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Review Article

Ovarian Hyper Stimulation Syndrome - Challenges, Updates and Review of Current Management

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Abstract

Ovarian hyper stimulation syndrome is an important iatrogenic complication of ovulation induction in assisted reproduction technology based on the subsequent enlarged ovarian and other endothelial surfaces, fluid shift from the intravascular space to the extravascular space (abdomen, pleura, pericardium), hemoconcentration, decreased renal clearance, oliguria/anuria, hyper viscosity of blood, modification in coagulation factors and thrombo-embolic risks. The incidence of Ovarian hyperstimulation syndrome is unknown globally based on multiple factors. It varies between units, treatments, patient groups and in countries due to the non-uniform systematic registrations. Ovarian hyperstimulation syndrome is classified from mild, moderate and severe depending on the presentation. Majority of cases of severe OHSS are sequel to *In-vitro* fertilization treatment though it can also occur after any form of supraphysiological ovarian stimulation such as gonadotrophin ovulation induction and clomiphene administration. Occurrence of OHSS is dependent on administration of human chorionic gonadotrophin (hCG). Other analogs of β-hCG, sex hormones (estrogen, estradiol), prostaglandins, prolactins, histamines, molecules of the renin- angiotensin system and vascular endothelial growth factor have been implicated to play an important role in pathophysiology of OHSS. Other factors of reference in OHSS pathology are inflammatory mediators such as cytokines and interleukins. Interleukin 6 has been noted to be associated with elevated estradiol concentration, hemoconcentration, increased vascular permeability and hepatic albumin inhibition production. The diagnosis of OHSS hinge on clinical history, examination, and investigation. It is mindful to note that unusual presentation OHSS can occur cases of respiratory disorder was noted with shortness of breath as the primary symptom. The management care plan of OHSS is important and need be known not only by medical personnel in the Reproductive medicine and infertility units but also front-line medical personnel in accident and emergency, Obstetrics and Gynecological units, general medical practice units to mention but a few.

Prevention of OHSS is an important component of management of Infertility which the clinician must be aware of and take into consideration. OHSS can be prevented by identifying the risk factors and institute management accordingly. Prevention are categorized into primary and secondary.

Treatment modalities involve maintaining diuresis, plasma expanders, fluid managements, albumin administration, ascites drainage, and use of anticoagulant.

Keywords: *Ovarian Hyperstimulation Syndrome; Assisted Reproductive Technology; Risk Factors; Diagnosis; Prevention; Management*

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) incidence has been on the increase over the last decades this could be attributed to the

advent of assisted reproductive technology and the use of various infertility treatments. It is a familiar syndrome to the clinicians in fertility and reproductive endocrinology units.

The Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of the luteal phase or/and early pregnancy after ovulation induction (provoking ovulation in anovulatory women) or of ovarian stimulation (in the context of intrauterine insemination or *in vitro* fertilisation) [1]. The clinical presentation of OHSS tends to be unfamiliar in some situation most especially to hospital staff since assisted reproductive treatment often occur in units outside the hospitals where uncommon severity of OHSS is seen. It is a threat to any patient undergoing fertility treatment and a potential cause of death though rare.

Several researchers have studied the clinical features of the syndrome and assessed pregnancy rates associated with the condition. The clinical pregnancy rate of IVF patients with severe OHSS was significantly higher than patients without the syndrome, with resultant longer hospital stay and higher abortions frequency with negative impact on the mother and developing pregnancy [2].

Key Content

- Assisted Reproductive Technology and it correlates with Ovarian Hyperstimulation Syndrome.
- The risk factors and diagnosis of Ovarian Hyperstimulation Syndrome.
- Prevention modalities of Ovarian Hyperstimulation Syndrome with pros and cons.
- Current management of Ovarian Hyperstimulation Syndrome with dynamics of severities of the complications.

Learning Objectives

- To understand the impact of OHSS on fertility treatment modalities.
- To understand the pathophysiology of OHSS and theories propounded.
- To understand the management protocols on the treatment of OHSS.

Ethical Issues

- Mis-diagnosis of Ovarian Hyperstimulation syndrome
- Should all medical staff outside fertility units be trained in the management?
- Financial and emotional implication of the complication on the couple
- Medicolegal implication on fertility treatment.

Incidence/etiology/risk factor

The exact incidence of OHSS worldwide is unknown however it varies from units to units and countries based on the non-uniform systematic registrations. The incidence of OHSS varies between treatments, patient groups and accurate estimates from the literature are difficult owing to the variety of classification schemes used historically. Most cases of severe OHSS are seen following IVF treatment but the syndrome can occur after any form of supraphysiological ovarian stimulation, including clomifene and gonadotrophin ovulation induction. Mild forms of OHSS is common constituting about 33% of IVF Cycle [3]. These forms are clinically assumed to be not significant in comparison to severe OHSS, however a mild form can become severe if not managed effectively. Moderate to severe OHSS incidence in IVF cycles has been reported in range of 3.1 - 8.0% and can be as high as 20% in high risk [3,4]. OHSS incidence is noted to be increased in young women, women with polycystic ovaries and in cycles where conception occurs, particularly multiple pregnancies [5].

Etiologically OHSS is a systemic disease sequel to hyper stimulated ovaries leading to release of vasoactive products. Its occurrence is dependence of the administration of HCG Human chorionic gonadotropins. Associated risks factors for development of OHSS have been identified and are classified as Primary and Secondary risk factors [6].

Primary risk factors

- Polycystic ovarian syndrome (PCOS)
- Patients with some characteristics of PCOS:
- High number of follicles in both ovaries at the quiescent state before stimulation (≥ 10 follicles of 4 - 10 mm in each ovary).
- LH/FSH ratio >2.
- Hyperandrogenism
- History of OHSS
- Young patients
- Lean women
- Allergic predisposition

Secondary risk factors

- Maximum serum estradiol > 3000 - 4000 pg/ml.
- No clear cut-off value
- Relatively poor predictive power (max. 73%).
- Oestradiol itself is no mediator since OHSS is also possible with low serum oestradiol values (stimulation with recFSH)
- The slope of the oestradiol rise is the main risk factor and is of more importance than the maximum level (PPV 77%).
- Number of follicles per ovary > 20 - 25.
- No clear cut-off value (10 - 35).
- Variation dependent upon operator and technique.
- Measurements of the absolute VEGF (vascular endothelial growth factor)- serum concentration are not useful for individual prediction [7].

