GYNECOLOGY

Risks of preoperative anemia in women undergoing elective hysterectomy and myomectomy

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BACKGROUND: Hysterectomy is one of the most common surgeries performed worldwide. Identification of modifiable risk factors for complications or readmissions could lead to targeted interventions to improve patient care and reduce health care costs. Preoperative anemia has been identified as a risk factor for adverse postoperative outcomes following noncardiac surgery. However, studies have not focused on young and healthy surgical populations, such as women undergoing gynecologic surgery for benign indications.

OBJECTIVE: The purpose of this study was to evaluate whether preoperative anemia in women undergoing elective hysterectomy or myomectomy for benign indications was associated with increased 30 day postoperative morbidity and mortality.

STUDY DESIGN: In this retrospective, population-based cohort study, we followed up adult women (≥18 years of age) who underwent elective hysterectomy or myomectomy (laparoscopic/laparotomy) between the years 2013 and 2015 for benign indications in Ontario, Canada. We used linked administrative data from a government-administered, single-payer provincial health care system using Canadian Classification of Health Interventions intervention codes, *International Classification of Diseases*, 10th revision, diagnostic codes, physician billing codes, and laboratory data from both community and hospital laboratories across the province. Our exposure of interest was preoperative anemia, defined as a hemoglobin value <12 g/dL on the complete blood count measured closest to the date of surgery. Our primary outcome was the composite of 30 day postoperative morbidity and mortality. Secondary outcomes were 5 individual components of the primary outcome: death, transfusion, surgical site infection, venothromboembolism, and return to the hospital within 30 days. To adjust for confounding, we generated a propensity score using a multiple logistic regression model in which the presence of anemia was regressed on all baseline characteristics. We matched anemic to nonanemic patients on the logit of the propensity score. Using an unadjusted log-binomial model estimated using generalized estimating equations to account for the matched pairs, we calculated the relative risk, 95% confidence intervals, and *P* values to evaluate the effect of anemia on outcomes.

RESULTS: Of the 16,218 women in the cohort, 3664 (22.6%) had anemia. After propensity matching, standardized differences in all baseline characteristics (n = 3261 per group) were <0.10. In the matched cohort, the primary outcome (death, complications, or readmission) occurred in 41.2% of anemic patients and 36.2% of nonanemic patients (relative risk, 1.14, 95% confidence interval, 1.07−1.21, $P < .0001$; absolute risk reduction, 5.03%, 95% confidence interval, 2.70−7.36; (number needed to harm = 20). The risk of transfusion was significantly higher in anemic patients (relative risk, 3.25, 95% confidence interval, 2.67−3.95, $P < .0001$; absolute risk reduction, 8.34%, 95% confidence interval, 7.06−9.63; number needed to harm = 12). There was no difference in other secondary outcomes. In a subgroup analysis (women >55 years vs ≤55, n = 736), older women were at increased risk of the primary outcome (relative risk, 1.40, 95% confidence interval, 1.12−1.76, $P = .004$), transfusion (relative risk, 4.20, 95% confidence interval, 1.65−10.72, $P = .003$), surgical site infection (relative risk, 1.35, 95% confidence interval, 1.01−1.81, $P = .04$), and return to the hospital (relative risk, 2.36, 95% confidence interval, 1.54−3.62, $P < .0001$).

CONCLUSION: Preoperative anemia in women undergoing elective hysterectomy/myomectomy was common and is an independent risk factor for 30 day postoperative adverse outcomes, especially in older women.

