

## GYNECOLOGY

# Life-threatening complications among women with severe ovarian hyperstimulation syndrome



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**BACKGROUND:** Ovarian hyperstimulation syndrome is a potentially life-threatening clinical condition.

**OBJECTIVE:** The objective of this study was to evaluate risk factors for life-threatening complications for patients with severe ovarian hyperstimulation syndrome in a United States nationwide sample.

**MATERIALS AND METHODS:** Ovarian hyperstimulation syndrome admissions from 2002 to 2011 from the Nationwide Inpatient Sample were included in this study. The association between patient and hospital factors and life-threatening complications (deep vein thrombosis/pulmonary embolism, acute respiratory distress syndrome, acute renal failure, intubation), nonroutine discharge (discharge to skilled nursing facility, transfer hospital), prolonged length of stay, and total hospital charges were analyzed. Survey-adjusted multivariable logistic regression analyses were performed for these outcomes, controlling for risk factors, with adjusted odds ratios with 95% confidence intervals as the measures of effect.

**RESULTS:** A total of 11,562 patients were hospitalized with severe ovarian hyperstimulation syndrome from 2002 to 2011. The majority were white (55.7%), with private insurance (87.7%), aged 25–39 years (84.6%), and hospitalized in an urban location (95%). In all, 19.3% of patients had medical comorbidities including hypertension, diabetes, obesity, hypothyroidism, and anemia. Life-threatening complications occurred in 4.4% of patients (deep vein thrombosis/pulmonary embolism, 2.2%; acute renal failure; acute respiratory distress syndrome, 0.9%; intubation, 0.5%). Patients  $\geq 40$  years old (odds ratio, 4.02; 95% confidence interval, 1.37, 11.76), those with comorbidities (odds ratio, 2.29;

95% confidence interval, 1.46, 3.57), and African American patients (odds ratio, 2.15; 95% confidence interval, 1.25, 3.70) were more likely to develop life-threatening conditions. Patients with medical comorbidities (odds ratio, 0.39; 95% confidence interval, 0.24, 0.63) were also less likely to be routinely discharged from the hospital. Adjusting for patient and hospital demographics, patients with comorbidities were more likely to develop deep vein thrombosis/pulmonary embolism (adjusted odds ratio, 2.44; 95% confidence interval, 1.28, 4.65) and acute renal failure (adjusted odds ratio, 2.26; 95% confidence interval, 1.21, 4.23). Patients who developed life-threatening complications had longer hospital length of stay (adjusted odds ratio, 3.72; 95% confidence interval, 2.28, 6.07) and higher hospital costs (adjusted odds ratio, 5.20; 95% confidence interval, 3.22, 8.39).

**CONCLUSION:** Patients with common medical comorbidities are at higher risk for life-threatening complications in the setting of severe ovarian hyperstimulation syndrome. Furthermore, these complications are associated with high hospital costs and hospital burden. Given the increasing number of in vitro fertilization patients with medical comorbidities, closer monitoring of at-risk patients may be indicated. As assisted reproductive technology practice changes in recent years with strategies designed to reduce ovarian hyperstimulation syndrome risk, future studies are needed to assess the impact of these changes on hospitalization and complication risk.

**Key words:** ovarian hyperstimulation syndrome, severe morbidity

Assisted reproductive technology (ART) has increased in popularity over the past 30 years as a treatment for infertility, with  $>1\%$  of all pregnancies in developed countries now occurring via ART.<sup>1</sup> Use of controlled ovarian stimulation (COS) is a key factor in the success of in vitro fertilization (IVF) because it allows for the development of multiple ovarian follicles at one time.<sup>2</sup> Although COS is generally a safe treatment modality, there is the possibility of

serious side effects including ovarian hyperstimulation syndrome (OHSS).<sup>3</sup> OHSS has a wide pathophysiologic spectrum that ranges from mild illness to severe morbidity and even death.<sup>4</sup>