In view of further assessment of patients for predictive risk of OHSS, a risk scoring system was developed by Shield., *et al*. using the coefficients from Poisson regression to aid patient's identification at high risk for developing OHSS. Risk factors with an increased risk of developing OHSS were younger age, higher oestradiol (E2) concentration (relative risk (RR) 1.43, $P < 0.001$), and higher follicle count (RR 1.40, $P < 0.001$). Lower body mass index (BMI) was not correlated with an increased risk of developing OHSS (RR 1.1, $P = 0.19$). Using this risk score could help clinicians reduce the incidence of OHSS by employing preventative strategies in high-risk patients [8].

Pathophysiology

The exact pathophysiology of OHSS is not fully explicit however with increasing research it is now better understood and different postulation propounded, increased vascular permeability and ovarian neo-angiogenesis has been postulated as one of the mechanism of pathophysiology of the cascade of the OHSS consisting of: neo-angiogenesis and increased capillary permeability of the enlarged ovarian and other endothelial surfaces, fluid shift from the intravascular space to the extravascular space (abdomen, pleura, pericardium), hemoconcentration, decreased renal clearance, oliguria/anuria, hyperviscositity of blood, modification in coagulation factors and thrombo-embolic risks. Hemoconcentration leads to an increase of the hematocrit, the concentration of platelets and leucocytes, creatinine, urea and liver enzymes in the plasma, as well as to hyperkalaemia and acidosis. Serum albumin decreases as a result of extravasation of fluid and ascites formation. The process is self-limiting as the HCG-effect decreases unless fetal HCG starts to be secreted [6].

The importance of the molecules of the renin- angiotensin system and vascular endothelial growth factor playing an important role in OHSS pathophysiology has been observed and implicated. The renin-angiotensin system regulate fluid balance and thereby noted to be a major contributor to the features of OHSS. Using monoclonal antibodies for comparative analysis of follicular fluid (FF) from IVF patients, Derck., *et al*. in 1987 found 40 times higher prorenin levels in plasma and 10 times higher renin levels in patients stimulated with human menopausal/human chorionic gonadotropin in comparism to unstimulated controls [9]. In the same light, elevated FF levels of renin, angiotensin II, and angiotensin III by Lightman., *et al*. was observed from stimulated compared to unstimulated controls [10].

In view of other possible mechanism of OHSS attention has been focused on relationship between OHSS and VEGF. Follicular fluids have been found to have high concentration of VEGF conforming to the possible role of ovarian VEGF in the development of OHSS. Vascular endothelial growth factor is a vasoactive glycoprotein (cytokine) which stimulates endothelial cell proliferation, cell permeability and angiogenesis.11 VEGF mRNA has been found to be expressed in granulosa cell culture [11].

Furthermore, VEGF levels have been shown to increase in response to the administration of luteinizing hormone (LH), follicle stimulating hormone (FSH) and hCG in granulosa cell culture [11]. VEGF concentrations was increased in serum and plasma concentrations in conjunction with ascitic fluid in OHSS patients [12-14]. The critical role of VEGF in OHSS development was further emphasised by Neulen., *et al*. in 1995 and 1998 by mRNA expression of VEGF in human luteinized granulosa cells which was time- and dose dependent of HCG [15,16]. Two VEGF-receptors exist (VEGFR-1 en VEGFR-2), both produced by endothelial cells, of which one exists in a soluble form, s(serum)VEGFR-1, acting as a negative modulator of the bioactivity of VEGF [16]. Pellicer., *et al*. in their study noted that Excess of bioactive pro-angiogenic VEGF increases the risk for OHSS; excess of antiangiogenic sVEGFR-1 (and other anti-angiogenic factors) decreases the ovarian response and the risk for OHSS and is accompanied by a decreased pregnancy rate [17]. Likewise, Levin., *et al*. studied the relationship between OHSS and VEGF.

Follicular fluids of 80 women undergoing hormonal induction for fertility treatment were analyzed and splitted into four groups. FFs were grouped according to oocyte production, from group I (0 - 7 oocytes) through group IV (23 - 31 oocytes). Group IV was comprised of four women with the most severe symptoms of OHSS. Endothelial cell (EC) permeability induced by the individual FF was highly correlated to oocytes produced. Identification of mechanism of increased cell permeability was also explored with alteration of the mechanism and resultant decrease permeability observed [18]. The ability of VEGF to enact increased cell growth or other actions is felt to be mediated at least in part by the generation of Nitrous oxide [19]. To determine a possible role for NO in the action of FF, L-NMMA (monomethyl L-arginine) was added before FF or exogenous VEGF addition. The increased permeability stimulated by Nitric Oxide was reversed 52% by inhibition of NO synthase in group IV FF. Similarly, exogenous VEGF-stimulated permeability was reversed 47% by this inhibitor of NO production [19]. FF from women undergoing hormonal ovarian stimulation significantly increased endothelial cell permeability, which correlated with the magnitude of oocyte production (an important index of the degree of stimulation). The actin cytoskeleton and ZO-1 protein mechanism at the EC tights junctions were noted to play an important role in increased permeability, VEGF is the Follicular fluid factor responsible for increased EC permeability and therefore is the likely factor leading to the important manifestations of OHSS. Antagonise the VEGF synthesis will prevent development of the syndrome [18].

Other mechanism of development of OHSS has been subject of review and investigations from the role of estradiol, LH, HCG and inflammatory mediators.

Sex hormone levels have been associated with OHSS, resulting into research and subsequent assertion that increase in the concentration of estradiol caused the syndrome. Further research in the low and high level disputed the assumption. A case of a woman with [17,20] desmolase activity deficiency in which ovarian induction with FSH was instituted both therapeutically and diagnostically for the specificity of the enzymatic deficiency, with ovarian hyperstimulation occurring despite the low level [20]. Similarly, high levels of estradiol alone did not result in OHSS without collaborated HCG elevation [21]. Elevated estradiol level is still considered one of the best predictors of OHSS

occurrence, as at-risk women demonstrate rapidly rising serum estradiol levels, or high absolute (> 2,500 pg/mL) and emergency of large numbered intermediates sized follicles [22].

