Original Article

Maternal-Fetal Medicine®

OPEN

Pregnancy Outcomes Associated with Ovarian Hyperstimulation Syndrome: A Retrospective Cohort Study of Infertile Women

Ajleeta Sangtani[1,*], Maryama Ismail[2], Amy Weaver[3], Zaraq Khan[1]

Abstract

Objective: To assess the relationship between ovarian hyperstimulation syndrome (OHSS) and adverse outcomes using population-based data in the United States. The hypothesis is that patients with OHSS were more likely to deliver preterm and more likely to have hypertensive disorders.

Methods: This retrospective cohort study identified 94 patients with OHSS and 183 matched referents in eight counties in Minnesota. Data were collected regarding pregnancy history, infertility treatment, and pregnancy outcomes. Using the Rochester Epidemiology Project, study subjects were identified from female patients, aged 18 to 49 years, who were diagnosed with infertility from January 2, 1995 to December 1, 2017, and had a pregnancy greater than 20 weeks' gestation. The primary outcome was preterm delivery or hypertensive disorder of pregnancy incidence in the OHSS group when compared with control patients. Chi-squared test, *t* test, and multivariate logistic models were used where appropriate.

Results: Patients with OHSS were more likely to deliver preterm (odds ratio, 2.14; 95% confidence interval, 1.26–3.65; $P < 0.01$), and their neonates were more likely to be small for gestational age (odds ratio, 4.78; 95% confidence interval, 1.61–14.19; $P < 0.01$). No significant differences between the groups were observed in any other outcome. Patients with OHSS are more likely to deliver preterm if they undergo fresh transfer compared with a freeze all and subsequent frozen transfer (odds ratio, 3.03, 95% confidence interval, 1.20–7.66, $P = 0.02$).

Conclusion: OHSS may lead to preterm birth and small-for-gestational-age neonates, which changes patient counseling and leads to arranging specialized obstetrical care for these patients with OHSS.

Keywords: Obstetric labor, premature; Hypertension; Frozen cycle; Fresh cycle

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a known complication following ovulation induction (OI) most seen during ovarian stimulation cycles for in vitro fertilization (IVF). OHSS has an unclear etiology, although several different theories have been proposed.[1] It tends to present in younger, nulligravid, black women who have adequate ovarian reserve but disorders of ovulation.[2] OHSS presents as worsening abdominal distension and gastrointestinal symptoms in the acute phase. Patients are also noted to have extravasation of fluid leading to ascites and pleural effusions.[3] If severe, it can lead to oliguria, renal failure, and, in rare instances, death.[3]

Despite the high morbidity, patients with OHSS are more likely to have a clinical pregnancy and a live birth as compared with those who do not develop the disease process.[2] These women are also more likely to have twin pregnancies,[2] and almost half of pregnancies after OHSS end in a cesarean delivery.[4] OHSS is more common after fresh embryo transfer, which itself is associated with worse pregnancy outcomes.[5] At present, there is little research looking at maternal and fetal outcomes after OHSS. Some studies show an increased risk of preterm birth and low birth weight associated with OHSS.[2,6–9] Others have also shown an increased risk of pregnancy-induced hypertension in patients with OHSS.[6] However, research on outcomes is limited.

Our study aims to assess whether there is a relationship between OHSS and adverse obstetrical and fetal outcomes using population-based data in the United States. The hypothesis was that patients with OHSS are more likely to delivery preterm and more likely to have hypertensive disorders of pregnancy (HDPs) than those without OHSS. By better assessing the effects of OHSS on pregnancy, we may be able to better counsel patients on the implication of developing OHSS.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.maternalfetalmedicine.org).

[1]Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN 55905, USA; [2]Mayo Clinic Alix School of Medicine, Mayo Clinic, Rochester, MN 55905, USA; [3]Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905, USA.

** Corresponding author: Ajleeta Sangtani, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN 55905, USA. (A.S. changed jobs between writing and publication of this article. Present address: Department of Maternal Fetal Medicine, Michigan Medicine, Ann Arbor, MI 48104, USA.). E-mail: ajleetas@gmail.com.*

Maternal-Fetal Medicine (2023) 5:3

Received: 9 May 2022 / Accepted: 17 March 2023

First online publication: 6 June 2023

http://dx.doi.org/10.1097/FM9.0000000000000192

Materials and methods

Cohort identification

This was a retrospective cohort study. Using the resources of the Rochester Epidemiology Project (REP), we identified female patients, aged 18 to 49 years, who were diagnosed with infertility using diagnosis codes (Supplementary Table 1, http://links.lww.com/MFM/A34) during January 2, 1995, through December 1, 2017, while they were a resident of one of eight counties in southeastern Minnesota (namely, Olmsted, Dodge, Mower, Goodhue, Fillmore, Wabasha, Freeborn, and Steele counties). Women were included if they had a pregnancy greater than 20 weeks' gestation. Women who had been denied access to their medical records for research purposes were excluded.

The REP is a medical records-linkage system that includes outpatient and inpatient records from providers in the community, including Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals, as well as smaller care providers.[10,11] Using the US Census estimates for 2014, the REP has a greater than 70% capture rate of the female residents in this eight-county region.[12] For Olmsted County, the county in which the affiliated hospitals are present, census information indicates that the age, sex, and ethnic characteristics of people living in the county are comparable to the rest of Minnesota and to the Midwestern United States, but the county is less ethnically diverse and has a higher socioeconomic status when compared with the United States in its entirety.[13]

Within the infertility cohort, we used the diagnosis codes (Supplementary Table 2, http://links.lww.com/MFM/A34) to identify women who received a diagnosis of OHSS, and their medical records were manually reviewed to confirm that the symptoms occurred after receiving infertility treatment and that the women had a viable birth.

