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Original Article

Impact of obstructive sleep apnea on perioperative complications among patients undergoing hysterectomy: a population-based analysis

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ABSTRACT

Introduction: Although obstructive sleep apnea (OSA) is a known risk factor for perioperative complications in various patient cohorts data is lacking for patients undergoing hysterectomies, one of the most frequently performed surgeries among women. Using national data we therefore aimed to assess the risk in this patient group.

Materials and methods: We extracted data on patients who underwent a hysterectomy between 2006 and 2014 from a large nationwide database (n = 459,508). OSA patients (identified by ICD-9 CM codes) were compared to non-OSA patients regarding perioperative outcomes: cardiac, central-nervous, gastrointestinal, genitourinary, renal, respiratory, and thromboembolic complications; as well as opioid prescription, need for blood transfusion, cost of hospitalization, length of stay and ICU admission. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

Results: Overall, 2.67% (n = 11,936) of patients were identified as having OSA. Compared to non-OSA patients, OSA was particularly associated with higher odds for renal (OR 1.98; 95% CI 1.70–2.32) and respiratory complications (OR 3.25; 95% CI 2.97–3.56), and ICU admission (OR 2.28; 95% CI 1.77–2.94). Further, while significant, OSA was associated with modestly increased cost of hospitalization (+6.24%; P < 0.0001) and length of stay (+2.58%; P < 0.0001).

Conclusions: In patients undergoing hysterectomies, OSA was associated with substantially increased risk of complications and modestly increased resource utilization. Further research is needed to assess currently used perioperative care strategies for OSA patients undergoing hysterectomies, with the goal to improve outcomes.

1. Introduction

Obstructive sleep apnea (OSA) – a disorder characterized by episodes of complete or partial upper airway collapse-has been identified as a risk factor for perioperative complications (eg increased risk of respiratory complications and mortality) in various surgical cohorts [1]. However, there is a lack of data on the prevalence of OSA and its association with outcomes in patients undergoing hysterectomies. With one out of nine women undergoing hysterectomy in her lifetime, this procedure is one of the most frequently performed surgeries among women [2]. Moreover, it has been shown that women are more frequently affected by OSA than previously suspected [3]. While there seem to be gender differences in the prevalence of OSA due to hormonal status, there is also evidence to support that OSA among female patients is underreported [3–5]. Furthermore, the prevalence of obesity – one of the major predisposing factors for OSA [6] – has steadily increased among women in the last decades and is expected to increase further [7]. Thus, patients

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undergoing hysterectomy might represent a large patient cohort at risk for OSA-associated complications.

Therefore, we analyzed the impact of OSA on perioperative outcomes among patients undergoing hysterectomy using a large national cohort. Analogous to other surgeries, we hypothesized that OSA in patients undergoing a hysterectomy would be associated with an increased risk of perioperative complications, increased cost of hospitalization and length of hospital stay.

2. Materials and methods

This study qualified for exemption from patient consent by the Institutional Review Boards of the Hospital for Special Surgery (New York, NY, USA; #2012-050-CR2) and Icahn School of Medicine at Mount Sinai (New York, NY; #14-00674) as only de-identified data were used.

Data was extracted from a large nationwide administrative claims database (Premier Healthcare Database, Premier Inc., Charlotte, NC) which contains data from approximately 20% of hospitalizations throughout the United States [8]. Data containing diagnosis codes and billing items are supplied from over 600 hospitals and entered into this administrative database. To assure validity and integrity of the data Premier Inc. continuously performs thorough data validation and quality assurance for all data entered to the database. This database has been used previously by several study groups to address a variety of clinical, pharmacological and epidemiological questions [9].