The role of human chorionic gonadotrophin (HCG) in the infertility treatment pathway has placed it in search light as a triggering hormone for the development of OHSS, however it is not a lone factor for the cause. hCG stimulate LH receptors in the ART cycles. HCG has biological activity about six to seven times higher than LH sequel to its longer half-life and receptor affinity [23]. In a retrospective analysis done with 109 pregnant patients with hCG > 150000 IU/L (max 344,350 IU/L) from 2001 - 2006, patients with excluding patients with gestational trophoblastic diseases, multiple pregnancies and iatrogenic OHSS excluded 27 patients remained. None of those patients experienced OHSS [24].

Other co factors in OHSS pathology comprise the inflammatory mediators such as cytokines and interleukins. Important to note that interleukin 6 was associated with elevated estradiol concentration, increased vascular permeability, hemoconcentration, and hepatic albumin inhibition production [25].

- Although the exact patho-physiology of this syndrome is not understood, it is postulated that OHSS is a sequel of ovarian neo-angiogenesis and increased vascular permeability (Figure 1).

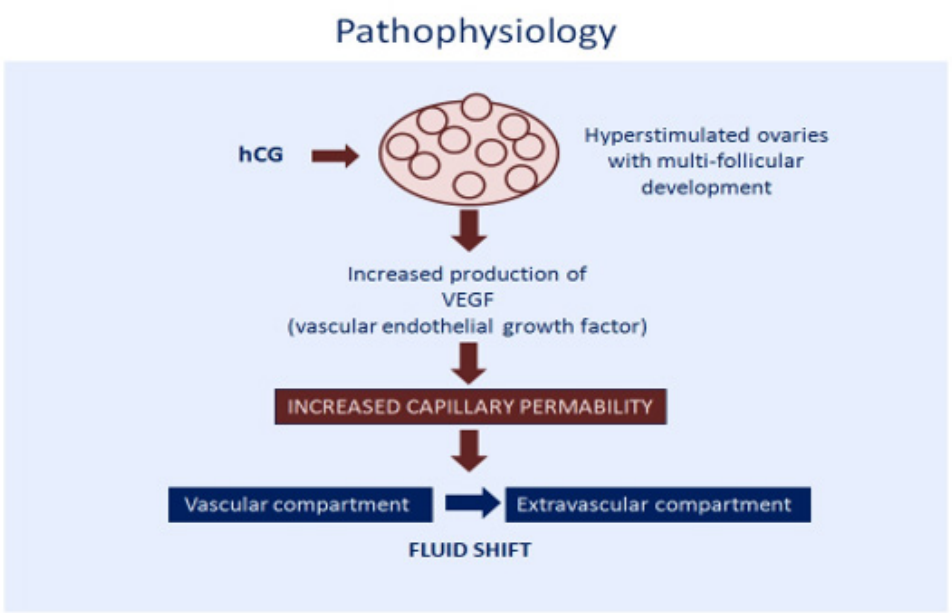

Figure 1: *Pathophysiology of OHSS. References: Bhutani R. Ovarian Hyperstimulation Syndrome (OHSS): A Radiologically Less Known Complication of Hormonal Therapy in Female Infertility. RSNA_2012. LL-OBE2237.*

- Vascular endothelial growth factor (VEGF) is thought to have a major role in the pathogenesis of OHSS. VEGF is a heparin-binding glycoprotein with vascular permeability-enhancing and angiogenic, properties.
- VEGF increases the vascular permeability, which is responsible for the development of ascites, pleural effusions, oedema, and haemoconcentration (Figure 2). VEGF levels have been seen to correlate with severity of OHSS.

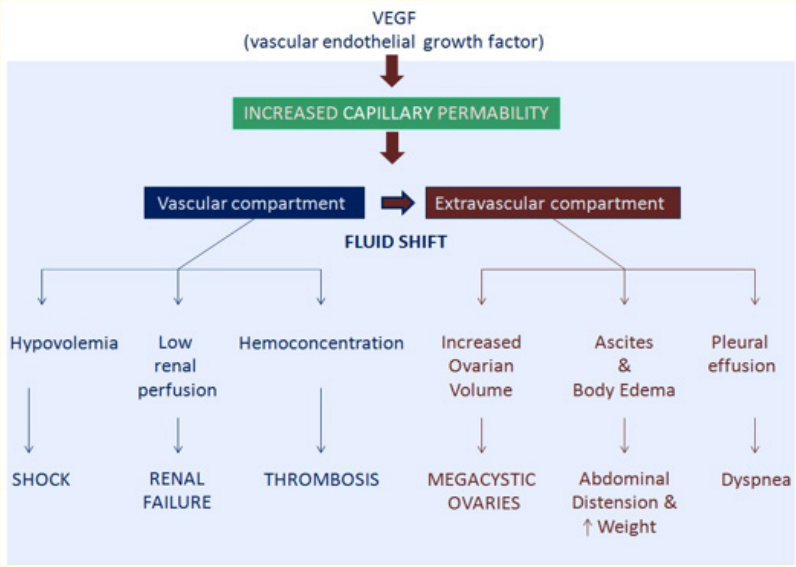

Figure 2: *Pathophysiology of OHSS. References: Bhutani R. Ovarian Hyperstimulation Syndrome (OHSS): A Radiologically Less Known Complication of Hormonal Therapy in Female Infertility. RSNA_2012. LL-OBE2237.*

Classification

Classification of severity of OHSS has undergone review in the last couple of years from 2 to 6 grades in some school of thoughts to the current classification of Mild, Moderate, Severe and Critical for simplicity and unification. Outline below is the classification as suggested by Mathur in 2005 and adopted by the Royal College of Obstetricians and Gynecologists. This has enhanced management of patients accordingly.

Grade	Symptom
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*
Severe OHSS	Clinical ascites (occasionally hydrothorax)
	Oliguria
	Hemoconcentration hematocrit > 45%
	Hypoproteinemia
	Ovarian size usually > 12 cm*
Critical OHSS	Tense ascites or large hydrothorax
	Hematocrit > 55%

	White cell count > 25000/ml
	Oligo/anuria
	Thromboembolism
	Acute respiratory distress syndrome

Table 1: *Classification of severity of OHSS grade symptoms.*

**Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.*

Prognosis of OHSS has been attributed to a lot of factors however division into 'early' and 'late', depending on the time of onset, may be useful. Study carried out by Dahl Lyons., *et al*. "Early" OHSS presented 3 - 7 days after the ovulatory dose of hCG and appeared to relate to the magnitude of the preceding ovarian response, whereas "late" OHSS was identified 12 - 17 days after the ovulatory dose of hCG in women with multiple gestations [27]. Study carried out by Mathus., *et al*. showed early OHSS relates to ovarian sensitivity and the magnitude of preovulatory ovarian response to stimulation. Late OHSS is only poorly related to the ovarian response; it may relate instead to the magnitude of endogenous hCG stimulation from implanting gestation(s). Late OHSS is more likely to be severe than the early form [28].