We expected to have approximately 70 patients with OHSS. Based on a two-sided Chi-squared test, we found that matching two referent women would give us an 80% power to detect a doubling from a baseline case rate of 7% for both HDPs and preterm delivery.[14]

For each woman diagnosed with OHSS, we randomly selected two referent women from the infertility cohort who had a viable birth and met the following criteria: age at delivery (±2.5 years), same parity (0 *vs.* ≥1), same type of infertility treatment (IVF, intrauterine insemination with OI either with oral or injectable medication, OI with oral medication, *vs.* OI with injectable medication), and same infertility diagnosis (anovulation/oligo-ovulation *vs.* all others) who had not yet been diagnosed with OHSS at the time of the delivery. Charts were manually reviewed to ensure that no patient had OHSS. The matching factors were selected based on factors that might influence the cause of infertility.[15]

Ethical approval

The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards (no. 17-010881). The patients gave their written consents to be included in the REP.

Data collection

For the OHSS cases and matched referents, "index" was defined as the time of the infertility treatment before the pregnancy of interest. Medical records were manually reviewed to abstract the data reported in this article. Baseline demographics and specific fertility treatment/IVF protocol information were collected. For patients with OHSS, information (if any present) on serum parameters such as hemoglobin, serum creatinine, electrolytes, and so on and information on any therapeutic modalities such as anticoagulation, peritoneal, or pleural taps and intensive care unit admission data were collected as well. Gestational age was divided into seven categories based on guidelines by the World Health Organization and the American College of Obstetricians and Gynecologists: extremely preterm (<28 weeks), very preterm (28–31 weeks), moderate to late preterm (32–36 weeks' gestation), early term (37–38 weeks' gestation), full term (39–40 weeks' gestation), late term (41 weeks' gestation), and postterm (42–43 weeks' gestation).[16–18] Size for gestational age was defined based on the Fenton growth chart for infants born at 23 to $36^{+6/7}$ weeks' gestation and based on the World Health Organization growth chart for infants born at 37 weeks' gestation and beyond.[19,20] Other collected information included data regarding HDP, use of antihypertensive medications in pregnancy, use of antenatal steroids, mode of delivery, singleton *vs.* multiple birth status, and 1- and 5-min Apgar scores.

Statistical analyses

Data were summarized using standard descriptive statistics. Continuous variables were summarized with mean and standard deviation (*SD*), or median and interquartile range, depending on the distribution of data. Categorical variables were summarized with the number of cases and percentage (%). Comparisons between groups were evaluated using the two-sample *t* test for continuous variables with a normal distribution, the Wilcoxon rank sum test for ordinal variables or continuous variable with a skewed distribution, and the Chi-squared test or Fisher exact test for categorical variables. Some data points were missing for patients during the manual review of the medical records, and therefore, the denominators are less for some comparisons as denoted in the tables. Statistically significant baseline data were obtained and included in multivariate logistic regression. Multivariate logistic regression models were

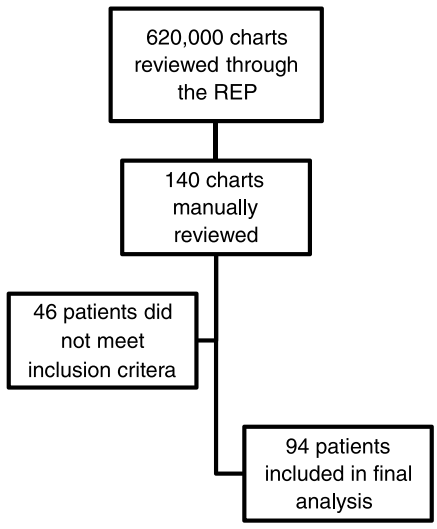

Figure 1. Flowchart showing patient selection. REP: Rochester Epidemiology Project.

Table 1

Characteristics of OHSS cases and matched referents at the time of the fertility treatment ("index") before the pregnancy of interest.

Characteristics	OHSS cases (*n* = 94)	Referents* (*n* = 183)	Statistical values	*P*†
Age (years)			–0.94‡	0.35
Mean ± *SD*	30.8 ± 3.5	31.2 ± 3.5		
Range	(22.7–38.0)	(22.9–40.2)		
Gravida, *n* (%)			0.37‡	0.71
1	58 (61.7)	115 (62.8)		
2	18 (19.1)	40 (21.9)		
3	10 (10.6)	15 (8.2)		
4–7	8 (8.5)	13 (7.1)		
Parity, *n* (%)			0.09‡	0.93
0	74 (78.7)	145 (79.2)		
1	15 (16.0)	29 (15.8)		
2	5 (5.3)	5 (2.7)		
3	0 (0.0)	4 (2.2)		
Body mass index (kg/m^2)			0.31‡	0.75
Mean ± *SD*	26.1 ± 6.7	25.7 ± 6.1		
Median (IQR)	24.2 (21.4–28.6)	24.1 (21.3–28.3)		
Body mass index, *n* (%)			1.30‡	0.19
<25 kg/m^2	48 (51.1)	106 (57.9)		
25–<30 kg/m^2	23 (24.5)	38 (20.8)		
30–<40 kg/m^2	11 (11.7)	31 (16.9)		
>40 kg/m^2	5 (5.3)	7 (3.8)		
Not documented	7 (7.4)	1 (0.5)		
Infertility diagnosis,§ *n* (%)				
Anovulation/oligo-ovulation	46 (48.9)	88 (48.1)	0.02‖	0.89
Male factor	33 (35.1)	62 (33.9)	0.04‖	0.84
Tubal	12 (12.8)	22 (12.0)	0.03‖	0.86
Other	25 (26.6)	54 (29.5)	0.26‖	0.61
Type of infertility treatment, *n* (%)				0.99¶
IVF	84 (89.4)	165 (90.2)		
IUI with OI/injectable medication	7 (7.4)	13 (7.1)		
OI with oral medication	1 (1.1)	2 (1.1)		
OI with injectable medication	2 (2.1)	3 (1.6)		
Race, *n* (%)				0.06¶
Caucasian	85 (90.4)	164 (89.6)		
Black or African American	1 (1.1)	0 (0.0)		
Asian	2 (2.1)	14 (7.7)		
American Indian	0 (0.0)	1 (0.5)		
Other or mixed	4 (4.3)	3 (1.6)		
Unknown/chose not to disclose	2 (2.1)	1 (0.5)		

*For each OHSS case, we randomly selected two referent women from the infertility cohort who met the following criteria: age at delivery (±2.5 years), same parity (0 *vs.* ≥1), same type of infertility treatment (IVF, IUI, OI with oral medication, *vs.* OI with injectable medication), and same infertility diagnosis (anovulation/oligo-ovulation *vs.* all others) who had not yet been diagnosed at OHSS at the time of the delivery. For 89 OHSS cases, we identified two matched referent women and only one matched referent each was identified for the five remaining OHSS cases for a total of 183 matched referents.