We included patients who underwent a hysterectomy between 2006 and 2014, by using International Classification of Diseases-9th revision-Clinical Modification (ICD-9 CM) procedure codes encompassing abdominal, vaginal and laparoscopic approaches as well as procedures with a change in surgical approach, irrespective of the indication for the surgery (specific ICD-9 CM codes are listed in Appendix 1). Exclusion criteria were: unknown discharge status (n = 1046), a hysterectomy performed at a hospital with <30 procedures to ensure a sufficient sample size per cluster (n = 768), and patients who did not have billing for opioid prescription (one of the study outcomes, see below) or had an opioid prescription >95th percentile to exclude outliers (n = 48,894).

The main effect of interest was a diagnosis of OSA (identified by ICD-9 CM codes listed in Appendix 2). This approach assumes that this is pre-operatively identified OSA and has been widely used in previously published studies [10–12]. Nonetheless, given the restrictions of the dataset we were unable to take time from OSA diagnosis to surgery into account as a variable.

Patient-related variables included age, race, obesity, and Deyo-Charlson Comorbidity Index (DCCI) to quantify overall comorbidity burden. In addition to the overall comorbidity burden separate variables were created for history of substance use/abuse, chronic pain conditions and psychiatric comorbidities as these are known to affect opioid prescription [13]. The DCCI is one of the most commonly used comorbidity indices to adjust for patient casemix [14]. The score was originally proposed by Charlson et al., [15], and then modified in the paper by Yurkovich et al., [14]. This method assigns a score to 12 chronic medical conditions and uses the weighted sum which equals the 'Index'. This sum was mainly used to predict long-term mortality but is now more commonly used as casemix adjustment as mortality risk is likely to coincide with patient casemix severity.

Healthcare related variables included insurance type, hospital location, hospital size, teaching status and mean annual number of hysterectomies per hospital. Procedure related variables included procedure year and procedure type. Anesthesia/analgesia variables included the type of anesthesia, use of patient controlled analgesia (PCA) and the use of non-opioid analgesics (intravenous acetaminophen, NSAID, COX-2 inhibitor, ketamine, pregabalin/gabapentin).

Outcome variables included cardiac, central-nervous (CNS), gastrointestinal (GI), genitourinary (GU), renal, respiratory, and thromboembolic (TE) complications as well as blood transfusions, opioid prescription, cost of hospitalization (Cost), length of stay (LOS) and intensive care unit (ICU) admissions. Blood transfusions, cardiac, CNS, GI, GU, renal, respiratory and TE complications were identified by using ICD-9 CM codes (Appendix 3). Data regarding opioid prescription, cost of hospitalization in U.S. dollars, length of stay in days and intensive care unit (ICU) admission were derived from billing data provided by Premier. For opioid prescription the amount of opioids billed for during the hospitalization was transformed into oral morphine equivalents (OME) using the GlobalRPH "opioid analgesic converter" [16] and the Lexicomp® "opioid agonist conversion" [17].

First, in univariable analyses we compared OSA patients to non-OSA patients regarding all study variables and outcomes using Chi-square and t-tests (or non-parametric tests where appropriate) for categorical and continuous variables, respectively. Subsequently, multilevel multivariable modeling was performed including variables that were found significant at the $P < 0.15$ level in the univariable analysis, and variables that were deemed to be clinically relevant. This is in line with the approach recommended by Hosmer and Lemeshow [18]. However, given the large sample size, parsimony is less of an issue in model building and therefore, in practice, this approach results in adding all available variables to the multivariable models.

Continuous outcome variables (opioid prescription, cost, LOS) were log-transformed due to the highly skewed nature of the data. For binary outcomes the results are reported as adjusted odds ratio ratios (OR) and 95% confidence intervals (95% CI); for continuous outcomes results are reported as percent difference compared to non-OSA patients and 95% CI. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

Of 459,508 patients undergoing a hysterectomy, 11,936 (2.67%) had a diagnosis code for OSA listed. Table 1 shows demographic as well as procedure, anesthesia and hospital related variables by OSA status. Notably, the proportion of patients with a diagnosis of OSA undergoing a hysterectomy gradually increased from 2006 to 2014. On average, OSA patients were older (52.3 ± 11.4 years vs. 48.4 ± 12.1 years; $P < 0.0001$) and had a higher DCCI (1.13 ± 1.79 vs. 0.55 ± 1.49; $P < 0.0001$) than non-OSA patients. Further, obesity was significantly more prevalent among OSA patients (54.2% vs. 12.4%, $P < 0.0001$).