Diagnosis - Signs and symptom, investigation

Diagnosis of OHSS is clinical following the basic history taking format in medicine history of fertility treatment with administration of human chorionic gonadotrophins or in some situation fertility antiestrogens in conjunction with classical characteristics of symptoms. OHSS has presented in uncommon ways such as a respiratory disorder initially in form of shortness of breath. Other differential diagnoses should be taken into consideration such as ectopic pregnancy, ovarian torsion, ovarian cyst rupture, acute appendicitis, pelvic infection and intra-abdominal haemorrhage.

Classical symptoms and sign of OHSS varies from mild, moderate and severity symptoms which are outline below.

Most Common symptoms and signs

- Nausea, with or without vomiting - Reducing and preventing intake of fluids and food
- Dyspnoea and Respiratory distress secondary to elevated diaphragm and hydrothorax
- Mild abdominal pain, Moderate abdominal pain -
- Abdominal bloating with Progressive increase in abdominal circumference measured at the level Umbilicus
- Ovarian enlargement up to > 12cm
- Rapid weight gain
- Reduced urinary output. Signs are oliguria, ascites.

Severe symptoms and signs

- Pleural effusion (more and more frequently at the right side)
- Adult Respiratory distress syndrome
- Ascites
- Hypotension

- Oliguria/anuria
- Multiple organ failure
- Death (1/500.000 cycles) [29].

Investigation

- FBC - Prominent evaluation Hemoconcentration (haematocrit > 45%),
- WBC - Leucocytosis >15.000/mm3, White cell count > 25 000/ml in critical OHSS
- U&E - Hyponatriemia 5.0 mEq/l
- Creatinine- Creatinine clearance 1.2 mg/dl
- Liver Function Test - Elevated liver enzymes, Hypoproteinemia and hypoalbuminemia
- Clotting profiles - Hypercoagulability.
- Chest x- ray - Indicate in cases of prominent respiratory symptoms
- Ultrasound Scan - Indicated in cases of prominent respiratory and abdominal symptoms
- ECG - Indicated in cases of prominent respiratory symptoms
- Echocardiogram - Indicated in cases of prominent respiratory symptoms
- Hypovolemia.

Prevention

Prevention of OHSS is an important component of management of Infertility which the clinician must be aware of and take into consideration. OHSS can be prevented by identifying the risk factors and promptly treating them. Prevention of OHSS can be divided into two namely primary and secondary prevention.

Primary prevention

The prevention of OHSS start from the onset of management of Infertility and planning of ART Cycle. However, there is no perfect method that can eliminate it completely. Baseline treatment such as modification of lifestyle with diet, exercise, managements of PCOS, thrombophilia, family history of thrombo-embolism and antiphospholipid antibodies syndrome. Preliminary administration of Oral ovulation induction, pulsed dose GnRH, laparoscopic ovarian surgery and low dose human Chorionic gonadotropin can be instituted with monitoring.

Stimulation protocol

Careful stimulation of the adequate oocytes without development of the OHSS is the hallmark. This could be achieved by starting with low dose of gonadotropins not exceeding 150 IU/L [30] and gradually reducing the dose with the step down protocol without affecting the pregnancy rates and comparable with those reported for step-up regimens, with a low incidence of complications (i.e. multiple gestation and ovarian hyperstimulation) was noted [31]. Other approach which currently advocated is the “step up” regime in which low dose of FSH (i.e. 75 IU) is used to initiate ovarian stimulation and increased gradually every 7 days (i.e. 37.5 IU) until an ovarian response as evidence by follicle >10 mm and continued till ovarian trigger criteria are met [32,33]. Suffice to note that this regimen was associated with lower risk of OHSS, cycle cancellation, higher rate of unifollicular development in comparison to step down protocol. Although the duration of stimulation is longer, the rate of ovarian hyperstimulation is much lower using the step-up protocol [34]. High dose of hCG has been associated with OHSS [35]. Administration of GnRH agonist is associated with higher incidence of OHSS probably due to major follicular recruitment [36]. Research by Al showed a marked reduction in incidence of OHSS when the GnRH antagonist protocol was used

[37] likewise Luwig., *et al*. also showed a reduction in OHSS incidence on the use of Centrorelix [38]. The use of other adjuvant therapy regimen such as Metformin, Aromatase inhibitors, avoidance of hCG for luteal phase support and individualising IVF treatment regimen have been tried. Tso., *et al*. Cochrane review of 798 women in 8 RCT noted lower risk of OHSS with the use of metformin (OR 0.29; 95% CI 0.18 - 0.49), increased pregnancy (Clinical) rate (OR 1.52; 95%CI 1.07 - 2.15) and 63% reduced rate of OHSS [39].

Close monitoring

Parameters for monitoring OHSS include estradiol levels and Ultrasound. However, research into the use of Anti-Mullerian Hormone has been promising. Estradiol monitoring has been effective in reduction of OHSS incidence, this is collaborated in the retrospective study of D'Angelo., *et al*. in which day 11 estradiol level was 3.354 pg/ml after ovarian stimulation with a sensitivity and specificity of 85% for detection risk of OHSS [40]. Anti-Mullerian hormone is another marker that has been increasingly used. Gnoth., *et al*. demonstrated AMH (AMH ≤ 0.18 pmol/L (1.26 mg/mL) identifying normal responders (≥ 4 oocytes retrieved) to controlled ovarian stimulation with 98% success rate in a prospective study of 316 women [41]. This predictive capacity extends to identifying women at risk of developing OHSS [42]. AMH in further research has been known to performed better than weight, age, or ovarian markers in identifying these women [43]. In view of the low inter and intracycle variability, AMH is a promising excellent predictive biomarker of ovarian function that required international standardization and resolution of validity [44].