The syndrome has a variety of symptoms, including shortness of breath, abdominal distension, pleural effusion, ascites, and edema.<sup>5</sup> The disease is thought to be a result of an increase in capillary permeability resulting in fluid shifts from intravascular to extravascular spaces that occurs due to increased ovarian secretion of cytokines and vascular endothelial growth factor.<sup>4</sup> Patients with mild disease often present with lower abdominal discomfort, mild nausea and vomiting, diarrhea, and abdominal distention, which usually resolve in a few days. However, the more severe forms of the disease can be

associated with life-threatening complications that can necessitate admission to the hospital for treatment.<sup>6</sup> Life-threatening complications associated with OHSS include pulmonary embolism and deep vein thrombosis (PE/DVT), acute renal failure (ARF), acute respiratory distress syndrome (ARDS), and intubation.<sup>6</sup>

Although these life-threatening complications are rare, there are limited data on risk factors for these outcomes and limited nationwide data from the United States as to the epidemiology of patients admitted to the hospital for OHSS. Little is known regarding the burden to the healthcare system from these admissions, including hospital costs. Given these knowledge gaps, this study aimed to analyze risk factors associated with OHSS complications, to characterize

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## AJOG at a Glance

**Why was this study conducted?**

To evaluate risk for adverse outcomes in severe ovarian hyperstimulation syndrome.

**Key findings**

Life-threatening complications are rare among women with severe ovarian hyperstimulation syndrome. Risk is highest among older women, black women, and women with medical comorbidities.

**What does this add to what is known?**

This study characterizes population-based risk for life-threatening complications from ovarian hyperstimulation syndrome.

trends in OHSS admissions, and to describe the resulting healthcare burden.

**Materials and Methods****Data**

The 2002 to 2011 Nationwide Inpatient Sample (NIS) was used for this study. The NIS is the largest publicly available all-payer inpatient database capturing 20% of all US inpatient discharges.<sup>7</sup> Assembled annually by the Agency for Healthcare Quality and Research's Healthcare Utilization Project (HCUP), the NIS consists of more than 7 million hospital admissions each year from more than 40 states and 1000 hospitals.<sup>7</sup> The NIS represents 20% of all US hospital discharges and contains a weighting system that allows for calculation of population estimates.<sup>7</sup> These weights were applied in this analysis. The years 2002–2011 were used for analysis, as the NIS underwent a design change in 2012. Therefore, the dataset was limited to before the redesign so as to not have an influence on results due to changes in the survey structure.

**Study population**

Patients were selected using the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code for OHSS (ICD-9-CM: 256.1). Demographic factors analyzed included age (categorized as 18–24, 25–29, 30–34, 35–39, and 40–48 years), race (non-Hispanic white, non-Hispanic black, Hispanic, Asian or Pacific Islander [API], Native American, other), payer (Medicare, Medicaid,

private insurance, no charge, self-pay, other), median income quartile based on ZIP code, and medical comorbidities. Medical comorbidities were identified with ICD-9-CM diagnosis codes and included anemia (ICD-9-CM 280.1–281.9, 285.21–285.29, 285.9), diabetes mellitus (ICD-9-CM 250.00–250.33, 250.40–250.93), depression (ICD-9-CM 300.4, 301.12, 309.0, 309.1, 311), hypertension (ICD-9-CM 401.1, 401.9, 642.00–642.04), hypothyroidism (ICD-9-CM 243–244.2, 244.8, 244.9), and obesity (ICD-9-CM: 278.0, 278.00, 278.01).

Hospital factors included hospital bed size (small, medium, large), teaching status (nonteaching, teaching), hospital region (Northeast, Midwest, South, West), and location (urban, rural). Bed size categories are based on hospital beds, and are specific to the hospital's location and teaching status. Given that the NIS does not contain unique patient identifiers, each discharge was treated as an independent event. Data were de-identified and deemed exempt by the Columbia University Institutional Review Board.