As shown in Table 2, the incidence of all complications, except GU complications, was significantly higher in OSA patients. Importantly, some complication rates (eg renal and respiratory) were over five times as high among OSA patients compared to non-OSA patients. OSA patients had significantly longer LOS (three days, interquartile range 2–3 vs. two days, interquartile range 1–3) and increased cost ($10,464, interquartile range $6387–12,236 vs. $7,984, interquartile range $5077–9312), compared to non-OSA patients. Interestingly, higher opioid prescription (334 mg OME, interquartile range 162–454 vs. 311 mg OME, interquartile range 155–415) among OSA patients was observed.

When adjusting for all relevant variables (Table 3), OSA was associated with significantly higher odds for ICU admission (OR 2.28; 95% CI 1.77–2.94, $P < 0.05$) and renal (OR 1.98; 95% CI 1.70–2.32, $P < 0.05$) or respiratory complications (OR 3.25; 95% CI 2.97–3.56, $P < 0.05$) in particular.

Additionally, OSA status was associated with modest but significant increases in cost of hospitalization (+6.2%; $P < 0.0001$), length of stay (+2.6%; $P < 0.0001$), and opioid prescription (+1.2%;

Table 1
Study variables by OSA status.

	Diagnosis of Sleep Apnea				P-value[b]
	Yes (n = 11,936)		No (n = 447,572)		
	n	%	n	%	
PATIENT RELATED					
Mean Age[a]	52.3	11.4	48.4	12.1	<0.0001
Race					
White	7855	65.8	278,992	62.3	<0.0001
Black	1941	16.3	68,520	15.3	
Hispanic	263	2.2	17,103	3.8	
Other	1877	15.7	82,957	18.5	
Mean Deyo-Charlson Comorbidity Index[a]	1.13	1.8	0.55	1.5	<0.0001
History of Substance Use/Abuse	1585	13.3	54,395	12.2	0.00021
Pain Conditions	4420	37.0	89,322	20.0	<0.0001
Psychiatric Comorbidities	3436	28.8	55,841	12.5	<0.0001
Obesity	6489	54.2	55,650	12.4	<0.0001
HEALTHCARE RELATED					
Insurance Type					
Commercial	7338	61.5	310,835	69.4	<0.0001
Medicaid	1123	9.4	43,245	9.7	
Medicare	2850	23.9	62,834	14.0	
Uninsured	252	2.1	15,265	3.4	
Unknown	373	3.1	15,393	3.4	
Hospital Location					
Rural	849	7.1	46,501	10.4	<0.0001
Urban	11,087	92.9	401,071	89.6	
Hospital Size					
<300 beds	3174	26.6	145,675	32.5	<0.0001
300-499 beds	4605	38.6	165,753	37.0	
≥500 beds	4157	34.8	136,144	30.4	
Hospital Teaching Status					
Non-Teaching	5852	49.0	266,041	59.4	<0.0001
Teaching	6084	51.0	181,531	40.6	
Mean number of hysterectomies/year per hospital[a]	263.3	159.7	310.6	213.3	<0.0001
PROCEDURE RELATED					
Year of Procedure					
2006	521	4.4	38,381	8.6	<0.0001
2007	1111	9.3	63,667	14.2	
2008	1205	10.1	57,177	12.8	
2009	1388	11.6	58,486	13.1	
2010	1537	12.9	55,764	12.5	
2011	1668	14.0	54,092	12.1	
2012	1768	14.8	48,051	10.7	
2013	1523	12.8	40,085	9.0	
2014	1215	10.2	31,869	7.1	
Procedure Type					
Abdominal	6245	52.3	226,833	50.7	<0.0001
Laparoscopic to Open	1152	9.7	22,794	5.1	
Laparoscopic	3229	27.1	119,999	26.8	
Vaginal	1310	11.0	77,946	17.4	
Diagnosis of Malignancy	1801	15.1	24,480	5.5	<0.0001
Robotic-Assisted	1770	14.8	38,674	8.6	<0.0001
Use of Morcellator	267	2.2	11,704	2.6	0.01049
ANESTHESIA/ANALGESIA					
Anesthesia Type					
General	9733	81.5	370,289	82.7	<0.0001
General + Neuraxial	1944	16.3	62,678	14.0	
Unknown/Missing	259	2.2	14,605	3.3	
Analgesia					
Intravenous Acetaminophen	1187	9.9	30,495	6.8	<0.0001
PCA	3612	30.3	150,301	33.6	<0.0001
NSAIDs	8234	68.8	335,919	75.1	<0.0001
COX-2 Inhibitors	305	2.5	9746	2.2	0.00623
Ketamine	312	2.6	7710	1.7	<0.0001
Pregabalin/Gabapentin	835	7.0	11,162	2.5	<0.0001