Key words: complications, transfusion

Hysterectomy is one of the most common surgeries performed worldwide, with more than 600,000 cases performed in the United States yearly.[1] Hysterectomy has been associated with up to a 13% complication rate and 5.5% readmission rate,[2] which has significant implications for patient safety and health care costs.[3] Identification of modifiable risk factors for complications or readmissions could lead to targeted interventions to improve patient care.[4–6]

Preoperative anemia has been identified as a risk factor for adverse postoperative outcomes following noncardiac surgery.[7,8] However, previous studies did not focus on young and healthy surgical populations, such as women undergoing gynecologic surgery for benign indications. One study investigating women undergoing gynecologic surgery confirmed that anemia is associated with adverse outcomes, but it did not differentiate by surgical indication.[9]

It is difficult to disentangle the role of anemia on postoperative complications when the study group is heterogeneous and includes women with malignancies, pregnancy, undergoing emergent procedures, or significant comorbidities (eg, chronic renal failure). Little evidence exists regarding the impact of anemia on postoperative outcomes for otherwise healthy women undergoing gynecologic surgery for benign indications.

With the availability of medical options for iron supplementation and menstrual suppression, physicians have a

Cite this article as: Murji A, Lam M, Allen B, et al. Risks of preoperative anemia in women undergoing elective hysterectomy and myomectomy. Am J Obstet Gynecol 2019;221:629.e1-18.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.07.018

AJOG at a Glance

Why was this study conducted?

Preoperative anemia has been identified as a risk factor for adverse postoperative outcomes following noncardiac surgery. However, studies tend not to focus on surgical populations that are young and healthy, such as women undergoing gynecologic surgery for benign indications.

Key findings

In women undergoing elective hysterectomy or myomectomy for benign indications, 23% were anemic. Preoperative anemia (hemoglobin <12 g/dL) was an independent risk factor for 30 day postoperative adverse outcomes. The risk of adverse outcomes was amplified in postmenopausal women (age >55 years) and those without a fibroid/uterine bleeding diagnosis at surgery.

What does this add to what is known?

Our study reports a high rate of preoperative anemia in women undergoing major gynecologic surgery and confirms that preoperative anemia is associated with adverse outcomes. Given these findings, surgeons should consider preoperative hemoglobin optimization prior to elective hysterectomy or myomectomy.

unique opportunity to correct anemia prior to elective gynecologic surgery. If indeed preoperative anemia is associated with adverse outcomes, clinicians have an opportunity to intervene.

Our objective was to evaluate whether preoperative anemia in women undergoing elective hysterectomy or myomectomy for benign indications is associated with 30 day postoperative morbidity and mortality.

Materials and Methods

Study design

This retrospective, population-based cohort study used linked administrative data from a government-administered, single-payer health care system in Ontario, Canada. The study included adult women who underwent elective hysterectomy or myomectomy between Jan. 1, 2013, and Sept. 1, 2015, for benign indications. The study was designed and conducted according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[10] and the Reporting of studies Conducted using Observational Routinely-collected health Data statement.[11] The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

Data sources

Unique, encoded patient identifiers allowed linkage and analyses across several administrative databases, which were performed at ICES. The following databases were used: (1) Canadian Institute for Health Information (CIHI) Discharge Abstract Database,[12] which records all hospital presentations; (2) CIHI National Ambulatory Care Reporting System for emergency department visits; (3) CIHI Same Day Surgery Database for day surgeries; (4) Ontario Health Insurance Plan (OHIP) for physician billings; (5) Corporate Provider Database for physician demographic data from Ontario's Ministry of Health and Long-Term Care; (6) Registered Persons Database for patient demographics; (7) Ontario Cancer Registry, a database of all patients with a cancer diagnosis; and (8) Ontario Laboratories Information System database, which holds laboratory data from both community and hospital laboratories across the province and represents more than 91% of annual provincial test volumes.[13]

Study patients

The study included adult women (age ≥18 years) who underwent hysterectomy (by any route) or myomectomy (laparoscopic or laparotomy) as determined using a combination of the Canadian Classification of Health Interventions (CCI) and physician billing codes (see Appendix A for code list). Patients who were pregnant, had previous hysterectomy, had an emergency surgery, or underwent hysteroscopic myomectomy were excluded.