†Comparisons between groups were evaluated using the Wilcoxon rank sum test for each continuous and ordinal variable and the Chi-squared test or Fisher exact test for each categorical variable.

‡Wilcoxon test statistic, standardized.

§Some patients had more than one infertility diagnosis.

‖Chi-squared test statistic.

¶Fisher exact test, no test statistic.

IQR: Interquartile range; IUI: Intrauterine insemination; IVF: In vitro fertilization; OHSS: Ovarian hyperstimulation syndrome; OI: Ovulation induction; *SD*: Standard deviation.

created with preterm birth and birth weight as the dependent variable, adjusting for confounders (peak estradiol as a continuous variable, the number of oocytes received as a continuous variable, and fresh *vs.* frozen as a categorical variable). Logistic regression results are presented as odds ratios (*ORs*); 95% confidence interval (*CI*), and *P* values. All calculated *P* values were two-sided, and *P* values less than 0.05 were considered statistically significant. Analyses were performed using the SAS version 9.4 software package (SAS Institute, Inc, Cary, NC) and RStudio (RStudio: Integrated Development for R; RStudio, PBC, Boston, MA).

Results

Figure 1 shows the enrollment flow. A total of 140 women were identified using the diagnosis codes from 620,000

Table 2

Infertility-related characteristics at the index fertility treatment for OHSS cases and matched referents who underwent IVF.

Characteristics	IVF, OHSS (n = 84)	IVF, referent (n = 165)	Statistical values	P*
Type of IVF protocol	% of 78[†]	% of 164[†]	3.04[‡]	0.39
Antagonist protocol	18 (23.1)	54 (32.9)		
Long luteal agonist protocol	58 (74.4)	105 (64.0)		
Coflare protocol	2 (2.6)	4 (2.4)		
Precycle estradiol antagonist protocol	0 (0.0)	1 (0.6)		
Number of days of stimulation			–0.84[§]	0.40
n	75[†]	119[†]		
Mean ± *SD*	11.5 ± 1.3	11.7 ± 1.5		
Median (IQR)	11 (11–12)	12 (11–13)		
Total units of gonadotropins used			–1.14[§]	0.26
n	75[†]	119[†]		
Mean ± *SD*	1900.1 ± 1096.9	2112.0 ± 1230.2		
Median (IQR)	1575 (1275–2250)	1800 (1350–2325)		
Peak estradiol (pg/mL)			4.78[§]	<0.01
n	77[†]	117[†]		
Mean ± *SD*	3277.1 ± 1575.9	2326.6 ± 1313.7		
Median (IQR)	3011 (2074–4225)	1956 (1355–2931)		
Type of trigger	% of 81[†]	% of 165[†]	0.52[‡]	0.82
hCG	76 (93.8)	156 (94.5)		
hCG + leuprorelin	5 (6.2)	9 (5.5)		
hCG trigger dose (units)	% of 80[†]	% of 163[†]	1.75[‡]	0.42
Dual trigger with Lupron (1500)	5 (6.3)	9 (5.5)		
Half dose (5000)	8 (10.0)	9 (5.5)		
Full dose (10,000)	67 (83.8)	145 (89.0)		
Number of follicles aspirated			6.30[§]	<0.01
n	76[†]	154[†]		
Mean ± *SD*	36.3 ± 13.6	24.5 ± 12.7		
Median (IQR)	36 (26–45)	21 (15–31)		
Number of oocytes retrieved			6.31[§]	<0.01
n	81[†]	150[†]		
Mean ± *SD*	23.4 ± 10.1	15.3 ± 7.3		
Median (IQR)	23 (17–29)	15 (10–19)		
Number of embryos transferred	% of 77[†]	% of 161[†]	1.19[§]	0.24
1	11 (14.3)	38 (23.6)		
2	48 (62.3)	88 (54.7)		
3	14 (18.2)	27 (16.8)		
4	4 (5.2)	8 (5.0)		
Freeze all			46.31[‡]	<0.01
No	54 (64.3)	159 (96.4)		
Yes	30 (35.7)	6 (3.6)		

*Comparisons between groups were evaluated using the Wilcoxon rank sum test for each continuous and ordinal variable and the Chi-squared test for each categorical variable.

[†]Infertility-related characteristics were incomplete for six patients with OHSS and 48 referent control subjects, leading to a variety of denominators for characteristics examined.

[‡]Chi-squared test statistic.

[§]Wilcoxon test statistic, standardized.

hCG: human chorionic gonadotropin; IQR: Interquartile range; IVF: In vitro fertilization; OHSS: Ovarian hyperstimulation syndrome; *SD*: Standard deviation.

available medical records. Charts were manually reviewed, and 46 women were excluded because they did not have a pregnancy meeting inclusion criteria. Ninety-four women with OHSS who met the study inclusion criteria were identified. The year of first OHSS diagnosis was 1995–1999 for 18 (19.1%), 2000–2004 for 31 (33.0%), 2005–2009 for 21 (22.3%), 2010–2014 for 14 (14.9%), and 2015–2016 for 10 (10.6%). For 89 OHSS cases, we identified two matched referent women, and only one matched referent was identified for each of the five remaining OHSS cases for a total of 183 matched referents. These five OHSS women included two nulliparous women with anovulation/oligo-ovulation who underwent IVF after age 35 years, one nulliparous woman with anovulation/oligo-ovulation who underwent OI at the age of 28, one parous woman with unexplained infertility who underwent IVF at the age of 27, and one parous woman with anovulation/oligo-ovulation who underwent intrauterine insemination at the age of 26. The average timing from index IVF cycle to delivery was 2.5 years.