[a] Continuous variable mean and standard deviation reported, instead of N and %, respectively.
[b] Chi-square test for categorical variables, t-test for continuous variables.

Table 2
Outcomes by OSA status.

	Diagnosis of Sleep Apnea				P-value[b]
	Yes (n = 11,936)		No (n = 447,572)		
	n	%	n	%	
Cardiac Complications	97	0.8	1811	0.4	<0.0001
Central Nervous System Complications	45	0.4	652	0.1	<0.0001
Gastrointestinal Complications	647	5.4	16,714	3.7	<0.0001
Genitourinary Complications	181	1.5	6221	1.4	0.2446
Intensive Care Unit Utilization	1241	10.4	23,537	5.3	<0.0001
Renal Complications	263	2.2	1885	0.4	<0.0001
Respiratory Complications	789	6.6	5254	1.2	<0.0001
Thromboembolic Complications	36	0.3	643	0.1	<0.0001
Blood Transfusion	1272	10.7	38,159	8.5	<0.0001
Oral Morphine Equivalents (mg)[a]	334	162–454	311	155–415	<0.0001
Length of Hospital Stay (days)[a]	3	2–3	2	1–3	<0.0001
Cost of Hospitalization (USD)[a]	$10,464	$6387-$12,236	$7984	$5077-$9312	<0.0001

[a] Continuous variable median and interquartile range reported, instead of N and %, respectively.
[b] Chi-square test for categorical variables, Kruskal–Wallis test for continuous variables.

P = 0.04), compared to patients without OSA. However, the odds for OSA patients to receive a blood transfusion was significantly reduced (OR 0.88; 95% CI 0.82–0.94, P < 0.05).

The C-statistics for the models assessing blood transfusions, cardiac, GI, GU, renal, and respiratory complications ranged from 0.70 to 0.88, suggesting good to very good discrimination. Models for TE and CNS complications had C-statistics below 0.70.

4. Discussion

In this cohort of patients undergoing hysterectomies, overall OSA prevalence was lower than reported in other surgical cohorts. However, there was a steady increasing trend throughout the study period. In addition, OSA-status was associated with a significantly increased risk of perioperative complications and modest increases in cost and length of stay.