Further exclusions included patients with a cancer diagnosis within 90 days prior to or 30 days following their procedure, patients who did not reside in Ontario or have a valid OHIP number at the time of surgery, patients with missing age or sex information, and patients without a complete blood count measurement within 60 days of surgery (and before 8:00 AM on the day of surgery).

For patients undergoing multiple procedures in the accrual period, only the first procedure was selected. For those who had both hysterectomy and myomectomy in the accrual period, hysterectomy was chosen as the index procedure.

Exposure of interest

Preoperative anemia was defined as a hemoglobin value of <12 g/dL (<120 g/L)[14–16] on the complete blood count (CBC) measured closest to the date of surgery (including up to 8:00 AM on the day of surgery).

Outcomes

The primary outcome was a composite of all-cause death, complications or readmission to any hospital in the province within 30 days of the index procedure. Complications included 1 or more occurrences of transfusion, hemorrhage, surgical site infection, venothromboembolism, sepsis, myocardial infarction, cardiac arrest, pneumonia, ventilator use, stroke, coma, acute renal failure, and unplanned return to the operating room.

Secondary outcomes, chosen for clinical relevance,[4,6,17] were 5 individual components of the primary composite outcome: death, transfusion, surgical site infection, venothromboembolism, and readmission to hospital/return to emergency department. Complications were defined based on previous studies[18,19] and were ascertained using Canadian

Classification of Health Interventions intervention codes, *International Classification of Diseases*, 10th revision, diagnostic codes and OHIP physician billing codes (see Appendix A).

Outcomes were observed from the admission date for the index procedure until 30 days postoperatively. The primary outcome was assigned as the first occurrence of any of the predefined outcomes. Secondary outcomes were identified as the first time a patient experienced the outcome during the follow-up period, even if they had experienced other secondary outcomes previously.

Covariates

We collected patient-specific characteristics such as age, Charlson comorbidity index,[20] comorbidities within 2 years prior to index procedure (coronary artery disease, stroke, previous venothromboembolism, chronic kidney disease), a previous history of diabetes[21] or chronic obstructive pulmonary disease,[22] cancer diagnosis within 5 years preoperatively, transfusion within 6 months preoperatively, quintile of median neighborhood income, and rurality.

Surgical characteristics included procedure type, route of procedure in which minimally invasive hysterectomy was defined as a vaginal and/or laparoscopic approach, surgery duration (categorized in quintiles), and diagnosis related to index procedure classified into 6 categories: abnormal uterine bleeding (AUB), fibroids, prolapse, pain/endometriosis, postmenopausal issues, and pelvic mass/dysplasia.

We also collected provider-specific variables such as surgeon age, number of years in practice, surgeon volume for hysterectomy in year preceding surgery, and duration of surgeon-patient relationship (calculated as time from earliest consult date to surgery). Institutional characteristics included identification of teaching hospitals and institutional volume for hysterectomy in the preceding year (as quintile).

Statistical analysis

Descriptive statistics were used to compare baseline demographics between anemic and nonanemic patients. An absolute standardized difference >0.10 was considered clinically important.[23] To adjust for confounding, we generated a propensity score using a multiple logistic regression model in which the presence of anemia was regressed on all baseline characteristics (except hysterectomy type, surgery duration, and duration of patient-surgeon relationship because these were either colinear to other variables in the model or were mediators).[24]

We matched anemic to nonanemic patients based on AUB/fibroid diagnosis and probable premenopausal status (age $\leq$55 years and $>$55 years). We matched on the logit of the propensity score using greedy nearest neighbor matching with caliper widths equal to 0.2 of the standard deviation of the logit of the propensity score.[25] Using an unadjusted log-binomial model estimated using generalized estimating equations to account for the matched pairs, we calculated the relative risk (RR), 95% confidence intervals (CI), and P values to evaluate the effect of anemia on outcomes. A value of $P < .05$ was considered statistically significant. Analyses were conducted using SAS for UNIX, version 9.2 (SAS Institute, Cary, NC).