Ultrasonographic monitoring of Ovarian follicle is an important tool in the prediction of OHSS, study by Kahnberg., *et al*. showed follicle size (medium/large) as an independent predictor of OHSS prior to administration of hCG with a sensitivity of 82.1% and specificity of 79.4% [45]. Comparative analysis of predictive response basal serum AMH and antra follicle count on excessive controlled ovarian stimulation and Ovarian hyperstimulation syndrome shows equal predictive potential of antra follicle count [46-48]. Further, prospective study of 1012 women by Jayaprakasan., *et al*. showed the risk of moderate to severe OHSS is 2.2% with AFC ≤ 24 and increases to 8.6% with AFC ≥ 24 [49].

Secondary prevention

This is the intervention strategies to prevent progression of OHSS once the ovarian stimulation has been initiated and exaggerated effect mounted. Current strategies comprise, coasting cryopreservation, cycle cancellation.

Coasting is a preventive strategy that involves temporarily withdrawing the gonadotrophins administration when a critical number of follicles or certain level of estradiol concentration are reached. The Estradiol level is monitored and when it is significantly decrease or plateau at a certain administration of the hCG is instituted once a safe level of E2 is attained. Subsequently Ooctye retrieval and embryo transfer and freezing are done in conjunction with the E2 concentration. This process is done less than 3 days period, [50,51]. however, some authors advocate up to 4 days without compromising IVF outcome [52,53]. Coasting reduces the granulosa cells available for luteinization [54] with resultant atresia of small follicles, however allowing maturation of larger follicles with risk reduction of OHSS [36]. Some authors have varied opinion when coasting should be commencing however Delvinge., *et al*. recommend dominant follicle ≥ 16 mm with estradiol levels > 4500 pg/ml, though no literature consensus (range of 3000 to 6000 pg/ml is advocated) [51]. Cochrane review of 4 RCTs by D'Angelo., *et al*. highlighted no difference in the incidence of moderate to severe OHSS (OR 0.53, 95% CI 0.23 - 1.23). Likewise, significant reduced oocyte were retrieved from the coasting group leading to recommendation that there was no benefit in coasting compared to other interventions [55]. However, it is the first line of secondary prevention while coasting does not avoid totally the risk of OHSS, it decreases its incidence in high-risk patients. Many questions remain unanswered about how coasting should be managed, and we suggest that a randomized prospective multicenter study is required [51].

Cryopreservation of embryo involves controlled ovarian stimulation with subsequent oocyte retrieval followed by cryopreservation. The embryos are now transferred in unstimulated IVF cycle where the woman's ovarian's response to hCG has normalized [56]. Devroy., *et al*. illustrated in their OHSS free Clinic that the use of GnRHa trigger followed by cryopreservation is the most effective method in

preventing OHSS [57]. Controversies do surround the pregnancy rate of cryopreservation in relation to fresh embryo transfer previously lower pregnancy rate due to older freezing methods was noted [58]. Cryopreservation has been noted to increase fertility preservation potentials, decrease obstetrics and perinatal morbidity, and overall better pregnancy rate than fresh embryo transfer [58-61]. In view of the positive findings vitrification is the modern technique been used with convincing evidence to suggest that cryopreservation *et al*. recommend the use of a GnRHa trigger followed by cryopreservation for averting OHSS [42].

Cycle cancellation

Definitive prevention of OHSS is by cycle cancellation but this is a strategy that is use as a last resort by clinicians. The emotional, psychological stress and high financial implication to women play a vital role in the management [50].

Other methods of prevention

IV Albumin: The administration of IV Albumin as prophylaxis for prevention of OHSS has been evaluated with borderline statistically lower incidence of severe OHSS with albumin utilization according to Cochrane review by Youssef., *et al*. with marked heterogeneity in the 8 RCTs (OR 0.67;95% CI 0.45 - 0.99; I^2 = 62%) [62]. Other researchers have different opinion on the effectiveness, Venetis., *et al*. in there systemic review showed lack of prevention against severe OHSS as well (OR 0.80; 95% CI 0.52 - 1.22), [63] likewise Jee BC., *et al*. in their meta-analysis do not support a benefit for IV albumin around the time of oocyte retrieval in preventing OHSS and even showed a deleterious effect on the pregnancy rate [64]. Further the risks of transmission of viruses, prions, or Creutzfield-Jacob disease should not be overlooked by any theoretical benefit.

Hydroxyethyl Starch (HES) Use of non-biological product such as HES which is a plasma expander has received wide attention in view of the side effects of albumin. Youssef., *et al*. in 3 RCTs showed statistically significant decrease in severe OHSS with administration of HES (OR 0.12, 95% CI 0.04 - 0.40) with no adverse effect on pregnancy [62]. In view of the cheaper cost and better safety in comparison to albumin it is been touted by some authors to be the first line management. Further clinical research is still required prior to recommending it for routine use.

Dopamine antagonist: The antiangiogenic mechanism of dopamine antagonist (Cabergoline) in preventing excessive increase in VEGF mediated vascular permeability in OHSS has been studied with positive feedback. Systemic review by Leitao., *et al*. with 7 RCTs showed the efficacy of Cabergoline in preventing moderate/severe OHSS (RR 0.38,95% CI 0.29 - 0.51, 7 studies, 858 women) without adverse effect on the clinical pregnancy or oocytes retrieved (RR 1.02, 95% CI 0.78 - 1.34, 4 studies 561 women, MD 1.15,95%CI -0.76 to 3.07 5 studies 628 women) [65]. In the same view Cochrane review by Tang., *et al*. of 230 women in 2 RCTs found Cabergoline to be effective in reducing significantly the incidence of moderate OHSS (OR 0.38: 95% CI 0.19 - 0.78) with no significant effect on clinical pregnancy rate (OR 0.94 95% CI 0.56 to 1.59; 2RCTs 230 women), miscarriage rate (OR 0.31, 95% CI 0.03 - 3.07; 1RCT 163 women) or any other adverse effect of treatment (OR 2.07, 95% CI 0.56 - 7.70; 1RCT, 67 women) [66]. Based on this finding cabergoline is recommended with commencement of treatment on hCG trigger for 8 days at a dose of 0.5 mg [67].