Similar to findings in the general population [19], our results show that OSA prevalence appears to be increasing over time. This may be due to true increases in prevalence or increased identification of cases due to a growing awareness of OSA among physicians. A case for the former can be made as the prevalence of obesity - a major contributing factor in the pathogenesis of OSA [6]- among women in the United States has been constantly increasing from 2005 to 2014 with the most significant increase in extreme obesity (BMI $\geq$ 40 kg/m^2) [7]. Alternately, the prevalence of OSA among our patient sample appears to be low compared with estimates for other surgical populations [12,20–22]. This could be due to several reasons including the database used, characteristics of this surgical cohort or OSA-related gender differences. Indeed, the Premier Healthcare database includes information from >600 hospitals throughout the US, however, with a higher representation of hospitals located in the South [8]. Next to potential database differences, the surgical cohort of interest, ie patients undergoing hysterectomies, may also provide some of the explanations for a lower OSA prevalence as these patients are generally younger and less comorbid when compared to lower joint arthroplasty or spinal fusion cohorts [11,12,20]. Crucially, while there seem to be gender differences in the prevalence of OSA [3,4], the prevalence of OSA among women in the general population has been shown to be considerably higher than previously expected and in postmenopausal women it might be almost as high as in men [3,4,23]. Furthermore, several studies have suggested that a large proportion of women with moderate to severe OSA remain undiagnosed [3,4]. Thus, it can be assumed that a large proportion of patients in our sample was also undiagnosed and therefore wrongly included in the non-OSA group. Hence, it may be possible that the true differences in perioperative complications, cost and length of stay between OSA and non-OSA patients are larger than demonstrated in our analysis. In regard to the widespread underdiagnosis of OSA, the known association between OSA and perioperative complications and the increasing number of patients undergoing surgery, preoperative screening for OSA has been advocated [24]. Nevertheless, the prevalence of OSA we found in this study may suggest that preoperative screening for OSA is not yet performed adequately among patients undergoing a hysterectomy. One of the possible reasons for inadequate screening may be lack of awareness of OSA among patients undergoing hysterectomy. Furthermore, it has been speculated that currently used screening tools might fail to reliably detect OSA in an all-female population since OSA has been shown to be associated with different symptoms in women than in men [3,4,23]. However, there is currently no conclusive evidence to suggest that established screening tools are ineffective in women.

As expected, the finding that OSA patients undergoing hysterectomy have an increased risk for perioperative complications correspond to findings from previous studies, in which OSA had

Table 3
Results from multivariable modeling; odds ratios (or % change) demonstrating the association between OSA and outcomes (reference is non-OSA patients). Odds ratios for binary outcomes and % change for continuous outcomes.

Outcome Variable	Diagnosis of Sleep Apnea
Cardiac Complications	1.18 (0.95; 1.48)
Central Nervous System Complications	1.37 (0.98; 1.90)
Gastrointestinal Complications	0.97 (0.89; 1.07)
Genitourinary Complications	0.97 (0.83; 1.13)
Intensive Care Unit Utilization	2.28 (1.77; 2.94)*
Renal Complications	1.98 (1.70; 2.32)*
Respiratory Complications	3.25 (2.97; 3.56)*
Thromboembolic Complications	1.16 (0.81; 1.67)
Blood Transfusion	0.88 (0.82; 0.94)*
Oral Morphine Equivalents	1.2% (0.1; 2.4%)*
Length of Hospital Stay	2.6% (2.1; 3.1%)*
Cost of Hospitalization	6.2% (4.9; 7.6%)*

Models adjusted for age, race, Deyo-Charlson comorbidity Index, history of substance use/abuse, chronic pain conditions, psychiatric comorbidities, and obesity, insurance type, hospital location, size, teaching status and hysterectomy volume, year of procedure, type of procedure, robotic use, morcellator use, anesthesia type, use of intravenous acetaminophen, PCA, NSAIDs, COX-2 inhibitors, ketamine, and pregabalin/gabapentin.
*P-value <0.05.

been identified as being independently associated with increased perioperative complications, cost and length of stay among other surgical cohorts such as patients undergoing orthopedic or bariatric surgery [1,12,20–22]. Although, to date, there is a shortage of data on the effects of OSA on perioperative outcomes in gynecological patient cohorts, our findings are also consistent with results from patients undergoing elective surgery that, amongst others, included gynecological, abdominal or laparoscopic procedures [1,22].

