RBMO

COMMENTARY

Trends in ovarian hyperstimulation syndrome hospitalization rates in the USA: an ongoing concern

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ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is a serious, almost exclusively, iatrogenic complication of ovarian stimulation. Many techniques have been developed over the past 25 years to decrease OHSS risks, and most have been in common use for 15–20 years. In view of these techniques, it could be hypothesized that severe OHSS rates would decrease or almost disappear. According to the US National ART Surveillance System, rates did not change significantly between 2000 and 2009, at 106 OHSS cases per 10,000 IVF cycles annually. In the present study, OHSS-related hospital admissions were evaluated to establish whether a decline has occurred in OHSS admissions since the development of preventative strategies. A retrospective-population-based study was conducted using data from the Health-Care Cost and Utilization Project-Nationwide-Inpatient-Sample database between 2004 and 2014 inclusively. Between 2004 and 2008, admissions of OHSS decreased in absolute numbers and rates; however, these statistics plateaued, remaining stable between 2008 and 2014. Despite this, OHSS remains a concern and is clearly not a disease of the past. The financial burden of OHSS hospitalizations likely persists. Although techniques have resulted in a decrease in OHSS admissions since 2004, this change has plateaued, and therefore efforts to further reduce OHSS must continue.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a serious, almost exclusively, iatrogenic complication associated with ovarian stimulation during assisted reproductive technology (ART) treatments. Over the years, several OHSS criteria have been published and used to classify OHSS severity. Mild OHSS is common whereas severe OHSS is rarer and can be life-threatening (*Mourad et al., 2017*).

Early studies suggested OHSS occurs in an estimated 20–33% of ART cycles, whereas moderate and severe OHSS were generally reported in an estimated 3–8% of ART cycles (*Golan, 1989*; *Delvinge and Rozenberg, 2002*). These data were obtained when HCG, which triggers vascular endothelial growth factor (VEGF) production, was the only option for oocyte maturation. The underlying pathophysiology of OHSS is attributed to an increase in vascular permeability that is mediated by VEGF, resulting in third spacing of fluid (*Golan, 1989*; *Delvinge and Rozenberg, 2002*; *Mourad et al., 2017*).

Many techniques have developed over the past 25 years to decrease OHSS risks. These include gonadotrophin releasing hormone (GnRH)-antagonist IVF cycles (first large randomized controlled trials [RCT] were published in 2000) (*Borm and Mannaerts, 2000*; *Ludwig et al., 2000*), GnRH agonist triggering of oocyte maturation (first RCT published in 1990) (*Gonen et al., 1990*); use of metformin in women

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KEYWORDS

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Severe OHSS

with polycystic ovary syndrome (first RCT for the indication of decreasing OHSS published in 2006) (*Tang et al., 2006*), and use of dopamine agonists to decrease VEGF production (early RCTs dating from 2007) (*Álvarez et al., 2007*; *Pfeifer et al., 2016*; *Mourad et al., 2017*). In view of these protective measures, it could be hypothesized that the rate of OHSS admissions would decrease, and that OHSS may be quite rare.

The aim of the present study was to evaluate whether a decline has occurred in OHSS admissions since the development of preventative strategies.

MATERIALS AND METHODS

A retrospective population-based study using data from the Health-Care Cost and Utilization Project-Nationwide Inpatient Sample database (HCUP-NIS) was conducted over 11 years (2004–2014), and based on the number of fresh IVF cycles per year as reported by the US National ART Surveillance System (NASS) during the study period. Between 2004 and 2014, hospital admissions were evaluated inclusively. Women aged between 18 and 43 years were queried for OHSS admissions using ICD-9 code 256.1. This resulted in a database of 12,608,757 admissions, 1900 for OHSS. Data were compared as absolute numbers, percentage of admissions per year in women age 18–43 years, and as a percentage of all IVF cycles annually reported to the NASS. The Mann–Kendall trend test (two-tailed) was used for the analysis. The description of demographics was by category and percentages for these categorical variables. Demographics were categorized in the database and evaluated by chi-squared tests.

The HCUP-NIS database is the largest inpatient database in the USA covering over 97% of the US population. Each year, the database provides information relating to 7 million inpatient stays, including patient characteristics, diagnosss and procedures. The database approximates a 20% stratified sample of all discharges from US community hospitals (*H-CUP, 2019*). This study used exclusively publicly accessible, anonymized data; hence, according to articles 2.2 and 2.4 of Tri-Council Policy statement (2010), institutional review board approval was not required.

RESULTS

During the study period, 1900 OHSS hospitalizations were reported out of 12,608,757 hospitalizations for women aged 18–43 years. This corresponds to 1.2–2.0 OHSS admissions per 10,000 women hospitalized per year.