**Outcomes**

The primary outcome of our study was a composite occurrence of life-threatening complications and nonroutine discharge disposition. The life-threatening complications analyzed included the following: acute respiratory distress syndrome (ARDS) (ICD-9-CM 518.5, 518.8x), deep vein thrombosis/pulmonary

embolism (DVT/PE) (ICD-9-CM 415.1x, 673.2x; 451.1x, 453.4x, 453.8x, 453.9, 671.3x–671.5x), intubation (Clinical Classifications Software: 216),<sup>8</sup> and acute renal failure (ARF) (ICD-9-CM 584.9x). Nonroutine discharge was defined as transfer to a short-term hospital, transfer to a skilled nursing facility or intermediate care facility, home healthcare, discharge against medical advice, or unknown. Length of stay (LOS) and total charges were included as continuous variables. Total inpatient charges were adjusted for inflation and reflect charges in 2016 US dollars. Secondary outcomes included individual life-threatening complications (ARDS, DVT/PE, intubation, ARF), as well as prolonged LOS (defined as  $\geq 90^{\text{th}}$  percentile,  $> 8$  days) and higher hospital charges (defined as  $\geq 90^{\text{th}}$  percentile,  $> \$39,483$ ).

**Analysis**

Unadjusted demographic analyses were performed using survey-adjusted univariable logistic regression for all patient, hospital, outcomes, and primary exposure factors to describe the study population. Our primary exposure of interest was the presence of common medical comorbidities listed above that are increasingly common in the population undergoing ovarian stimulation for ART. Multivariable survey-adjusted logistic regression analyses were fit to assess the relationship between medical comorbidities, demographic factors, and hospital factors with the primary and secondary outcomes. Because it is possible that polycystic ovary syndrome (PCOS) may be associated with increased risk of adverse outcomes, we fit a sensitivity analysis model assessing life-threatening complications adjusting for the aforementioned patient and hospital demographic factors with the presence of common medical comorbidities and PCOS. Models fitted for prolonged LOS and higher inpatient charges were additionally adjusted for by presence of life-threatening complications. Results are presented as unadjusted odds ratios (OR) and

**TABLE 1**  
**Demographic characteristics of women admitted for OHSS**

	All patients (n = 11,0562)		No life-threatening complication (n = 11,048)		Life-threatening complication (n = 514)	
Length of stay, days, mean	4.08		3.93		7.35	
Total charges, mean	\$19,620.22		\$19,105.98		\$53,230.58	
	n	%	n	%	n	%
<b>Discharge status</b>						
Nonroutine discharge	422	3.7%	339	3.08%	79	15.45%
Routine discharge	11,139	96.4%	10,681	96.92%	430	84.55%
<b>Age category, y</b>						
18–24	1011	8.8%	987	8.96%	24	4.73%
25–29	3144	27.3%	3016	27.37%	128	25.13%
30–34	4178	36.2%	4000	36.30%	178	34.97%
35–39	2423	21.0%	2313	20.99%	110	21.63%
40+ years old	773	6.7%	704	6.39%	69	13.54%
<b>Race/ethnicity</b>						
White	6443	55.7%	6142	55.74%	278	54.55%
Black	1033	8.9%	942	8.54%	92	18.01%
Hispanic	739	6.4%	713	6.47%	27	5.27%
Asian Pacific Islander	472	4.1%	438	3.98%	34	6.65%
Native American	66	0.6%	66	0.60%	n/a	n/a
Other	499	4.3%	479	4.34%	20	3.93%
Missing	2310	20.0%	2241	20.33%	59	11.59%
<b>Payer information</b>						
Medicare	148	1.3%	139	1.26%	10	1.87%
Medicaid	567	4.9%	543	4.92%	24	4.68%
Private insurance	10,134	87.7%	9663	87.68%	444	87.28%
Self-pay	290	2.5%	285	2.59%	n/a	n/a
No charge	38	0.3%	38	0.35%	n/a	n/a
Other	357	3.1%	326	2.96%	26	5.17%
Missing	26	0.2%	26	0.24%	n/a	n/a
<b>Comorbidity status</b>						
No comorbid conditions	9331	80.7%	8987	81.55%	336	65.93%
Comorbidity present <sup>a</sup>	2230	19.3%	2033	18.45%	173	34.07%
<b>PCOS status</b>						
No PCOS	10,576	91.7%	10,149	92%	428	84%
PCOS	953	8.3%	871	7.9%	81	15.9%