Baseline characteristics of OHSS cases and referents

Baseline characteristics used in the matching are presented in Table 1, along with race, gravidity, and body mass index. Although 90% of the patients were Caucasian, a slightly higher proportion of the referents were Asian (7.7% *vs.* 2.1%, $P = 0.06$). Nearly 90% of the patients with OHSS underwent IVF. Table 2 summarizes infertility-related characteristics for OHSS cases and matched referents who underwent IVF. The median number of follicles aspirated at the time of oocyte retrieval (median, 36 *vs.* 21; $P < 0.01$) and the median number of oocytes retrieved (median, 23 *vs.* 15; $P < 0.01$) were higher among patients with OHSS compared with referents. Likewise, the median peak estradiol was higher for patients with OHSS (median, 3011 *vs.* 1956; $P < 0.01$), and OHSS cases were less likely to undergo a fresh transfer after retrieval (64.3% *vs.* 96.4%, $P < 0.01$).

Clinical characteristics of patients diagnosed with OHSS

The characteristics of the patients with OHSS during the antenatal period are summarized in Table 3. Fifty-four percent of the patients with OHSS were diagnosed within one week of induction, and 95.7% (89/93) were diagnosed within a month. Almost one-fourth of patients diagnosed with OHSS underwent a peritoneal tap, and 38.3% of women with OHSS ended up with an admission to the hospital for a mean of 4.5 days. Sixteen (17.0%) of the patients with OHSS received treatment with either cabergoline or bromocriptine.

Table 3

Clinical characteristics of patients diagnosed with OHSS.

Characteristics	Total ($n = 94$)
Days from index to OHSS diagnosis*	% of 93[†]
0–7 d	50 (53.8)
8–30 d	39 (41.9)
31–63 d	4 (4.3)
Hemoglobin (g/dL)	
n	77[‡]
Mean ± *SD*	14.1 ± 1.3
Median (IQR)	14.0 (13.1–15.1)
Hematocrit (%)	
n	76[‡]
Mean ± *SD*	41.3 ± 4.0
Median (IQR)	41.1 (38.6–43.5)
Creatinine (mg/dL)	
n	69[‡]
Mean ± *SD*	0.9 ± 0.2
Median (IQR)	0.9 (0.8–1.0)
Medical treatment for OHSS	16 (17.0)
Peritoneal tap	22 (23.4)
Thoracic tap	5 (5.3)
Hospitalization during pregnancy	36 (38.3)
Number of days in hospital among those hospitalized	
Mean ± *SD*	4.5 ± 4.4
Median (IQR)	3 (2–5)
ICU admission	0 (0.0)
Anticoagulation	13 (13.8)

*"Index" was defined as the time of the infertility treatment before the pregnancy of interest.

[†]The date of the infertility treatment was not available in the medical record for one patient.

[‡]Laboratory data were not collected in 17 patients, and incomplete laboratory data were collected in an additional eight patients.

ICU: Intensive care unit; IQR: Interquartile range; OHSS: Ovarian hyperstimulation syndrome; *SD*: Standard deviation.

Pregnancy outcomes of OHSS cases and referents

Ninety-four OHSS patients and 183 matched control subjects were analyzed for maternal and fetal outcomes. Table 4 contrasts pregnancy and delivery outcomes between the OHSS cases and their matched referents. Patients with OHSS were more likely to deliver preterm (<37 weeks) compared with referents (*OR*, 2.14; 95% *CI*, 1.26–3.65; $P < 0.01$), and the median birth weight was smaller (median, 2930 *vs.* 3195 g; $P = 0.027$), yielding a higher proportion of infants who were small for their gestational age (*OR*, 4.78; 95% *CI*, 1.61–14.19; $P < 0.01$). We did not observe a statistically significant difference between the two groups in the incidence of HDP, gestational diabetes, placental abruption, thromboembolism, mode of delivery, Apgar scores, or intrauterine fetal death.

Among OHSS cases and matched referents who underwent IVF, OHSS patients were more likely to deliver preterm compared with referents (unadjusted *OR*, 2.09; 95% *CI*, 1.19–3.68; $P = 0.01$). This finding remained statistically significant in a multivariable logistic regression analysis adjusted for peak estradiol and the number of oocytes retrieved (both as numeric variables) among the subset of 193 of 249 IVF patients with data on both parameters (adjusted *OR*, 3.36; 95% *CI*, 1.50–7.80; $P < 0.01$).

Pregnancy outcomes of OHSS cases after IVF, same cycle (fresh embryo transfer) vs. delayed cycle (freeze all and then frozen embryo transfer)

Among 84 IVF patients with OHSS, 45 had a viable pregnancy after a fresh embryo transfer, the same cycle as the OHSS. Conversely, 39 patients had a pregnancy in a subsequent cycle after a frozen embryo transfer. Patients in the two groups were not statistically different on age, parity, cause of infertility, or body mass index (Table 5). Because no baseline demographics were different between these groups, we did not have any confounding variables. We found that patients were more likely to have preterm infants if they delivered in the same cycle as the OHSS (after a fresh embryo transfer) compared with those who had a viable pregnancy in a subsequent cycle (*OR*, 3.03; 95% *CI*, 1.20–7.66; $P = 0.02$) after freezing all embryos at first. The birth weight was also significantly lower (mean ± *SD*, 2650.4 ± 860.2 *vs.* 3058.6 ± 805.6 g; $P = 0.03$), but the difference in the proportion small for gestational age was not statistically significant (*OR*, 1.85; 95% *CI*, 0.43–7.93; $P = 0.49$) in this subset analysis (Table 6).

Discussion

Principal findings

OHSS is a known complication following assisted reproduction with unknown pregnancy outcomes. Although there is adequate data assessing early pregnancy outcomes in women with OHSS, information on long-term pregnancy outcomes that can direct care for patients is poorly

Table 4

Maternal and neonatal outcomes of OHSS cases and matched referents.