The mean number of OHSS admissions per year during 2004 and 2007 was 261.5 (range 245–300; SD 25.8) and decreased to 171 in 2008–2014 (range 157–191; SD–14.2). Between 2004 and 2014, a decrease occurred in the number of OHSS hospitalizations ($P = 0.004$) and the frequency of OHSS admissions per 10,000 women ($P = 0.035$) (FIGURE 1). This decline, however, was demonstrated only in 2004–2008. Between 2008 and 2014, the number of OHSS admissions per year ($P = 0.734$) as well as OHSS admissions per 10,000 hospitalizations among women ($P = 0.733$) plateaued (FIGURE 1). The number of fresh IVF cycles per year as reported by the NASS has increased annually from 94,242 to 128,268 during the study period. When dividing the number of OHSS hospitalizations in the database by the number of fresh IVF cycles per year reported by NASS, we demonstrate similar trends. A decrease occurred in the number of OHSS hospitalizations per IVF cycle, per year, during the study period ($P = 0.002$), overall (mean 0.002; range 0.001–0.003; SD 0.0006) and in 2004–2007 (mean 0.003; range 0.002–0.003; SD 0.0002). Between 2008 and 2014, however, a plateau occurred ($P = 0.308$) (mean 0.0015; range 0.001–0.002; SD 0.0002).

To evaluate whether the characteristics of hospitalized women with OHSS changed, the demographics of those admitted during 2004–2007 ($n = 1046$) were compared with those admitted in 2008–2014 ($n = 854$), inclusively. No significant differences in age were identified (age 18–25 years 12.0% and 13.3%; age 26–34 years 63.5% and 59.4%, and age 35–43 years 24.6% and 27.3% in 2004–2007 and 2008–2014, respectively; $P = 0.19$, categorical inclusion) or ethnicity (white 72.2% and 68.3%; black 9.4% and 10.2%; Hispanic 6.8% and 9.2%; Asian or Pacific 5.7% and 5.1%; Native American 0.6% and 0.7%; and other 5.3% and 6.6%, in 2004–2007 and 2008–2014, respectively; $P = 0.39$). Incidences of obesity (3.1% versus 7.7%, $P = 0.0001$) and thyroid disease (4.9% versus 10.8%, $P < 0.0001$) were higher in 2008–2014 than in 2004–2007. The presence of uterine fibroids was similar in both time frames (1.5% versus 1.6%, $P = 1.0$). In 2004–2007 versus 2008–2014, patients had different rates of medical insurances (Medicare/Medicaid 5.1% versus 8.3%; private insurance 89.3% versus 84.2%; self-pay 2.7% versus 3.5%; no charge 0.3% versus 0.4%; and other insurance 2.7% versus 3.7%, respectively ($P = 0.01$).

DISCUSSION

Techniques for OHSS prevention have been studied and implemented in the past 3 decades since the first reports on the subject emerged in the early 1990s (*Gonen et al., 1990*) and large reviews of OHSS prevention were published in the mid-2000s (*Mourad et al., 2017*). Interventions to prevent OHSS classified as moderate quality or Grade A by the Cochrane Collaboration and American Society for Reproductive Medicine include ovarian stimulation protocols with GnRH antagonists for ovulation suppression; GnRH agonist triggering versus HCG for oocyte maturation; dopamine agonists; and metformin use for patients with polycystic ovary syndrome (*Pfeifer et al., 2016*; *Mourad et al., 2017*).

It could be hypothesized that the rate of OHSS admissions would decrease or almost disappear, given these techniques, and the favoured use of GnRH antagonist cycles currently. According to the US NASS (based on over 95% of US ART cycles), OHSS was the most commonly reported complication of ART, and rates of OHSS did not change significantly between 2000 and 2009, estimated 106 per 10,000 IVF cycles yearly (*Kawwass et al., 2015*). The 2015 European Society of Human Reproduction and Embryology (ESHRE) annual report cited OHSS rates as occurring in 0.44% of ART cycles in 2015, 0.3% in 2014, 0.4% in 2013 and 0.6% in 2012, remaining the most common complication throughout the years (*Calhaz-Jorge et al., 2016*; *Geyter et al., 2020*). In this ESHRE report, no differentiation is made between severe OHSS or admissions for OHSS and mild or moderate OHSS that can occur with agonist trigger alone but has minimal clinical significance. In our data, we found that, between 2004 and 2008, US OHSS admissions decreased, but this trend stabilized between 2008 and 2014. Several factors could account for