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(continued)

adjusted odds ratios (aOR), as appropriate, with 95% confidence intervals (CI) as the measures of effect. Given that the HCUP data use agreement

precludes reporting cell sizes  $\leq 10$ , rare outcomes are not reported. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

## Results

Between 2002 and 2011, a total of 11,562 patients were hospitalized nationally with OHSS, which represents 0.88% of

**TABLE 1**  
**Demographic characteristics of women admitted for OHSS** (continued)

	All patients (n = 11,0562)		No life-threatening complication (n = 11,048)		Life-threatening complication (n = 514)	
Length of stay, days, mean	4.08		3.93		7.35	
Total charges, mean	\$19,620.22		\$19,105.98		\$53,230.58	
	n	%	n	%	n	%
Median ZIP code income						
Lowest	1437	12.4%	1364	12.38%	73	14.36%
Second	1960	17.0%	1862	16.90%	88	17.30%
Third	2595	22.5%	2490	22.59%	101	19.75%
Highest	4088	35.4%	3873	35.14%	198	38.90%
Missing	1481	12.8%	1432	12.99%	49	9.69%
Hospital region						
Northeast	2904	25.1%	2765	25.09%	134	26.40%
Midwest	2645	22.9%	2541	23.05%	90	17.59%
South	3985	34.5%	3813	34.60%	164	32.23%
West	2027	17.5%	1902	17.26%	121	23.79%
Hospital teaching status						
Nonteaching	4128	35.7%	3961	35.94%	155	30.48%
Teaching	7399	64.0%	7030	63.79%	354	69.52%
Missing	34	0.3%	30	0.27%	n/a	n/a
Hospital bed size						
Small	1312	11.4%	1276	11.58%	31	6.03%
Medium	2658	23.0%	2530	22.96%	120	23.66%
Large	7557	65.4%	7184	65.19%	358	70.31%
Missing	34	0.3%	30	0.27%	n/a	n/a
Hospital location						
Rural	516	4.5%	516	4.68%	n/a	n/a
Urban	11,012	95.2%	10,475	95.05%	509	100%
Missing	34	0.3%	30	0.27%	n/a	n/a

OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome.

<sup>a</sup> Medical comorbidity includes presence of hypertension, diabetes, anemia, obesity, and/or thyroid condition.Selter et al. Risk factors for life-threatening complications in severe OHSS. *Am J Obstet Gynecol* 2019.

patients out of all national ART cycles documented in the Society for Assisted Reproductive Technology Clinical Outcome Reporting System for 2002–2011.<sup>9</sup> The number of hospitalized patients per year and ART cycles per year are noted in [Supplemental Table 1](#). Patients were most likely to be 30–34 years of age (n = 4178, 36.1%), non-Hispanic white (n = 6443, 55.7%), from the South (n = 3985, 34.4%), to

have private insurance (n = 10,134, 87.7%), and to live in the highest-income ZIP code quartile (n = 4088, 35.4%) ([Table 1](#)). The majority of admissions occurred in teaching hospitals (n = 7399, 64.0%) that were large (n = 7557, 65.3%) and located in urban environments (n = 11,012, 95.2%). Overall, 19.4% of the patients had medical comorbidities. The total average length of stay for all patients was 4.08 days, with

a mean total adjusted charge of \$19,620 ([Table 1](#)). The number of deaths from this analysis is not reported, given that HCUP's data use agreement precludes reporting cell sizes ≤10.