Sensitivity and post hoc analyses

To determine whether outcomes of patients who were excluded for not having a hemoglobin value within 60 days of surgery were different from nonanemic patients, we propensity matched unknown anemia to nonanemic patients. In a separate sensitivity analysis, we reintroduced patients excluded because of perioperative cancer into the cohort to reevaluate the impact of anemia.

In a post hoc analysis, we removed transfusion from the primary composite outcome. To estimate the effect of hemoglobin on the risk of transfusion, we fit a logistic regression model using the initial cohort (ie, before propensity matching), adjusting for all variables in the previously mentioned propensity score model. We then chose a representative person for all covariates (ie, set all covariates, except for hemoglobin, equal to the median/mode) and created 106 copies with each person having a hemoglobin value from 5 g/dL to 15.5 g/dL in increments of 0.1. he fitted logistic regression model was applied to these 106 representative women. This allowed us to estimate the probability of transfusion for a representative woman as hemoglobin increased.

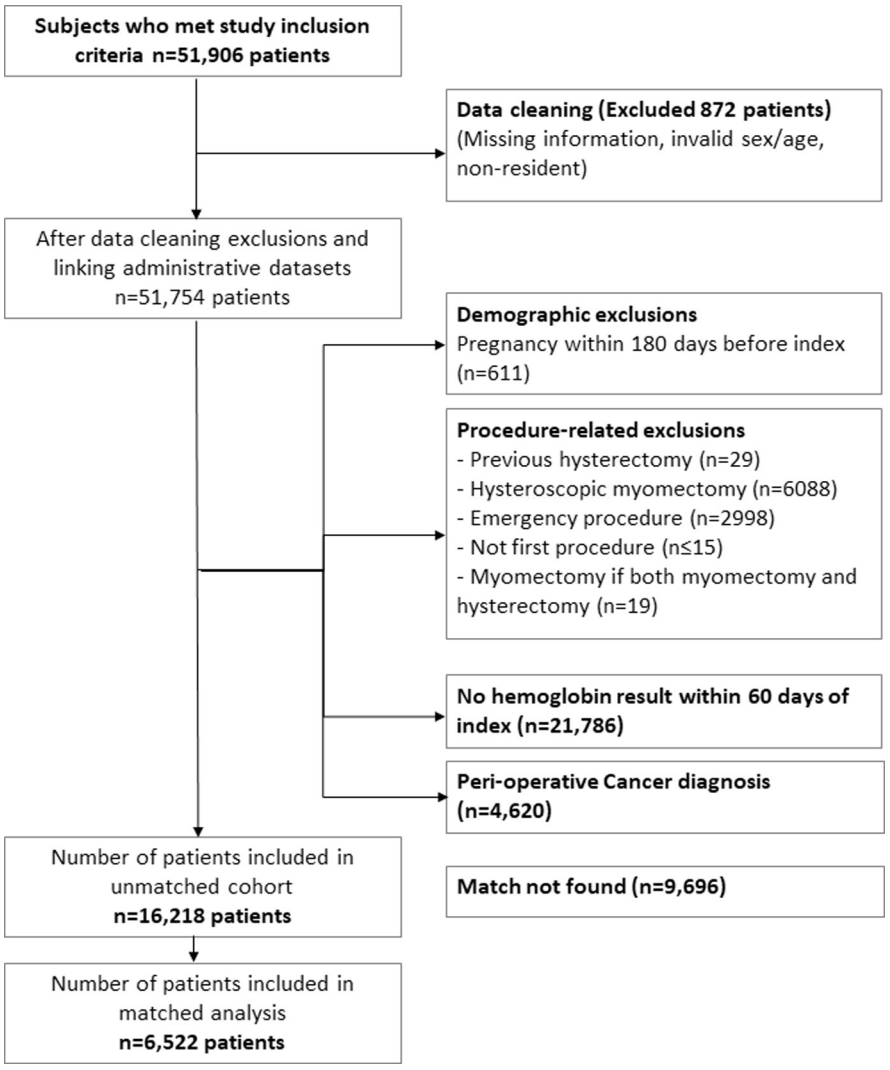
Results

The creation of the study cohort is shown in Figure 1. After data cleaning, 51,754 women had undergone a hysterectomy or myomectomy during the accrual period. Following demographic and procedure-related exclusions, 21,786 patients (42%) were excluded for missing preoperative hemoglobin values. An additional 4620 patients (9%) were excluded for perioperative cancer diagnosis. Of the remaining cohort (16,218 patients), 3664 (22.6%) had anemia and 12,554 (77.4%) did not have anemia.

Hemoglobin was available within 15 days preoperatively in 62% of patients; between 16 and 30 days preoperatively in 24%; and between 31 and 60 days in 14%. The distribution of timing of preoperative hemoglobin in relation to surgery is presented in Table 2 of Appendix B. There were significant differences between the anemic and nonanemic patients (Table 1). After propensity matching, 3261 anemic patients were compared with the same number of nonanemic patients (89% of anemic patients were successfully matched). In the propensity-matched cohort, the baseline characteristics were well balanced with standardized differences of <0.1 between groups.

