OHSS and ١٥ control patients who did not develop OHSS. A positive predictive value of ٧٥٪ and negative predictive value of ٩٢٪ was

obtained, using a cut-off value of ٢٠٠ pg/ml on the day of hCG administration ***(Ludwig et al., 1999)***.

Several studies reported that serum VEGF was significantly higher in the group that developed severe OHSS compared with that in those who did not ***(Krasnow et al., 1996; Abramov et al., 1997; Levin et al., 1998; Aboulghar et al., 1999).*** Therefore, serum VEGF was proposed to be useful for predicting the risk of OHSS.

The European Society of Human Reproduction, summarized and categorized risk factors for OHSS into primary and secondary risk factors;

A- Primary risk factors: *Before controlled ovarian hyperstimulation (COH);*

١- ***Polycystic ovarian syndrome (PCOS):*** This syndrome appears to be the major predisposing factor for OHSS in a large number of studies.

٢- ***Incomplete forms of PCOS:*** A higher incidence is also observed in patients who suffer from certain isolated characteristics of PCOS, but not from a complete form that fulfils all the clinical, ultrasound and biological criteria.

٣- ***A high number of resting follicles****:* ≥ ١٠ follicles of ٤-١٠ mm in each ovary.

٤- ***A luteinising hormone - follicle-stimulating hormone (LH - FSH) ratio:*** >٢.

٥- ***Hyper-androgenism.***

٦- *Previous history of OHSS.*

٧- *Age**.

٨- *Low body weight**.

٩- *Allergies**.

B- Secondary risk factors: *During controlled ovarian hyperstimulation (COH);*

١-*Serum estradiol value : >٣٠٠٠ pg/ml - ٤٠٠٠ pg/ml*

However, there is no clear cut-off value as serum estradiol levels have a poor predictive value (٨٪-٧٣٪). Since the syndrome can also develop in the presence of low serum estradiol levels, it appears that the slope of the estradiol rise is the main risk factor and more important than the maximum serum estradiol value.

٢- ***Follicle numbers:*** >٢٠-٢٥ in both ovaries.

٣- ***Other predictors not used routinely:*** Vascular endothelial growth factor (VEGF) of >٢٠٠ pg/ml ***(European Society of Human Reproduction (ESHRE), 2005).***

* The scientific evidence to confirm these factors is weak