Of the patients admitted to the hospital for OHSS, 4.4% experienced life-threatening complications. 2.2% of patients experienced DVT/PE, 1.5% ARDS, 0.9% ARF, and 0.5% intubation ([Table 2](#)). Demographic, hospital, and

**TABLE 2**  
**Risk for individual life-threatening complications**

Life-threatening complications	n	%
Acute respiratory distress syndrome		
Absent	11,454	99.1%
Present	108	0.9%
Intubation/ventilation		
Absent	11,503	99.5%
Present	59	0.5%
Acute renal failure		
Absent	11,384	98.5%
Present	177	1.5%
Deep venous thrombosis/pulmonary embolism		
Absent	11,305	97.8%
Present	256	2.2%

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comorbid risk factors were evaluated in relation to risk for life-threatening complications (Table 3). In unadjusted analyses, patients  $\geq 40$  years of age were significantly more likely to have life-

threatening complications (OR, 4.02; 95% CI, 1.47, 11.76) compared to women 18–24 years of age. Black women were more likely to have life-threatening complications compared to

white women (OR, 2.15; 95% CI, 1.25, 3.70). Medical comorbidities were also significantly more likely among women with a life-threatening complication (34.1%) than among women without a life-threatening complication (18.4%) ( $P < .01$ ) (OR, 2.29; 95% CI, 1.46, 3.57).

Similar findings were noted in multivariable analyses. Black women were more likely than white women to develop a life-threatening complication (aOR, 2.08; 95% CI, 1.18, 3.66) as were women  $\geq 40$  years of age compared to women 18–24 years of age (aOR, 3.38; 95% CI, 1.06, 10.76). Women with a comorbid medical condition were significantly more likely to develop a life-threatening complication than women without a comorbid condition (aOR, 2.09; 95% CI, 1.33, 3.30). Demographic factors including ZIP code income quartile and type of insurance and hospital factors such as region, size, teaching status, and location were not significantly associated with life-threatening complications (Table 3). When examining individual complications (Table 4),

**TABLE 3**  
**Adjusted and unadjusted models for life-threatening complications for patients hospitalized with OHSS**

Race/ethnicity	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
White	1.00	Reference	1.00	Reference
Black	2.15	1.25, 3.70	2.08	1.18, 3.66
Hispanic	0.83	0.34, 2.05	0.70	0.28, 1.75
Asian Pacific Islander	1.71	0.69, 4.22	1.34	0.54, 3.30
Native American	n/a	n/a	n/a	n/a
Other	0.92	0.33, 2.59	0.95	0.34, 2.63
Payer Information				
	OR	95% CI	OR	95% CI
Medicare	1.49	0.35, 6.28	0.78	0.15, 3.97
Medicaid	0.96	0.37, 2.44	0.75	0.27, 2.09
Private insurance	1.00	Reference	1.00	Reference
Self-pay	0.38	0.05, 2.88	0.36	0.05, 2.35
No charge	n/a	n/a	n/a	n/a
Other	1.76	0.74, 4.16	1.82	0.76, 4.37
Comorbidity status				
	OR	95% CI	OR	95% CI
No comorbid conditions	1.00	Reference	1.00	Reference
Comorbidity present	2.29	1.46, 3.57	2.09	1.33, 3.30

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(continued)

**TABLE 3**  
**Adjusted and unadjusted models for life-threatening complications for patients hospitalized with OHSS** (continued)

Race/ethnicity	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
PCOS status	OR	95% CI	OR	95% CI
No PCOS	1.00	Reference	1.00	Reference
PCOS present	2.21	1.29, 3.78	1.75	0.98, 3.13
Age, y	OR	95% CI	OR	95% CI
18–24	1.00	Reference	1.00	Reference
25–29	1.74	0.68, 4.46	1.87	0.69, 5.08
30–34	1.83	0.70, 4.78	1.81	0.63, 5.24
35–39	1.95	0.70, 5.43	1.75	0.59, 5.15
40+	4.02	1.37, 11.76	3.38	1.06, 10.76
Median income quartile by ZIP code	OR	95% CI	OR	95% CI
Income quartile 1	1.05	0.57, 1.92	1.16	0.62, 2.15
Income quartile 2	0.93	0.52, 1.63	1.00	0.55, 1.80
Income quartile 3	0.79	0.43, 1.45	0.91	0.48, 1.73
Income quartile 4	1.00	Reference	1.00	Reference
Hospital region	OR	95% CI	OR	95% CI
Northeast	1.00	Reference	1.00	Reference
Midwest	0.73	0.36, 1.47	0.88	0.42, 1.87
South	0.89	0.46, 1.69	0.86	0.44, 1.65
West	1.31	0.68, 2.52	1.38	0.68, 2.80
Hospital teaching status	OR	95% CI	OR	95% CI
Nonteaching	1.00	Reference	1.00	Reference
Teaching	1.29	0.80, 2.06	1.32	0.81, 2.15
Hospital bed size	OR	95% CI	OR	95% CI
Small	1.00	Reference	1.00	Reference
Medium	1.98	0.67, 5.84	2.02	0.65, 6.30
Large	2.07	0.73, 5.84	2.37	0.79, 7.06
Hospital location	OR	95% CI	OR	95% CI
Urban	n/a	n/a	n/a	n/a
Rural	1.00	Reference	1.00	Reference