In this matched cohort, the primary outcome (death, complications, or readmission) occurred in 41.2% of anemic patients and 36.2% of nonanemic patients (RR, 1.14, 95% CI, 1.07−1.21, $P <$ .0001; absolute risk reduction, 5.03%, 95% CI, 2.70−7.36; number needed to harm = 20). The risk of transfusion was significantly higher in anemic patients (RR, 3.25 95% CI, 2.67−3.95, $P <$ .0001; absolute risk reduction, 8.34%, 95% CI, 7.06−9.63; number needed to harm = 12) in which for every 12 anemic patients, 1 received a perioperative blood

FIGURE 1
Study flow diagram



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transfusion (ie, transfusion on the day of the index procedure or 30 days postoperatively). There was no difference between groups in the other secondary outcomes (Table 2).

The difference between groups in the composite primary outcome was driven by transfusions because the post hoc analysis removing transfusions from the primary outcome showed no difference between groups (RR, 1.03, 95% CI, 0.96−1.1, $P = .39$).

Anemia increased the risk of the primary outcome or of transfusion in all predefined subgroups (Table 3). Additionally, anemic women without an AUB or fibroid diagnosis during the index surgery admission had an increased the risk of readmission (RR, 1.40, 95% CI, 1.06−1.85, $P < .018$). In probable postmenopausal women (aged >55 years), anemia increased the risk of surgical site infection (RR, 1.35, 95% CI, 1.01−1.81, $P = .043$) and readmission (RR, 2.36, 1.54−3.62, $P < .0001$).

Sensitivity and post hoc analyses

Compared with nonanemic patients (n = 12,994), those with unknown anemia status (n = 12,994) had a similar risk of the primary outcome (RR, 0.97, 95% CI, 0.93−1.00, $P = 0.05$) but an increased risk of transfusion (RR, 1.25, 95% CI, 1.1−1.42, $P < .001$). Baseline characteristics of patients in the nonanemic and unknown anemia cohorts are shown in Table 1 of Appendix B. When patients with perioperative cancer diagnosis were reintroduced into the cohort, the effect of anemia on the primary outcome (RR, 1.15, 95% CI, 1.09−1.21, $P < .001$) and transfusion (RR, 3.30, 95% CI, 2.78−3.93, $P < .001$) were consistent.

The predicted probability of transfusion by preoperative hemoglobin value is shown in Figure 2. The probability of transfusion with a hemoglobin of 12 g/dL was 2.6%. The probability of transfusion increased by 54% when preoperative hemoglobin was 11 g/dL (probability, 4.0%) and by 135% when hemoglobin was 10 g/dL (probability, 6.1%). Compared with the threshold of 12 g/dL, the probability of transfusion decreased 38% when preoperative hemoglobin was 13 g/dL (probability, 1.6%).