OSA patients are at risk for a number of perioperative complications such as difficult airway, respiratory complications and surgical site infections and seem to be more sensitive to certain drugs including opioids and sedatives [25,26]. Accordingly, guidelines currently recommend to use multimodal analgesia, regional or neuraxial anesthesia techniques whenever possible and to avoid opioids, sedatives, and other drugs that negatively affect the patient's airway musculature and breathing [24]. Conversely, just a small proportion of the OSA patients in our patient sample received neuraxial anesthesia and the difference of opioid prescription between OSA and non-OSA patients was only modest, although statistically significant. Furthermore, it is recommended to monitor patients longer and more intensely in the perioperative period in a monitored postoperative setting such as on a step-down unit, an ICU or by using telemetry [24]. In addition to an increased risk for perioperative complications, OSA has also been shown to be frequently associated with a considerable comorbidity burden [27]. Specifically, women diagnosed with OSA have been shown to be in poorer health conditions and to have higher mortality rates than women in the same age group without OSA or when compared to men with an equally pronounced diagnosis of OSA [3,4,19,23,28].

Our findings showed that OSA patients undergoing hysterectomy were approximately twice as likely to be admitted to an ICU. Yet, it is not possible to deduce from this data if patients with OSA were referred to an ICU for preventive postoperative monitoring, because of OSA-related complications or because of non-OSA-related reasons. To date, there is still a shortage of evidence about beneficial effects of guideline-based perioperative proceedings among OSA patients [24]. Awareness and implementation of guidelines for perioperative handling of OSA patients among practitioners is still suboptimal [29]. Nonetheless it has been suggested that some perioperative complications can be prevented by choosing guideline-based treatment [30–32] and further research is needed to improve perioperative care strategies for OSA patients.

There are several limitations to this study that are inevitable when using an administrative database. First and foremost, ICD-9 codes only provide limited information about diagnoses and therapies and one validation study conducted in Canada suggested suboptimal validity of these codes; it, is however unknown how this relates to the US as coding practices may differ between countries [33,34]. Moreover, there is no information on the severity of OSA or the time between OSA diagnosis and surgery in our patient sample. The latter may be important as a longer duration of diagnosed OSA would likely result in longer treatment which may mitigate a potential negative effect on outcomes as the ones included in our study. Thus, the demonstrated associations between OSA and complications in this study may be an underestimation of the true effect of OSA on outcomes. Indeed, future studies should address the effect of preoperative OSA treatment on the risk of perioperative complications as this will provide more evidence to support current guidelines [24] on the approach to OSA patients presenting for surgery. Notably, the definition of OSA in this study does not take into account undiagnosed OSA which likely represents the majority of the OSA burden [35]. Yet, this burden of undiagnosed OSA represents real-world clinical practice. Moreover, this will likely also lead to an underestimation of the true effect of OSA on perioperative complications as the control group (the group without diagnosed OSA) is a mix of those with (undiagnosed OSA) and without OSA, therefore representing a group with a higher baseline risk than would be expected if this control group truly represented all patients without OSA. While the provider of the database rigorously checks for incorrect data, we cannot completely eliminate the possibility of inaccurate data entry or factually flawed data. Furthermore, as in any observational study design, we can only provide results interpretable as associations but not causal relationships. Additionally, we only have access to data related to the in-hospital portion of a particular patient's care and therefore complications occurring after discharge cannot be accounted for.

In conclusion, the prevalence of diagnosed OSA among hysterectomy patients found in this particular dataset was lower compared to other surgery cohorts. Irrespectively, OSA status was associated with substantially increased risk of perioperative complications and modestly increased costs and length of stay. Therefore, it seems advisable to conduct routine preoperative screening for OSA among patients undergoing hysterectomies but further research is needed to assess currently used perioperative care strategies for OSA patients undergoing hysterectomies, with the goal to improve outcomes. Practitioners should keep in mind that OSA patients may require more focused attention and monitoring than patients without OSA and adapt their treatment regimen and resource distribution to account for this disease.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2019.01.021.

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