Outcome measure	OHSS cases (n = 94)	Referents (n = 183)	Statistical values	P*
Maternal				
HDP				0.69[†]
Normotensive	78 (83.0)	143 (78.1)		
Chronic HTN	2 (2.1)	5 (2.7)		
Any HDP	14 (14.9)	35 (19.1)		
Gestational HTN	5	18		
PE superimposed on chronic HTN	1	2		
Eclampsia	0	1		
PE without severe features	3	5		
PE with severe features	4	7		
HELLP syndrome	1	2		
Severe range blood pressures	5 (5.3)	8 (4.4)		0.77[†]
Use of antihypertensives	5 (5.3)	9 (4.9)		0.99[†]
Gestational diabetes	6 (6.4)	14 (7.7)	0.15[‡]	0.70
Placental abruption	4 (4.3)	2 (1.1)		0.18[†]
Deep vein thrombosis or pulmonary embolism during pregnancy	1 (1.1)	1 (0.5)		0.99[†]
Antenatal steroids	% of 89[§]	% of 179[§]	2.76[‡]	0.10
No	75 (84.3)	163 (91.1)		
Yes	14 (15.7)	16 (8.9)		
Age at delivery (years)			–0.26[‖]	0.80
Mean ± *SD*	31.9 ± 3.6	32.1 ± 3.5		
Mode of delivery			0.73[‡]	0.87
Spontaneous vaginal	43 (45.7)	81 (44.3)		
Cesarean	39 (41.5)	82 (44.8)		
Vacuum-assisted	3 (3.2)	7 (3.8)		
Forceps-assisted	9 (9.6)	13 (7.1)		
Postpartum magnesium	4 (4.3)	6 (3.3)		0.74[†]
Postpartum blood pressure medications	7 (7.4)	10 (5.5)	0.42[‡]	0.51
Infant				
IVF patients only, ratio of number of infants to number of embryos (implantation rate)	% of 77 with data on number of embryos	% of 161 with data on number of embryos	0.15[¶]	0.88
100%	31 (40.3)	67 (41.6)		
66.7%	4 (5.2)	5 (3.1)		
50%	31 (40.3)	62 (38.5)		
33%	9 (11.7)	21 (13.0)		
25%	2 (2.6)	6 (3.7)		
Gestational age			–3.48[¶]	<0.01
Extremely preterm (20–27 wk)	3 (3.2)	3 (1.6)		
Very preterm (28–31 wk)	4 (4.3)	7 (3.8)		
Moderate to late preterm (32–36 wk)	31 (33.0)	34 (18.6)		
Early term (37–38 wk)	27 (28.7)	46 (25.1)		
Full term (39–40 wk)	27 (28.7)	77 (42.1)		
Late term (41 wk)	2 (2.1)	16 (8.7)		
Number of infants delivered				—
1	61 (64.9)	141 (77.0)		
2	29 (30.9)	38 (20.8)		
3	3 (3.2)	4 (2.2)		
4	1 (1.1)	0 (0.0)		
Born alive—born stillborn				
0—1	1 (1.1)	0 (0.0)		
1—0	60 (63.8)	141 (77.0)		
1—1	1 (1.1)	1 (0.5)		
2—0	28 (29.8)	37 (20.2)		
2—1	0 (0.0)	1 (0.5)		
3—0	3 (3.2)	3 (1.6)		
4—0	1 (1.1)	0 (0.0)		

(*continued*)

Table 4
(continued).

Outcome measure	OHSS cases (*n* = 94)	Referents (*n* = 183)	Statistical values	*P**
Intrauterine fetal demise	2 (2.1)	2 (1.1)		0.61[†]
Birth weight (g)**			–2.22[‖]	0.03
n	93[§]	183		
Mean ± *SD*	2792.0 ± 886.9	3022.4 ± 775.9		
Median (IQR)	2930 (2165–3510)	3195 (2580–3560)		
Size for gestational age**	% of 93[§]	% of 183	9.34[‡]	<0.01
Small for gestational age	11 (11.8)	5 (2.7)		
Appropriate for gestational age	66 (71.0)	143 (78.1)		
Large for gestational age	16 (17.2)	35 (19.1)		
Apgar score at 1 min[††]	% of 90[§]	% of 181[§]		
Stillborn or 1–6 (*vs.* 7–10)	24 (26.7)	36 (19.9)	1.60[‡]	0.21
Apgar score at 5 min[††]	% of 90[§]	% of 181[§]		
Stillborn or 1–6 (*vs.* 7–10)	7 (7.8)	6 (3.3)		0.13[†]

*Comparisons between groups were evaluated using the two-sample *t* test for age at delivery and birth weight, the Wilcoxon rank sum test for gestational age categories and ratio of number of infants to number of embryos, and the Chi-squared test or Fisher exact test for categorical variables.

[†]Fisher exact test, no test statistic.

[‡]Chi-squared test statistic.

[§]Birth data were incomplete for five patients with OHSS and four referents.

[‖]Two-sample *t* test statistic.

[¶]Wilcoxon test statistic, standardized.

**Birth weight and size for gestational age are based on the smallest infant in there where there were multiple gestations.

[††]Apgar score is based on the lowest score if there were multiple gestations.

—: Not applicable; HDP: Hypertensive disorders of pregnancy; HELLP: Hemolysis, elevated liver enzymes, and low platelet count syndrome; HTN: Hypertension; IQR: Interquartile range; IVF: In vitro fertilization; OHSS: Ovarian hyperstimulation syndrome; PE: Preeclampsia; *SD*: Standard deviation.

studied.[21] Although there have been smaller studies in the past, the differences in outcome highlight the need for more data.[22] In this retrospective population-based cohort study, we found that patients with OHSS were more likely to deliver preterm compared with referents and more likely to have neonates that were small for gestational age. Among those who underwent IVF, patients with OHSS were also more likely to have preterm neonates when they had a viable pregnancy in the same cycle as the OHSS as opposed to freezing all embryos and waiting for a frozen embryo transfer in a subsequent cycle. This suggests that OHSS has an adverse effect on long-term pregnancy outcomes.