CI, confidence interval; n/a, not applicable; OHSS, ovarian hyperstimulation syndrome; OR, odds ratio; PCOS, polycystic ovary syndrome.  
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after adjusting for patient and hospital demographic factors, patients with medical comorbidities were more likely to develop DVT/PE (aOR, 2.47; 95% CI, 1.29, 4.75) and ARF (aOR, 2.26; 95% CI, 1.21, 4.23). Medical comorbidities were not significantly associated with risk for ARDS or intubation.

Demographic and hospital risk factors were evaluated in relation to

routine discharge (Table 5). Women who experienced a life-threatening complication were less likely to be routinely discharged (84.5%) than women without a life-threatening complication (96.9%) (OR, 0.39; 95% CI, 0.24, 0.63). Conversely, older age (35–39 years: OR, 2.78; 95% CI, 1.19, 6.47) and urban hospital location (OR, 2.66; 95% CI, 1.36, 5.21) were

associated with higher odds of routine discharge compared to age 18–24 years and rural hospital location, respectively. Similar findings were noted upon adjustment in adjusted analyses. Patient race, median income quartile, hospital teaching status, and hospital size were not associated with significantly different odds of routine discharge (Table 5).

**TABLE 4**  
**Adjusted models for individual life-threatening conditions**

	ARDS	ARF	DVT/PE	Intubation
Medical comorbidities				
Absent	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Present	2.32 (0.92, 5.86)	2.26 (1.21, 4.23)	2.44 (1.28, 4.65)	2.49 (0.72, 8.54)

ARDS, acute respiratory distress syndrome; ARF, acute renal failure; DVT/PE, deep venous thrombosis/pulmonary embolism.

Data are adjusted odds ratio (95% confidence interval). Each model is additionally adjusted for demographic and hospital factors.

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Last, we examined the impact of both medical comorbidities and life-threatening complications on high hospital charges and prolonged LOS. After adjusting for other demographic and hospital factors, we found that patients with medical comorbidities and patients

who developed life-threatening complications were at increased risk for longer hospital LOS and higher hospital charges (Table 6). Patients with comorbid conditions (aOR, 1.67; 95% CI, 1.18, 2.38) and those with life-threatening complications (aOR, 3.71; 95% CI, 2.28, 6.05)

were significantly more likely to have prolonged LOS. Patients with comorbidities had twice the odds (aOR 2.01, 95% CI 1.43, 2.83) and patients with life-threatening complications had more than 5 times the odds (aOR 5.21, 95% CI 3.23, 8.41) of high hospital charges. In