An additional post hoc subgroup analysis showed that anemia increased the risk of the primary outcome in both minimally invasive hysterectomy (RR, 1.13, 95% CI, 1.01−1.28, $P = .037$) and open hysterectomy (RR, 1.15, 95% CI, 1.06−1.24, $P < .001$). In a subgroup of women undergoing laparoscopic/open myomectomy, the rate of transfusion was 13%. Preoperative anemia increased the risk of transfusion in women undergoing myomectomy (RR, 1.95, 95% CI, 1.3−2.9, $P = .001$).

Comment

Principal findings

In a large cohort of women undergoing elective hysterectomy or myomectomy for benign indications, 23% had anemia. Preoperative anemia (hemoglobin <12 g/dL) was an independent risk factor for 30 day adverse outcomes. This increase in postoperative morbidity in anemic women was primarily driven by an increased risk of perioperative transfusion in which the number needed to harm was 12. The risk of adverse outcomes was amplified in postmenopausal women (aged >55 years) and those without a fibroid/uterine bleeding diagnosis at surgery. Among the 42% of women without bloodwork within 60

TABLE 1
Baseline characteristics of patients before and after propensity score matching

Covariates	Before matching			After matching		
	Not anemic (n = 12,554)	Anemic (n = 3664)	St. Diff	Not anemic (n = 3261)	Anemic (n = 3 ,261)	St. diff
Demographics						
Age, mean (SD)	50.55 ± 11.88	47.03 ± 10.16	0.32	46.55 ± 9.33	46.96 ± 10.08	0.04
Charlson Comorbidity Index						
0, n, %	184 (1.5%)	63 (1.7%)	0.05	1036 (31.8%)	1038 (31.8%)	0
1, n, %	1820 (14.5%)	557 (15.2%)	0.02	83 (2.5%)	78 (2.4%)	0.01
2, n, %	6920 (55.1%)	2622 (71.6%)	0.04	74 (2.3%)	60 (1.8%)	0.03
≥3, n, %	3630 (28.9%)	422 (11.5%)	0.06	30 (0.9%)	24 (0.7%)	0.02
No hospitalizations	8924 (71.1%)	3242 (88.5%)	0.02	2038 (62.5%)	2061 (63.2%)	0.01
Comorbidities						
Diabetes, n, %	1580 (12.6%)	529 (14.4%)	0.05	459 (14.1%)	454 (13.9%)	0
Coronary artery disease, n, %	545 (4.3%)	161 (4.4%)	0	122 (3.7%)	135 (4.1%)	0.02
Stroke, n, %	32 (0.3%)	18 (0.5%)	0.04	17 (0.5%)	12 (0.4%)	0.02
COPD, n, %	873 (7.0%)	149 (4.1%)	0.13	126 (3.9%)	132 (4.0%)	0.01
Previous VTE, n, %	57 (0.5%)	33 (0.9%)	0.05	18 (0.6%)	25 (0.8%)	0.03
Chronic kidney disease, n, %	243 (1.9%)	117 (3.2%)	0.08	109 (3.3%)	90 (2.8%)	0.03
Previous cancer diagnosis, n, %	2774 (22.1%)	676 (18.4%)	0.09	570 (17.5%)	587 (18.0%)	0.01
Transfusion within 6 months prior to index, n, %	91 (0.7%)	325 (8.9%)	0.39	84 (2.6%)	88 (2.7%)	0.01
Income quintile						
First quintile (highest), n, %	2089 (16.6%)	745 (20.3%)	0.1	665 (20.4%)	671 (20.6%)	0
Second quintile, n, %	2392 (19.1%)	762 (20.8%)	0.04	676 (20.7%)	685 (21.0%)	0.01
Third quintile, n, %	2634 (21.0%)	802 (21.9%)	0.02	717 (22.0%)	716 (22.0%)	0
Fourth quintile, n, %	2837 (22.6%)	787 (21.5%)	0.03	717 (22.0%)	695 (21.3%)	0.02
Fifth quintile (lowest), n, %	2569 (20.5%)	553 (15.1%)	0.14	486 (14.9%)	494 (15.1%)	0.01
Rurality						
Rural, n, %	1495 (11.9%)	236 (6.4%)	0.19	212 (6.5%)	204 (6.3%)	0.01
Urban, n, %	11,059 (88.1%)	3428 (93.6%)		3049 (93.5%)	3057 (93.7%)	
Surgical characteristics						
Procedure type						
Hysterectomy, n, %	11,802 (94.0%)	3,298 (90.0%)	0.15	2,928 (89.8%)	2,921 (89.6%)	0.01
Myomectomy, n, %	752 (6.0%)	366 (10.0%)		333 (10.2%)	340 (10.4%)	
Hysterectomy type						
Total hysterectomy, n, %	11,032 (93.5%)	2935 (89.0%)	0.16	2645 (81.1%)	2587 (79.3%)	0.04
Subtotal hysterectomy, n, %	730 (6.2%)	344 (10.4%)	0.15	272 (8.3%)	318 (9.8%)	0.05
Radical hysterectomy, n, %	40 (0.3%)	19 (0.6%)	0.04	11 (0.3%)	16 (0.5%)	0.02
Route of hysterectomy						
Minimally invasive, n, %	7006 (59.4%)	1387 (42.1%)	0.35	1264 (38.8%)	1276 (39.1%)	0.01
Open, n, %	4796 (40.6%)	1911 (57.9%)		1664 (51.0%)	1645 (50.4%)	0.01