Previous research results

Several prior studies have looked at live birth as an outcome, but few look at pregnancy outcomes.[2] Some prior studies did show delivery at earlier gestational ages in patients with OHSS and lower birth weights in neonates of patients affected by OHSS. However, these studies focused only on patients with severe OHSS and did not calculate the size in relation to gestational age.[5,6] These studies also focused on patients with IVF pregnancies and excluded patients with other forms of assisted reproduction that resulted in OHSS. One prior study showed an increased rate of pregnancy-related hypertension, but the sample size was only 40 patients with OHSS.[5] Furthermore, they did not control for factors that affect the age at delivery, such as the age of the patient or the cause of infertility.[15,23] No prior studies have looked at maternal and fetal outcomes after delayed *vs.* same-cycle pregnancy for OHSS patients.

Clinical implications

Prior studies have shown that elevated estradiol is an independent risk factor for low birth weight.[24] In our study, the median peak estradiol was 1055 pg/mL higher in patients with OHSS than those without OHSS. This may help account for the difference in birth weight noted in patients with and without OHSS. Another prior study showed that patients with a higher number of oocytes retrieved (>20) were more likely to have preterm birth and low birth weight compared with those with fewer oocytes retrieved.[24] In our study, patients with OHSS had a median of 23 *vs.* 15 oocytes retrieved, which may additionally account for some of the difference seen. These differences are attributed to the effect of ovarian hyperstimulation on uterine receptivity and, subsequently, placental implantation.[24] However, even when accounting for these variables, patients with OHSS are more likely to have preterm neonates, suggesting that OHSS may potentiate this effect (unadjusted *OR*, 2.09 (95% *CI*, 1.19–3.68) *vs.* adjusted *OR*, 3.36 (95% *CI*, 1.50–7.80)).

Same-cycle (fresh embryo) transfers were observed to have a higher rate of preterm delivery in OHSS patients as compared with subsequent-cycle (frozen embryo) transfers in the current study, suggesting that the risk of preterm delivery with OHSS patients is primarily related to fresh embryo transfer. Prior studies have shown that patients with frozen embryo transfer have higher live birth rates than those with fresh embryo transfer in patients without OHSS.[25,26] However, not all studies show this.[27] Studies also show that patients with frozen embryo transfer are less likely to get OHSS.[26] Our study shows the detrimental effects of fresh embryo transfer in patients with OHSS,

Table 5

Baseline demographic data of OHSS cases after IVF, same cycle (fresh) embryo transfer *vs.* delayed cycle (frozen) embryo transfer.

Characteristics	Same cycle pregnancy (*n* = 45)	Delayed cycle pregnancy (*n* = 39)	Statistical values	*P**
Age (years)			–0.29†	0.77
Mean ± *SD*	31.2 ± 3.5	30.7 ± 3.4		
Range	(24.4–37.7)	(22.7–38.0)		
Gravida, *n* (%)			0.40†	0.68
1	29 (64.4)	24 (61.5)		
2	9 (20.0)	7 (17.9)		
3	4 (8.9)	4 (10.3)		
4–7	3 (6.7)	4 (10.3)		
Parity, *n* (%)			–0.26†	0.79
0	36 (80.0)	32 (82.1)		
1	7 (15.6)	6 (15.4)		
2	2 (4.4)	1 (2.6)		
Body mass index (kg/m^2)			–1.00†	0.31
Mean ± *SD*	26.1 ± 6.5	24.6 ± 4.8		
Median (IQR)	24.6 (21.4–28.8)	23.7 (22.0–26.2)		
Body mass index, *n* (%)			–1.52†	0.13
<25 kg/m^2	22 (48.9)	24 (61.5)		
25–<30 kg/m^2	11 (24.4)	11 (28.2)		
30–<40 kg/m^2	7 (15.6)	2 (5.1)		
>40 kg/m^2	2 (4.4)	1 (2.6)		
Not documented	3 (6.7)	1 (2.6)		
Infertility diagnosis,‡ *n* (%)				
Anovulation/oligo-ovulation	21 (46.7)	16 (41.0)	0.27§	0.60
Male factor	16 (35.6)	17 (43.6)	0.57§	0.45
Tubal	6 (13.3)	5 (12.8)	<0.01§	0.94
Other	13 (28.9)	11 (28.2)	<0.01§	0.94
Race, *n* (%)				0.06‖
Caucasian	38 (84.4)	38 (97.4)		
Black or African American	0 (0.0)	1 (2.6)		
Asian	2 (4.4)	0 (0.0)		
Other or mixed	4 (8.9)	0 (0.0)		
Unknown/chose not to disclose	1 (2.2)	0 (0.0)		

*Comparisons between groups were evaluated using the Wilcoxon rank sum test for each continuous and ordinal variable and the Chi-squared test or Fisher exact test for each categorical variable.

†Wilcoxon test statistic, standardized.

‡Some patients had more than one infertility diagnosis.

§Chi-squared test statistic.

‖Fisher exact test, no test statistic.

IQR: Interquartile range; IVF: In vitro fertilization; OHSS: Ovarian hyperstimulation syndrome; *SD*: Standard deviation.

suggesting that perhaps the intensity of OHSS is curtailed in patients with frozen embryo transfer, leading to less severe outcomes. Further, patients with frozen embryo transfer have a longer time period between the incidence of OHSS and delivery, which may further curtail the effects of OHSS.

Research implications

Although poor uterine receptivity has been proposed as a mechanism by which OHSS may cause preterm delivery and small for gestational age, the exact mechanism by which OHSS affects future pregnancies is currently unknown. Further research looking at mechanisms of effect may lead to insight into preterm delivery and future prevention. Additionally, the protective benefit of frozen embryo transfer is also unknown at present.

Strengths and limitations

The strengths of this study include the use of a comparison group matched on parity, maternal age, and cause of infertility to limit the impact of other factors affecting data. Additionally, the use of the REP helps generalize the data to similar populations.[10] There were some limitations to the study. Overall, because of the relatively low incidence of OHSS, the study sample was still small, and not all patients had complete data, resulting in bias. Additionally, not enough information was found in the charts to classify each patient's OHSS as mild, moderate, or severe. Moreover, to obtain a sufficient sample for the study, the study period spanned many years, during which time fertility care and obstetric care significantly changed and were not accounted for in the study. Risk factors for preterm birth such as previous preterm delivery, socioeconomic status, diabetes, and so on

Table 6

Pregnancy and delivery outcomes of OHSS cases after IVF, same cycle (fresh) embryo transfer *vs.* delayed cycle (frozen) embryo transfer.