Relcovaptan: (Vasopressin Induced VEGF Secretion Blockade) this is one of the latest research therapies that is under review in prevention of OHSS based on its ability to inhibit VEGF by vasoconstriction modulation and vascular smooth muscle proliferation. It is a vasopressin Via receptor antagonist which led to lower concentration of VEGF-A in the peritoneal fluid and lesser ovarian weight gain with significant decrease in the number of corpora lutea in comparison to control group in hyper stimulated rat model [68].

Current management

Management of OHSS are cleared divided into Mild/ Moderate cases and Severe/Critical cases management. The mode of management differs in relation to admission criteria.

Management of mild/moderate OHSS

- Most of the cases are managed as outpatients but will need admission if condition deteriorate
- Drinking to thirst, maintaining daily fluid balance
- Daily Weighing
- Analgesia - Pain relief using paracetamol.

Management of severe/critical OHSS1

Clinical management

Criteria for hospitalisation

- Hematocrit > 45%
- Any sign of severe OHSS.

Elements of outpatient follow-up

- Daily fluid balance
- Daily weighing
- Increase in umbilical abdominal circumference
- Instruction to contact the centre at any sign of deterioration
- Outpatient follow-up every 48-72 hours with blood tests and ultrasound examination.

Elements of hospital follow-up

- Heartrate
- Blood pressure
- Daily fluid balance
- Echografic assessment: Ascites volume, ovarian dimensions
- RX thorax (if dyspnoeic) to diagnose pleural effusion
- ECG (to exclude pericardiac effusion)
- Hematological examination: hematocrit, RBC count, WBC count, electrolytes, kidney function tests, liver enzymes, total serum protein and albumin, coagulation tests.

Treatment strategy

Maintain diuresis!

Fluid management

- Intravenous administration of Ringer lactate solution
- First 24 hours: 1500 - 3000 ml. In order to avoid over administration of fluid, some centres restrict total fluid intake (inclusive oral) to 1500 ml.
- Subsequent days: fluid volume in function of fluid balance
- Combination of Ringer lactate + Dextrose 5% solution or NaCl 0.9% + Dextrose 5% (standard) solution.

Plasma expanders

- HEAS (hydroxyethyl starch) 6% solution in isotonic NaCl.
- Maximal daily dose: 33 ml/kg in 250 - 500 ml per day, dropwise, utilising slow administration to avoid lung congestion.

Albumin administration

- Is only started if hypo-albuminemia (< 28 mg/dl is demonstrated because of the risk for hepatitis, over dosage with albumin, renal function disorders and high cost should definitely be started when ascitic fluid is punctured because this causes huge loss of protein.

Anticoagulant drugs

Low molecular weight heparin preparations are preferable given primarily in all cases of severe OHSS with hospitalisation but certainly if:

- Clinical signs of thrombo-embolic complication
- Documented thrombophilia
- History of hypercoagulability or thrombo-embolism
- Uncorrected haemo-concentration after 48hr of usual intravenous treatment.

As a prevention of thrombo-embolic complications especially in patients who are immobilised due to obesity or other reason, low dose aspirin administration has been suggested. When ascites puncture is performed this has to be wiped against the risk of bleeding.

Ascites drainage

Can be performed both abdominally and vaginally but always under sonographic guidance [69,70]. It is considered when there is severe abdominal discomfort and dyspnea and results in quick subjective relief for the patient. It is also results in advanced venous return, increased cardiac output diuresis, creatinine clearance and lung ventilation. It should be performed gradually, maximally 4litres over 12 hours. Removal of large quantities means losing huge amount of protein which must be substituted. One litre of ascites contains 3.0 - 3.5g of albumin; daily administration of 30 - 35g of Albumin daily is recommended.

Case reports - Use of thawed in management of severe OHSS (Reported by Kamath MS)

27 year old female with history of primary infertility who underwent ART and developed features of severe OHSS (refractory case) - with prophylactic measures and early aggressive treatment with no improvement in clinical condition. She had rapid re-accumulation of ascitic fluid and had repeated paracentesis due to worsening symptoms to relieve her discomfort. In view of drop in serum albumin levels, intravenous albumin was given. However, after three doses, patient developed severe reaction to albumin, precluding its further usage. However, due to rapid collection of ascitic fluid and consequently abdominal paracentesis was done 6 times to ameliorate the symptoms.

This lead to further fall in albumin levels and with oral high protein intake proving to be highly inadequate, alternative means of albumin replacement became imperative. Hydroxy ethyl starch was considered as an alternative volume expander, but due to albumin levels falling below 2 g/L, finally thawed plasma was considered. Inputs from medical oncologists were taken on 20th day regarding usage of thawed plasma in such clinical conditions where rapid albumin replacement was required. It served the dual purpose of rapid albumin replacement and volume expander. We decided to use it after weighing its risks and benefits due to continued deterioration in the patient's condition and lack of viable alternatives to reverse the trend.

Patient was transfused four units of thawed plasma in 48h. The transfusion volume was calculated (10 - 15 mL/kilo body weight). This resulted in a dramatic improvement in the patient's condition as reflected by significant increase in urine output and stabilization of

abdominal girth (indicating no clinically significant re-accumulation of ascitic fluid). Most importantly her serum albumin level started rising (2.5 g/dL immediate post-transfusion). No further paracentesis was required, and patient was discharged day 26 post-retrieval [71].

Case report - Atypical case of preterm ovarian hyperstimulation syndrome (Reported by Dr Michelle a Durst)

Preterm ovarian hyperstimulation syndrome is a rare syndrome in which preterm infant girls have hypogastric, upper leg and labial swelling accompanied by elevated serum estradiol levels and ovarian follicular cysts on ultrasound. Our case is an infant born at 23 weeks gestational age who at 30 weeks postconceptional age (PCA) developed elevated 17-hydroxyprogesterone on her newborn screen with associated clitoromegaly and a ventral groove on the inferior aspect of the erectile tissue. An initial pelvic ultrasound at 32 weeks PCA demonstrated a normal appearing uterus, but the ovaries were not visualized. At 39 weeks PCA, follicular ovarian cysts were noted bilaterally (31 × 26 × 21 mm on left and 38 × 25 × 36 mm on right). Without treatment, estradiol and testosterone levels began normalizing by 42 weeks PCA. After this point, the right ovarian cysts had resolved, and the left ovarian cyst continued to diminish in size [72].