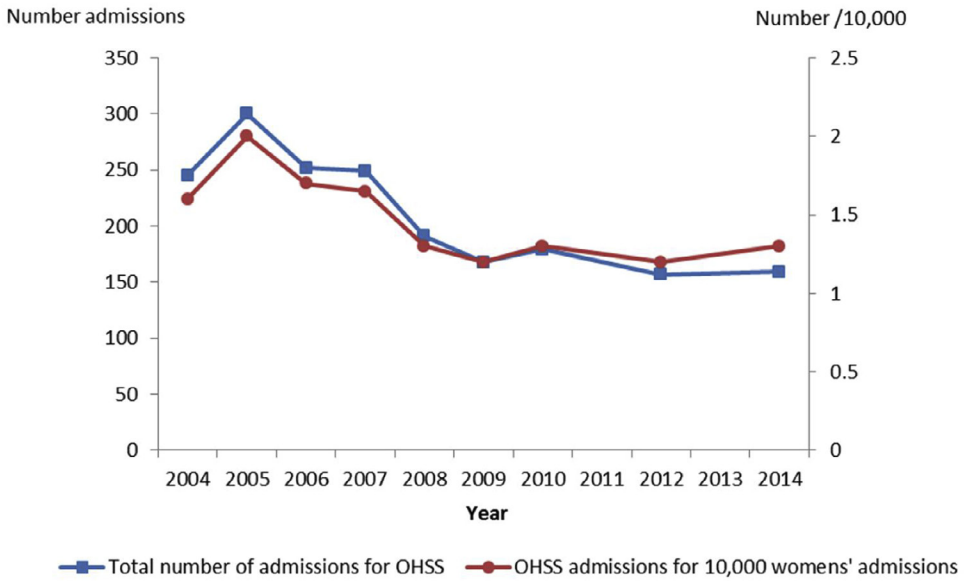

FIGURE 1 Trends in the total number and the frequency of ovarian hyperstimulation syndrome (OHSS) admissions per 10,000 admissions in women aged 18–43 years. The number of admissions decreased from 2004–2014 (P = 0.004), but the decrease was non-significant from 2008–2014 (P = 0.734); a decrease in OHSS admissions per 10,000 women occurred from 2004–2014 (P = 0.035), but was non-significant from 2008–2019 (P = 0.733).

this plateau. Concurrently, the use of ART is increasing and, therefore, more women are at risk for OHSS, thereby maintaining a stable number of cases. This, however, does not explain the rate of OHSS admissions being constant as a function of the number of IVF cycles. It is likely that the protocols used to decrease the risk of OHSS are not adequately exploited and that, in some centres, agonist triggering or dopamine antagonists are not used sufficiently. Another explanation can be that, in many cases when agonist triggering is used, the physician continues with a fresh embryo transfer and luteal support using HCG (*Pfeifer et al., 2016*; *Mourad et al., 2017*). In many of these cases, an agonist trigger combined with a policy of freeze all embryos could have further reduced the OHSS risk. Although uncommon, OHSS may sometimes be unpredictable, occurring in low-risk women with few follicles after ovarian stimulation, or in high-risk women despite cautious treatment (*Stouffs et al., 2019*). Rare FSH receptor mutations (*Stouffs et al., 2019*) may predispose some stimulated patients with low-risk factors to OHSS.

No clear relationships were demonstrated between the change in OHSS admission and demographic characteristics in the two timeframes. The increased rates of obesity and thyroid disease mirror trends with time in the USA.

The increase in Medicaid and the decrease in private insurance covered patients in 2008–2014 compared with 2004–2007 is small and most probably does not account for the change in the number of admissions, and nor does the small increase in the number of self-paying patients (0.8%) who, if anything, would have tried to avoid admission if possible.

The databases used in this study have several limitations. Data are based on hospital records according to the ICD-9 code, which may mask bias. Severe OHSS patients may have been admitted under other diagnoses, such as hyponatraemia or venus thrombus. This might, however, have caused a further underestimation of the OHSS hospitalization rate altogether, but would likely not have affected the trends. The data consist of women who were hospitalized. It is not possible to capture severe or moderate OHSS that were managed in an outpatient setting. Furthermore, although HCUP-NIS is the largest inpatient sample database in the USA, it does not include non-community-based hospitals, potentially excluding other OHSS admissions. Clearly, the number of OHSS admissions and the OHSS rates per number of IVF cycles are higher than we demonstrated.

The HCUP-NIS database includes data up to 2017. Nevertheless, in the third quarter of 2015, the HCUP-NIS database converted from ICD-9 to ICD-10 codes, which are not comparable; as such, recent data were not included in the analysis. In the database, data are missing for OHSS admission for the years 2011 and 2013, which is an inherent error in the database.

As such, we cannot say for certain that OHSS rates remain constant today. As IVF cycle numbers continue to increase, however, and no new major avoidance techniques have been introduced since 2005, it is unlikely that downward pressure on OHSS rates are occurring.

Despite data limitations, it is still evident that OHSS is not a disease of the past. Admission rates of OHSS remain a concern. This is demonstrated by similar frequencies of OHSS admissions from 2008–2014. The financial burden of OHSS hospitalizations likely persists. Given this data, it is important that further efforts to reduce OHSS continue.

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