**TABLE 5**  
**Unadjusted and adjusted models for routine discharge among women hospitalized for OHSS**

	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Race/ethnicity				
White	1.00	Reference	1.00	Reference
Black	0.58	0.30, 1.12	0.56	0.28, 1.12
Hispanic	11.02	0.32, 2.41	1.08	0.42, 2.73
Asian Pacific Islander	1.30	0.41, 4.14	1.16	0.32, 4.13
Native American	n/a	n/a	n/a	n/a
Other	1.50	0.99, 1.52	3.62	0.51, 25.72
Payer information	OR	95% CI	OR	95% CI
Medicare	0.18	0.06, 0.48	0.43	0.15, 1.25
Medicaid	0.93	0.31, 2.76	1.67	0.56, 4.94
Private insurance	1.00	Reference	1.00	Reference
Self-pay	n/a	n/a	n/a	n/a
No charge	0.27	0.03, 2.25	0.28	0.03, 2.80
Other	0.97	0.29, 3.27	1.22	0.36, 4.21
Comorbidity status	OR	95% CI	OR	95% CI
No comorbid conditions	1.00	Reference	1.00	Reference
Comorbidity present	0.39	0.24, 0.63	0.47	0.28, 0.77
Age, y	OR	95% CI	OR	95% CI
18–24	1.00	Reference	1.00	Reference
25–29	1.79	0.86, 3.71	1.75	0.79, 3.89
30–34	1.95	0.91, 4.19	1.92	0.84, 4.37
35–39	2.78	1.19, 6.47	3.21	1.29, 8.01

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(continued)

**TABLE 5**  
**Unadjusted and adjusted models for routine discharge among women hospitalized for OHSS** (continued)

Race/ethnicity	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
40+ years old	0.70	0.29, 1.66	1.02	0.39, 2.64
Median income quartile based on ZIP code	OR	95% CI	OR	95% CI
Income quartile 1	0.75	0.38, 1.46	0.96	0.46, 1.99
Income quartile 2	0.73	0.40, 1.32	0.91	0.49, 1.70
Income quartile 3	0.88	0.48, 1.60	0.92	0.50, 1.67
Income quartile 4	1.00	Reference	1.00	Reference
Hospital region	OR	95% CI	OR	95% CI
Northeast	1.00	Reference	1.00	Reference
Midwest	1.06	0.57, 1.97	1.15	0.62, 2.12
South	1.46	0.76, 2.82	1.83	0.90, 3.72
West	0.97	0.50, 1.86	1.03	0.52, 2.05
Hospital teaching status	OR	95% CI	OR	95% CI
Nonteaching	1.00	Reference	1.00	Reference
Teaching	1.29	0.80, 2.08	1.17	0.70, 1.95
Hospital bed size	OR	95% CI	OR	95% CI
Small	Reference	Reference		Reference
Medium	1.24	0.52, 2.93	1.39	0.62, 3.09
Large	1.12	0.53, 2.37	1.31	0.65, 2.64
Hospital location	OR	95% CI	OR	95% CI
Urban	2.66	1.36, 5.21	2.48	1.15, 5.35
Rural	Reference	Reference		Reference

CI, confidence interval; n/a, not applicable; OHSS, ovarian hyperstimulation syndrome; OR, odds ratio.

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our sensitivity analysis, PCOS was not associated with composite life-threatening complications (OR, 1.75; 95% CI, 0.98, 3.13).

### Comment

Although the overall risk for life-threatening complications among women admitted for OHSS is approximately 1 in 25, patients with common medical comorbidities are at significantly higher risk. Other significant risk factors included maternal age  $\geq 40$  years and non-Hispanic black race/ethnicity. Underlying medical comorbidity was associated with both prolonged hospital stays and higher hospital costs. These findings support that patients with

comorbidities and OHSS should be followed closely to minimize risk for subsequent life-threatening complications.

Guidelines from the American Society for Reproductive Medicine released in 2016 outline factors associated with higher risk of OHSS, including maternal age, body mass index, race, ovarian reserve markers, and type of IVF stimulation protocol.<sup>6</sup> Although awareness of OHSS risk factors is important clinically, our study also illustrates factors associated with risk for further complications once patients have developed OHSS severe enough to require hospitalization, specifically medical comorbidity, maternal age, and race. Most studies examining age as it relates to OHSS show

higher risk for younger patients in developing OHSS<sup>10,11</sup> However, this study shows that if patients do acquire OHSS, older patients are actually at higher risk for life-threatening complications. When reproductive endocrinology practitioners are determining eligibility for IVF treatment and planning stimulation criteria, they may want to consider certain protocols, including use of gonadotropin-releasing hormone (GnRH) agonist triggers and freeze-all cycles in patients with these comorbidities to decrease risk of developing OHSS.<sup>6</sup>

Not only are patients with comorbid conditions at higher risk for life-threatening complications associated