Outcome measure	Same cycle pregnancy (*n* = 45)	Delayed cycle pregnancy (*n* = 39)	Statistical values	*P**
Maternal				
HDP				0.36[†]
Normotensive	39 (86.7)	31 (79.5)		
Chronic HTN	1 (2.2)	0 (0.0)		
Any HDP	5 (11.1)	8 (20.5)		
Gestational HTN	1	3		
PE superimposed on chronic HTN	0	1		
PE without severe features	2	1		
PE with severe features	2	2		
HELLP syndrome	0	1		
Severe range blood pressures	2 (4.4)	3 (7.7)		0.66[†]
Use of antihypertensives	4 (8.9)	3 (7.7)		0.99[†]
Gestational diabetes	1 (2.2)	5 (12.8)		0.09[†]
Placental abruption	4 (8.9)	0 (0.0)		0.12[†]
Deep vein thrombosis or pulmonary embolism during pregnancy	0 (0.0)	0 (0.0)		—
Antenatal steroids	% of 44[‡]	% of 36[‡]	1.85[§]	0.17
No	34 (77.3)	32 (88.9)		
Yes	10 (22.7)	4 (11.1)		
Age at delivery (years)			–0.89[‖]	0.37
Mean ± *SD*	31.8 ± 3.5	32.5 ± 3.2		
Range	(25.1–38.4)	(24.3–41.0)		
Mode of delivery				0.73[†]
NSVD	22 (48.9)	15 (38.5)		
Cesarean	17 (37.8)	18 (46.2)		
VAVD	2 (4.4)	1 (2.6)		
FAVD	4 (8.9)	5 (12.8)		
Postpartum magnesium	1 (2.2)	3 (7.7)		0.33[†]
Postpartum blood pressure medication	4 (8.9)	3 (7.7)		0.99[†]
Infant				
Gestational age			2.52[¶]	<0.01
Extremely preterm (20–27 wk)	1 (2.2)	1 (2.6)		
Very preterm (28–31 wk)	3 (6.7)	0 (0.0)		
Moderate to late preterm (32–36 wk)	19 (42.2)	9 (23.1)		
Early term (37–38 wk)	11 (24.4)	12 (30.8)		
Full term (39–40 wk)	11 (24.4)	15 (38.5)		
Late term (41 wk)	0 (0.0)	2 (5.1)		
Number of infants:				—
born alive—born stillborn				
0—1	1 (2.2)	0 (0.0)		
1—0	26 (57.8)	29 (74.4)		
1—1	1 (2.2)	0 (0.0)		
2—0	15 (33.3)	9 (23.1)		
3—0	2 (4.4)	1 (2.6)		
Intrauterine fetal demise	2 (4.4%)	0 (0%)		0.50[†]
Birth weight (g)**			–2.23[‖]	0.03
Mean ± *SD*	2650.4 ± 860.2	3058.6 ± 805.6		
Median (IQR)	2645 (2125–3460)	3410 (2350–3670)		
Size for gestational age**				0.64[†]
Small for gestational age	6 (13.3)	3 (7.7)		
Appropriate for gestational age	32 (71.1)	28 (71.8)		
Large for gestational age	7 (15.6)	8 (20.5)		
Apgar score at 1 min[††]	% of 44[‡]	% of 37[‡]		
Stillborn or 1–6 (*vs.* 7–10)	12 (27.3)	10 (27.0)	<0.01[§]	0.98
Apgar score at 5 min[††]	% of 44[‡]	% of 37[‡]		
Stillborn or 1–6 (*vs.* 7–10)	3 (6.8)	3 (8.1)		0.99[†]

*Comparisons between groups were evaluated using the two-sample *t* test for age at delivery and birth weight, the Wilcoxon rank sum test for gestational age categories, and the Chi-squared test or Fisher exact test for categorical variables.

[†]Fisher exact test, no test statistic.

[‡]Birth data were incomplete for four patients with OHSS.

[§]Chi-squared test statistic.

[‖]Two-sample *t* test statistic.

[¶]Wilcoxon test statistic, standardized.

**Birth weight and size for gestational age are based on the smallest infant in there where there were multiple gestations.

[††]Apgar score is based on the lowest score if there were multiple gestations.

—: Not applicable; FAVD: Forceps-assisted vaginal delivery; HDP: Hypertensive disorders of pregnancy; HELLP: Hemolysis, elevated liver enzymes, and low platelet count syndrome; HTN: Hypertension; IQR: Interquartile range; IVF: In vitro fertilization; NSVD: Normal spontaneous vaginal delivery; OHSS: Ovarian hyperstimulation syndrome; PE: Preeclampsia; *SD*: Standard deviation; VASD: Vacuum-assisted vaginal delivery.

could not be accounted for in multivariate analyses because of inability to collect this information with validity. Additionally, the known association between number of oocytes retrieved and preterm birth may explain the findings of the study; however, our multivariate modeling did account for that. The analysis between patients undergoing same-cycle pregnancies *vs.* subsequent-cycle pregnancies may have been underpowered because of small numbers. Finally, reasons for delivery, such as spontaneous *vs.* induced labor, were not collected.

Conclusion

In conclusion, OHSS is associated with an increased risk of preterm delivery and small-for-gestational-age fetuses. This is different from previously reported studies and may change management and counseling of patients with OHSS. Future studies should assess long-term patient outcomes after OHSS, such as long-term development of hypertension, cardiovascular disease, obesity, and other pregnancy outcomes.

Acknowledgments

Parts of this study were presented in abstract form at the American Society for Reproductive Medicine Annual Meeting in Philadelphia, PA, onOctober 15, 2019, and at the American College of Obstetrics and Gynecology in Nashville, TN, on May 4, 2019.