Furthermore research carried out by Gu-Feng Xu., *et al*. with an assessment of the intellectual ability of offspring of patients with OHSS using a cohort study comprising of 86 offspring of OHSS patient and 172 offspring of non-OHSS patients employing the Revised Chinese Version of the Weschsler Intelligence Scale for Children (C-WISC). Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full Intelligence Quotient (FIQ) it was shown that OHSS offspring displayed reduced intellectual ability with proposition that prenatal estradiol might be involved in the underlying mechanism [73].

Case report - Post laparoscopic massive vulva oedema in a woman with ovarian hyperstimulation syndrome (Reported by Drs Negjyp Sopa and Mette Toffager)

39-year-old female gravida 2 Para 0 presented for IVF treatment on account of previous salpingectomy on account of ectopic pregnancy with acute abdominal pain. She had standardized GnRH antagonist protocol 150 is of human menopausal gonadotrophin (hMG, Menopur®) daily for ten days. Choriogonadotropin (hCG Ovitrelle®) 6500 IU was administered for ovulation induction. Twenty-two oocytes were collected from 25 follicles. One blastocyst on day 5 was transferred with achievement of pregnancy. Vaginal progesterone tablets (Lutinus®) 100 mg three times daily for two weeks was administered for luteal support. Eighteen days post oocyte retrieval, she was admitted sequel to acute lower abdominal pain and symptoms of moderate ovarian hyperstimulation syndrome (OHSS) with a provisional diagnosis of Adnexal torsion with subsequent, emergency laparoscopy done that with unconfirmed adnexal torsion with pain attributed to OHSS. Massive vulva edema was developed gradually two days postoperatively. Investigation parameter of p-albumin showed significant decrease to a value of 18 g/L (normal range 36 - 48g/L) with resolution of the decrease value of p-albumin to within normal after administration of infusion of human albumin "CSL Behring" solution (20% 100 ml daily for one week). Vulva edema was completely resolved after one week and ultrasound scan showed singleton intrauterine pregnancy at seven weeks gestation.

The pathogenesis of post laparoscopic vulvar edema is still unclear. It was believed that the rapid decrease of p-albumin to levels significant below normal range has contributed to the development of the vulva edema, with diminished oncotic pressure. One could further speculate that placement of the laparoscopic ports may have create a fistula where ascites fluid is forced into the interstitial space of the vulva area. The patient was successfully treated with infusion of human albumin [74].

Case report - FSH-secreting pituitary adenoma: Do not miss this diagnosis in cases of spontaneous ovarian hyperstimulation syndrome! (Reported by Hortense Bosselut., *et al*.)

Spontaneous ovarian hyperstimulation syndrome is a complication that do occur in female of reproductive age however a diagnosis of etiological cause from gonadotropin producing pituitary adenoma is extremely rare. Hortense Bosselut., *et al*. reported an atypical case of a 25 year -old infertile woman with abdominal pains and menstrual disturbance. Further evaluation with transvaginal ultrasound scan

revealed an enlarged ovary with multiple cysts with a schedule operative laparoscopy for atypical bilateral ovarian tumours, however a hormonal analysis revealed normal serum FSH level with suppressed luteinizing hormone and elevated oestradiol and prolactin levels. Magnetic Resonance Imaging of the pituitary showed a macroadenoma extending to the right carvenous sinus. Sequel to the clinical scenario an emergency transsphenoidal pituitary surgery after a laparoscopic detorsion for a bilateral ovarian torsion. A mark resolution of the clinical condition was noted with normalizing of the ovarian size and all hormonal values. Regular menstrual cycle occurred and subsequent conception with delivery of a normal child by the patient. Timely diagnosis of Gonadotroph adenoma which can be achieved with high index of suspicion in patients with spontaneous OHSS by gynaecologist will prevent potential and unnecessary damaging pelvic surgical procedures [75]. It is imperative that different etiological causes of spontaneous OHSS must be evaluated in view of the few reported cases till date (32 cases).

Case report - Multiorgan failure associated with severe ovarian hyperstimulation syndrome due to inadequate protocol optimization: a rare but avoidable complication (Reported by Lorraine Sheena Kasaven., *et al.*)

Ovarian hyperstimulation syndrome is a preventable complication in ovarian stimulation but a proactive approach is necessary for effective prevention of the complication, however complication can also arise with different presentations. Lorreine Sheena Kasaven., *et al*. reported a Multiorgan failure that is associated with severe ovarian hyperstimulation sequel to inadequate protocol optimization. A case in study is 25 years old nulligravida with 4-year history of subfertility and multiple risk factors for development of OHSS underwent COS. However, sequel to the oocyte retrieval the patient developed symptoms of early -onset severe OHSS with precipitated multiple organ failure as the clinical condition of the patient deteriorate with involvement of the hepatic and renal dysfunction. The patient was transferred to a specialist tertiary liver centre for further treatment despite supportive management in the intensive care unit of the referring hospital [76]. A clinical lesson of note was learnt in this condition thereby reinforcing the need to follow protocols holistically.

Case report - Ovarian hyperstimulation syndrome leading to ventriculoperitoneal shunt malfunction (Reported by Amit Azriel., *et al.*)

OHSS complication should not be limited to the traditional areas that are known which warrant an eagle eye when evaluating the systems of the body, case report by Armit Azriel., *et al*. of an OHSS patient with ascites leading to malfunction of the ventriculoperitoneal shunt highlighted this fact. Shunt pressure is influenced by the pressure gradient between the ventricles and the peritoneal cavity, malfunction may be caused by elevation of the intra-abdominal pressure. Resolution of the complication (shunt dysfunction) was achieved by peritoneocentesis [77]. This clearly outline the importance of prompt management of abdominal etiologies of the ventriculoperitoneal shunt malfunction.

Case Report - An abnormal trend in hCG levels in a pregnancy complicated with Ovarian hyperstimulation syndrome (Reported by Ariel Benor., *et al.*)

The role of (hCG) as biomarker of early pregnancy based on its production from by the trophoblast cells of surrounding a growing embryo has been of utmost value in management of pregnancy. Serves as guide in giving an insight into the viability and health of pregnancy. The American College of Obstetricians and Gynaecologists expected a rise of 49% in 48hr for an initial value under 1500 mIU/ml [78]. Other researchers have proposed different rate, reference to Barnhart's., *et al*. an expected minimal rise of 53% should be seen in a viable intrauterine pregnancy.79 Levels below this value in practice is often extrapolated to extra-uterine or failing pregnancy with course of management altered. Study by Chung K., *et al*. should that the rate of rise of hCG in IVF pregnancies is like that in spontaneous conceptions [80].