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TABLE 1
Baseline characteristics of patients before and after propensity score matching *(continued)*

Covariates	Before matching			After matching		
	Not anemic (n = 12,554)	Anemic (n = 3664)	St. Diff	Not anemic (n = 3261)	Anemic (n = 3 ,261)	St. diff
Surgery duration, min						
First quintile (0–95), n, %	2650 (21.1%)	778 (21.2%)	0	719 (22.0%)	705 (21.6%)	0.01
Second quintile, (96–118), n, %	2613 (20.8%)	825 (22.5%)	0.04	710 (21.8%)	745 (22.8%)	0.03
Third quintile, (119–145), n, %	2565 (20.4%)	743 (20.3%)	0	669 (20.5%)	654 (20.1%)	0.01
Fourth quintile, (146–186), n, %	2312 (18.4%)	673 (18.4%)	0	608 (18.6%)	601 (18.4%)	0.01
Fifth quintile, (187–651), n, %	2170 (17.3%)	588 (16.0%)	0.03	525 (16.1%)	514 (15.8%)	0.01
Diagnosis related to index procedure						
AUB, n, %	4091 (32.6%)	1857 (50.7%)	0.37	1640 (50.3%)	1631 (50.0%)	0.01
Prolapse, n, %	3743 (29.8%)	454 (12.4%)	0.44	411 (12.6%)	432 (13.2%)	0.02
Pain/endometriosis, n, %	3063 (24.4%)	880 (24.0%)	0.01	809 (24.8%)	777 (23.8%)	0.02
Postmenopausal issues, n, %	259 (2.1%)	31 (0.8%)	0.1	28 (0.9%)	28 (0.9%)	0
Fibroids, n, %	5484 (43.7%)	2513 (68.6%)	0.52	2180 (66.9%)	2238 (68.6%)	0.04
Mass/dysplasia, n, %	1389 (11.1%)	280 (7.6%)	0.12	225 (6.9%)	223 (6.8%)	0
Other, n, %	360 (2.9%)	39 (1.1%)	0.13	27 (0.8%)	29 (0.9%)	0.01
Bleeding/fibroid diagnosis						
AUB/fibroid, n, %	7689 (61.2%)	3074 (83.9%)	0.52	2743 (84.1%)	2743 (84.1%)	0
Other, n, %	4865 (38.8%)	590 (16.1%)		518 (15.9%)	518 (15.9%)	
Provider related characteristics						
Surgeon age, mean (SD)	51.15 ± 9.81	51.70 ± 10.09	0.06	51.72 ± 10.19	51.77 ± 10.08	0.01
Surgeon years in practice, mean (SD)	25.74 ± 10.10	26.33 ± 10.37	0.06	26.38 ± 10.47	26.48 ± 10.30	0.01
Surgeon volume for hysterectomy, mean (SD)	47.93 ± 30.02	45.19 ± 30.87	0.09	45.07 ± 29.81	45.52 ± 30.84	0.01
Duration of patient-specialist relationship, mos, mean (SD)	6.04 ± 5.62	5.83 ± 5.74	0.04	6.14 ± 5.73	5.89 ± 5.73	0.04
Institution related characteristics						
Teaching hospital						
Yes, n, %	3649 (29.1%)	915 (25.0%)	0.09	780 (23.9%)	786 (24.1%)	0
Hospital volume for hysterectomy (cases per year)						
First quintile (≤37), n, %	286 (2.3%)	73 (2.0%)	0.02	56 (1.7%)	64 (2.0%)	0.02
