Review Article

Challenges of OHSS in modern reproductive medicine practice

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) remains a significant complication of fertility treatment whenever ovarian stimulation is used to increase the number of eggs and embryos available. This condition has been known since the advent of gonadotropins for ovarian stimulation, and over the years there have been many advances in our understanding of its pathophysiology. We know now that OHSSS is the end result of a complex interaction of cytokines and vaso-active molecules produced by hyperstimulated ovaries, with activation of secondary mediators as part of the process.[1] To a limited extent, this has aided in the development of measures that reduce the chance of a woman developing OHSS, but the challenge remains to translate basic scientific knowledge into clinical treatment.

At the same time that understanding of the mechanisms of OHSS is improving, there have been advances in clinical reproductive endocrinology that are relevant to the incidence of OHSS. In this review, I consider whether OHSS still remains a clinical problem in modern reproductive practice, where we are able to apply these advances in routine practice. Specifically, I use the term 'modern reproductive medicine practice' to include the following:

(1) Ovarian stimulation using FSH doses based on ovarian reserve tests (anti-Mullerian hormone and/or antra follicle count).
(2) Routine gonadotropin-releasing hormone antagonist (GnRH-ant) use, particularly in women with high ovarian reserve.
(3) Gonadotropin-releasing hormone agonist (GnRH-a) trigger in women at increased risk of OHSS.
(4) Freeze-all (cryopreservation of all embryos) in women at increased risk of OHSS.

This review addresses whether OHSS is still a significant problem even with the application of the above measures, and goes on to consider aspects of OHSS where a challenge persists.

INCIDENCE

To determine whether OHSS is a problem in modern practice, one must begin with how frequently it occurs in clinical practice. Unfortunately, we are not able to answer this question in a convincing way. A number of studies have examined the incidence of OHSS in individual centres over a limited study period, and are summarised in an excellent review.[2] Considering IVF

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alone, 'moderate' OHSS occurred in 3% to 6% and 'severe' OHSS in 0.1% to 2% of all cycles.

These numbers provide our best estimates for the incidence of OHSS before the introduction of the innovations listed above, which constitute modern practice. Subsequent studies are fewer in number. Following the introduction of GnRH-ant, the incidence of OHSS requiring hospitalisation in 2524 consecutive IVF cycles was 2.1%.[3] Importantly, final follicular maturation occurred with 10,000 IU of human chorionic gonadotropin (hCG). A more recent retrospective study of 1492 consecutive cycles using GnRH-ant and a liberal use of GnRH-a trigger and freeze-all found an incidence of moderate or severe OHSS of 1.6%.[4]

Ideally, data on the incidence of OHSS should be obtained from national or global sources with mandatory reporting. This does not currently exist to our knowledge, with the exception of the requirement of the UK Human Fertilisation and Embryology Authority (HFEA) for clinics to report all cases of 'severe' or 'critical' OHSS. HFEA data show a stable annual incidence of 0.1% to 0.2% of all IVF cycles.[5] A criticism that can be made of the HFEA data is that if clinics are not aware of cases of OHSS looked after by other providers, they would be unable to report them resulting in under-reporting.

One approach to overcome the problem of underreporting is to use hospital admission data. Rotshenker-Olshinka *et al.*[6] looked at hospital admissions with a diagnosis of OHSS in the Health-Care Cost and Utilization Project-Nationwide Inpatient Sample database (HCUP-NIS) over 11 years (2004–2014), and found an incidence of 1.2 to 2.0 OHSS admissions per 10,000 women hospitalized per year. Further, the incidence measured in this way declined between 2004 and 2014, albeit with a plateau after 2008.

A Danish study examined hospital admissions with a diagnosis of OHSS over 17 years (2001–2017) and found 2261 (1.2%) women admitted for OHSS from 186,168 stimulated IVF cycles, yielding an annual incidence of OHSS of 0.9% to 1.4% of cycles, with no overall change over time.[7]

Based on these studies, it is reasonable to say that, even with modern reproductive medicine practice, OHSS still remains a significant problem for our patients. However, despite the availability of these data, we are left in the dark about the true incidence of clinically significant OHSS. While hospital admission is no doubt a significant event for the patient and utilises significant healthcare resources, but it does not capture the full spectrum of morbidity and ill health caused by OHSS. Increasingly, even severe OHSS can be safely managed in an outpatient setting, which may further reduce the usefulness of hospital admission data in understanding the true impact of OHSS on our patients.

Classification of OHSS

Discussions about the incidence of OHSS presuppose that there is a universally agreed-upon definition and classification of this condition. Unfortunately, this is not the case. Historically, classifications of OHSS were developed by a number of investigators, as summarised by Humaidan *et al.*[8] in 2016. These authors proposed a definition of OHSS for the purpose of reporting in a clinical trial and with the aim of standardising how this is recorded. However, the definition does not lend itself to the clinical management of patients with OHSS of varying severity. The RCOG classification has gained acceptance in the UK and elsewhere, represents a refinement of previous schemes, and can form the basis for clinical management and guidelines (RCOG 2016).[9]

Prevention

As alluded to above, several developments have given us a number of tools to reduce the risk of OHSS in clinical endocrinology and laboratory technique. A major and effective measure is the GnRH-ant regime, with GnRH-a trigger and freeze-all. This completely eliminates the risk of late OHSS, which is the more severe form of the illness. However, clinicians tend to implement this only when the ovarian response is excessive. Contrary to this practice,[10] it is observed that significant OHSS can still occur in women with a high ovarian reserve if a fresh embryo transfer is carried out in the face of a 'normal' response. In other words, the ovarian reserve is a better predictor of the risk of OHSS than the response.

A network meta-analysis of pharmacological preventative measures showed that intravenous calcium, hexa-ethyl starch and cabergoline were effective in preventing OHSS, while aspirin, letrozole, metformin, steroids and albumin did not reduce the incidence of OHSS.[11]

The challenge remains to identify how these treatments should be targeted, to reduce the persistent incidence of OHSS despite the availability of these measures.

Diagnosis and management

Patients who develop OHSS are often seen in clinics other than those carrying out their treatment. In some cases, they may come under the care of clinicians with relatively little experience in the diagnosis and management of

OHSS. Major problems can arise both with over- and under-diagnosis of OHSS, including serious complications such as appendicitis, pelvic sepsis and ovarian torsion that are missed. It should be borne in mind that OHSS in itself does not cause high temperatures or signs of infection. Severe pain should always prompt a search for causes, including ovarian torsion and ectopic pregnancy.

The evidences of many cases of severe OHSS can be safely managed on an outpatient basis, through early outpatient paracentesis and fluid management is accumulating.[12] This may reduce the impact of the complication on patients and the health system and requires clinical and cost-effectiveness evaluation in different health systems. A multi-centre trial in the United Kingdom is examining this question in the context of the UK National Health Service (see https://www.sheffield.ac.uk/scharr/research/centres/ctru/stop-ohss).

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Conflicts of interest

There are no conflicts of interest.

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