Limited studies have been carried out to determine the standard rate of rise in OHSS patients. Ariel Benor., *et al*. presented a patient with OHSS post administration of gonadotropin ovarian stimulation and intrauterine insemination (IUI) late rate of hCG rise yet ultimately resulted in a viable pregnancy. 24-year-old presented with one-year history of primary infertility with associated diagnosis of

polycystic ovary syndrome. Had management commenced with clomiphene citrate with failed ovulation and further administration of gonadotrophin stimulation for ovulation induction.

During the treatment cycle she had a maximum estradiol level of 2176 pg/mL and had two follicles >16 mm noted on pelvic sonogram. Ovulation was triggered with 250 μg of recombinant hCG, and she underwent IUI 36 h later. Five days after insemination, she complained of nausea, anorexia, dyspnea, and bloating. On physical exam abdominal distention, tachypnea and a fluid wave were noted; on ultrasound, she was noted to have hyper-stimulated ovaries measuring 113 × 91 mm on the left and 87 × 95 mm on the right, in addition to pelvic ascites. Her lab values revealed evidence of hemoconcentration with a hematocrit of 45 mg/dL, hyponatremia with a sodium level of 132 mmol/L, and leukocytosis with a WBC of $19 \times 10^3/\mu L$.

Her hCG level of 62 mIU/mL rose over 48 h to 76 mIU/mL: a mere 23% increase, which is well below the expected rate for viability. Initially, she was managed conservatively with intravenous hydration and supportive care as she declined a culdocentesis for symptomatic relief. She was subsequently managed as an outpatient with clinical and laboratory assessment of her hypovolemia and hemoconcentration. While her symptoms of OHSS slowly resolved, her hCG levels continued to increase sub-optimally over the next 48h (by 29%, from 72 to 98 mIU/mL). While there was concern about a non-viable or ectopic pregnancy, the patient remained stable and was managed conservatively with observation. Her symptoms continued to improve, and hCG assessment six days later showed a reassuring increase to 665 mIU/mL, followed by 4476 mIU/mL seven days later. An ultrasound scan that day confirmed an intrauterine pregnancy, and 14 days later the patient had an hCG level > 40×10^3 mIU/mL and sonographic evidence of a normal-appearing eight-week intrauterine pregnancy with a well-formed fetus and a fetal heart rate of 165.

The fluid shift to the interstitium from intravascular compartment was most likely attributed to the suboptimal or abnormal hCG rise in an otherwise normal pregnancy. In OHSS, there is extravasation of fluid into tissue and cavities, causing intravascular hemoconcentration. This patient, for instance, had notable ascites and lab values demonstrating hemoconcentration. Subsequently, during the recovery phase, that extravascular fluid shifts back into the intravascular compartment, creating in effect hemodilution. This hemodilution creates the falsely low hCG rise, while it is an artefact of a rapid increase in intravascular fluid. Once the fluid shift resolved, though, the hCG level rose in a more "normal" fashion.

This case report demonstrates that the standard hCG curve does not always rise in a "normal" fashion. There are many factors that contribute to the increase in level, and providers should not deem a pregnancy abnormal until all factors have been considered. We believe that OHSS should be an important clinical factor for providers to consider when measuring β-hCG levels in early pregnancy [81]. The need for critical analysis on case by case basis in recommending diagnostic or treatment modalities in situation of this nature most especially in desired pregnancy is important.

Complication of OHSS are myriad however it is important to be mindful of the ovarian torsion in view of the prominent reference to the ovary which is the main organ of reference. Cases of Ovarian torsion was critically evaluated in relation to Ovarian Hyperstimulation Syndrome, this was studied retrospectively by R. Mandelbaum., *et al*. with a Nationwide Inpatient sample between 2001 - 2005 representing over 97% of the United States population.14,623 women were admitted with OHSS during this period, and 313 (2.1%, 95% confidence interval [CI] 1.9 - 2.4) had ovarian torsion. Of all women admitted with OHSS 1330 (9.1%) women were pregnant, and pregnant women had a greater risk of torsion compared to non-pregnant women (3.2% vs 2.0%, OR 1.6 95% CI 1.1 - 2-2, P = 0.008).

In comparative analysis 1 in 50 women admitted with OHSS had ovarian torsion with oophorectomy, a devastating outcome for fertility-seeking patients was performed in over 10%. Basically, torsion was noted to have occurred more frequently in pregnant patients and was associated with fewer medical complications supporting the hypothesis that torsion in OHSS results from increased ovarian volumes rather than increased capillary permeability. Also, the rate of torsion and oophorectomy had a collative difference based on the

geographical region and teaching hospital status respectively. The need for heightened awareness regarding risk of torsion and effect urgent medical evaluation once suspected is important based on the current trend of management of non-severe OHSS on outpatient management [82].

Ethical issues

Ovarian hyperstimulation syndrome is a complication of assisted reproductive technology and fertility treatment whose severity is dreaded based on its effect on the management protocol, financial commitments and psychological impact on the couple. During the period of the complication the level of frustration and emotional stress cannot be borne by some with subsequent resultant termination of the fertility treatment cycle in extreme cases. It is imperative that the couples should be fully counselled on this complication, adequate time to decide and information leaflets along with the treatment modalities. Comprehensive line of management and experts contact telephone in the events of the complication should be outlined in the clinical folders of all patients for the benefits of medical care practitioners that are not familiar with the complication.

Conclusion

The advancement in the field of Reproductive medicine with the progressive and good management modalities availability at the disposal of experts is commendable, however the adverse effect of the treatment in relation to OHSS has had negative impact on the universal acceptance of the treatment. OHSS can be anticipated and managed if diagnosed early and patients duly counselled. The RCOG and NICE guideline are important tools that should be used with additional experts' (gynaecological and non-gynaecological) inputs in refractory cases. Mandatory training of staffs, regular audits, and patient feedback will optimise the management. Medico-legal implication of misdiagnosis should always be kept in mind.

Contribution to Authorship

OA initiated the ideal of the topic, researched and wrote the manuscript. The author approved the final version for submission.

Disclosure of Interest

OA have no funding, or conflict of interest to declare.

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Volume 16 Issue 4 April 2020