Funding

This study was made possible using the resources of the REP, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Contributions

Ajleeta Sangtani: Conception, design, data collection, analysis, writing, and revision; Maryama Ismail: Data collection, writing, and revision; Amy Weaver: Analysis, writing, and revision; Zaraq Khan: Conception, design, supervision, and revision.

Conflicts of Interest

None.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] Choux C, Barberet J, Ginod P, et al. Severe ovarian hyperstimulation syndrome modifies early maternal serum beta-human chorionic gonadotropin kinetics, but obstetrical and neonatal outcomes are not impacted. Fertil Steril 2017;108(4):650–658.e2. doi: 10.1016/j.fertnstert.2017.07.1160.

[2] Luke B, Brown MB, Morbeck DE, et al. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology (ART) treatment and outcome. Fertil Steril 2010;94(4):1399–1404. doi: 10.1016/j.fertnstert.2009.05.092.

[3] Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update 2003;9(1):77–96. doi: 10.1093/humupd/dmg005.

[4] Abramov Y, Elchalal U, Schenker JG. Obstetric outcome of in vitro fertilized pregnancies complicated by severe ovarian hyperstimulation syndrome: a multicenter study. Fertil Steril 1998;70(6):1070–1076. doi: 10.1016/s0015-0282(98)00350-1.

[5] Roque M, Haahr T, Geber S, et al. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. Hum Reprod Update 2019;25(1):2–14. doi: 10.1093/humupd/dmy033.

[6] Courbiere B, Oborski V, Braunstein D, et al. Obstetric outcome of women with in vitro fertilization pregnancies hospitalized for ovarian hyperstimulation syndrome: a case-control study. Fertil Steril 2011;95(5):1629–1632. doi: 10.1016/j.fertnstert.2010.12.015.

[7] Haas J, Baum M, Meridor K, et al. Is severe OHSS associated with adverse pregnancy outcomes? Evidence from a case-control study. Reprod Biomed Online 2014;29(2):216–221. doi: 10.1016/j.rbmo.2014.04.015.

[8] Vainer-Rotbart S, Sheiner E, Harlev A, et al. The association between ovarian hyperstimulation syndrome and pregnancy complications following fertility treatments. Am J Perinatol 2021. doi: 10.1055/s-0041-1732458.

[9] Buca D, D'Antonio F, Liberati M, et al. Ovarian hyperstimulation syndrome and adverse pregnancy outcome. Minerva Obstet Gynecol 2022;74:178–185.

[10] St Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester Epidemiology Project. Am J Epidemiol 2011;173(9):1059–1068. doi: 10.1093/aje/kwq482.

[11] Rocca WA, Yawn BP, St Sauver JL, et al. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc 2012;87(12):1202–1213. doi: 10.1016/j.mayocp.2012.08.012.

[12] Rocca WA, Grossardt BR, Brue SM, et al. Data resource profile: expansion of the Rochester Epidemiology Project medical records-linkage system (E-REP). Int J Epidemiol 2018;47(2):368–368j. doi: 10.1093/ije/dyx268.

[13] St Sauver JL, Grossardt BR, Leibson CL, et al. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. Mayo Clin Proc 2012;87(2):151–160. doi: 10.1016/j.mayocp.2011.11.009.

[14] Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010;88(1):31–38. doi: 10.2471/BLT.08.062554.

[15] Boomsma CM, Eijkemans MJC, Hughes EG, et al. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006;12(6):673–683. doi: 10.1093/humupd/dml036.

[16] World Health Organization. Preterm birth, 2022. https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth. Accessed December 1, 2017.

[17] ACOG Committee Opinion No. 579: definition of term pregnancy. Obstet Gynecol 2013;122(5):1139–1140. doi: 10.1097/01.AOG.0000437385.88715.4a.

[18] World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development, 2006. https://www.who.int/publications/i/item/924154693X. Accessed January 1, 2017.

[19] Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59. doi: 10.1186/1471-2431-13-59.

[20] de Onis M, Onyango AW, Borghi E, et al. Comparison of the World Health Organization (WHO) child growth standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programmes. Public Health Nutr 2006;9(7):942–947. doi: 10.1017/phn20062005.

[21] Papanikolaou EG, Tournaye H, Verpoest W, et al. Early and late ovarian hyperstimulation syndrome: early pregnancy outcome and profile. Hum Reprod 2005;20(3):636–641. doi: 10.1093/humrep/deh638.

[22] Raziel A, Schachter M, Friedler S, et al. Outcome of IVF pregnancies following severe OHSS. Reprod Biomed Online 2009;19(1):61–65. doi: 10.1016/s1472-6483(10)60047-8.

[23] Wiser A, Levron J, Kreizer D, et al. Outcome of pregnancies complicated by severe ovarian hyperstimulation syndrome (OHSS): a follow-up beyond the second trimester. Hum Reprod 2005;20(4):910–914. doi: 10.1093/humrep/deh713.

[24] Pereira N, Elias RT, Christos PJ, et al. Supraphysiologic estradiol is an independent predictor of low birth weight in full-term singletons born after fresh embryo transfer. Hum Reprod 2017;32(7):1410–1417. doi: 10.1093/humrep/dex095.

[25] Roque M, Lattes K, Serra S, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril 2013;99(1):156–162. doi: 10.1016/j.fertnstert.2012.09.003.

[26] Chen ZJ, Shi Y, Sun Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med 2016;375(6):523–533. doi: 10.1056/NEJMoa1513873.

[27] Vuong LN, Dang VQ, Ho TM, et al. IVF transfer of fresh or frozen embryos in women without polycystic ovaries. N Engl J Med 2018;378(2):137–147. doi: 10.1056/NEJMoa1703768.

Edited By Yang Pan

How to cite this article: Sangtani A, Ismail M, Weaver A, Khan Z. Pregnancy Outcomes Associated with Ovarian Hyperstimulation Syndrome: A Retrospective Cohort Study of Infertile Women. Maternal Fetal Med 2023;5(3):144–154. doi: 10.1097/FM9.0000000000000192.