**TABLE 6**  
**Adjusted models for prolonged length of stay and hospital charges  $\geq 90^{\text{th}}$  percentile**

	Prolonged length of stay		Hospital charges $\geq 90^{\text{th}}$ percentile	
	OR	95% CI	OR	95% CI
Life-threatening complication				
No complication	1.00	Reference	1.00	Reference
Complication present	3.71	2.28, 6.05	5.21	3.23, 8.41
Medical comorbidity				
No comorbidity	1.00	Reference	1.00	Reference
Comorbidity present	1.67	1.18, 2.38	2.01	1.43, 2.83

CI, confidence interval; OR, odds ratio.

Each model is adjusted for prior patient and hospital demographic factors.

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with OHSS, but comorbidities also lead to higher risk of nonroutine discharge from the hospital, supporting that morbidity may be present after hospital discharge. This finding of comorbidities leading to increased complications and longer hospital LOS and cost is not unique to the OHSS population and has been shown in a variety of different inpatient populations.<sup>12-14</sup> Nevertheless, as a wider range of patients undertake IVF procedures, as well as more patients with comorbidities including diabetes, hypertension, and obesity, among others,<sup>15</sup> changes in surveillance may be required with this patient population to obviate increasing risk.

An important finding in this analysis was that non-Hispanic black women were at increased risk for life-threatening complications. Previous studies additionally support that black patients are at increased risk for OHSS compared to Hispanic and non-Hispanic white patients.<sup>16</sup> The cause of this increased risk for this disparity could not be determined by this analysis, but could be due to a range of factors including both unmeasured differences in risk factors and differences in care.

This study has important limitations. First, the use of administrative data may lead to both under- or overascertainment of diagnoses and outcomes. Misclassification may also be a concern, given that these data are collected primarily for billing purposes. We could not review patient charts, imaging, and other

important clinical information. This database does not have access to specific IVF protocols used, so it is impossible to examine how different protocols (ie, ovulation induction with gonadotropin/intrauterine insemination vs. IVF vs. donor oocyte/autologous oocyte cycles) could affect complications. Although rare, some patients even could have developed OHSS without undergoing fertility treatment, and this population could not be specifically examined. In addition, given that only inpatient data were reviewed, data for management of a large proportion of OHSS that is managed on an outpatient basis<sup>17</sup> was not able to be reviewed. Despite this limitation, it is likely that patients with OHSS with the highest acuity would be hospitalized and thus captured in this analysis. Furthermore, the database does not capture the most recent years of data. Practice has changed in recent years to decrease the risk of OHSS through the use of GnRH agonist triggers and frozen embryo transfers.<sup>6</sup> Although these protocol changes have successfully reduced the risk, they have not eliminated OHSS in all patients.<sup>18-20</sup> Therefore, future studies could examine the impact of these changes on hospitalization and complication risk up to the present. Finally, we used intubation as an outcome in our analysis; this outcome itself is not a life-threatening complication and is instead representative of a critical care scenario.

A strength of this analysis is that analysis of administrative data is

appropriate in determining broad overviews of resource use and disease burden.

In summary, this study is the first to examine US national data to determine the incidence of severe complications from OHSS. We illustrate that patients with common comorbidities have a higher risk of life-threatening complications when they develop OHSS requiring hospitalization, and that these complications are associated with higher cost and longer hospital stays. Because IVF is an elective procedure, it is important for providers to be aware of the possible risks for patients and to consider these factors when determining IVF protocols for their patients. ■

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**SUPPLEMENTAL TABLE 1****Number of ovarian hyperstimulation syndrome hospitalizations and total assisted reproductive technology cycles by year**

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total ART cycles <sup>a</sup>	115,392	112,988	119,461	123,200	126,726	132,745	140,795	142,241	146,693	154,412
OHSS hospitalizations	1291	1139	1194	1515	1254	1296	973	867	933	1100

ART, assisted reproductive technology; OHSS, ovarian hyperstimulation syndrome.

<sup>a</sup> Data are taken from the Society for Assisted Reproductive Technology Clinical Outcome Reporting System National Summary Reports.

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