Second quintile (≤ 117), n, %	970 (7.7%)	309 (8.4%)	0.03	282 (8.6%)	272 (8.3%)	0.01
Third quintile (≤206), n, %	2320 (18.5%)	710 (19.4%)	0.02	674 (20.7%)	649 (19.9%)	0.02
Fourth quintile (≤311), n, %	2939 (23.4%)	989 (27.0%)	0.08	883 (27.1%)	870 (26.7%)	0.01
Fifth quintile (≤704), n, %	6039 (48.1%)	1583 (43.2%)	0.1	1366 (41.9%)	1406 (43.1%)	0.02

AUB, abnormal uterine bleeding; *COPD*, chronic obstructive pulmonary disease; *St. Diff.*, standardized difference; *VTE*, venothromboembolism.
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days prior to their elective surgery, the risk of transfusion was significantly higher compared with nonanemic women, suggesting a quality care gap in patient management that needs to be addressed.

Results in context

These findings are consistent with and extend those from prior reports. A

TABLE 2
Clinical outcomes of anemic compared with nonanemic patients in the propensity matched cohort

Outcome	Anemic (n = 3261)	Nonanemic (n = 3261)	RR (95% CI)	*P* value
Primary (death, complication, readmission)	41.2%	36.2%	1.14 (1.07–1.21)	< .001
Death	≤0.15%[a]	≤0.15%[a]	—[a]	—[a]
Transfusion	12.1%	3.7%	3.25 (2.67–3.95)	<0.001
Surgical site infection	27.5%	26.6%	1.03 (0.95–1.12)	.42
Venothromboembolism	≤0.15%[a]	≤0.15%[a]	—[a]	—[a]
Readmission	16.3%	15.7%	1.03 (0.93–1.15)	.56

CI, confidence interval; *RR*, relative risk.

[a] Small cell counts (<6) were suppressed to prevent reidentification.

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population-based cohort study using data from the American College of Surgeons National Surgical Quality Improvement Program showed an increased risk of 30 day postoperative morbidity and mortality in anemic women undergoing hysterectomy and myomectomy.[9] Their cohort included emergency procedures, cancer diagnoses, and pregnant women, whereas these more complex patients were excluded in our study.

With propensity matching, we were able to adjust for a more complete list of potential confounders, most importantly surgical diagnosis, route of surgery (open vs minimally invasive), preoperative transfusion, surgeon (age, training, volume), and hospital characteristics. These differences may explain why we did not find the increased mortality risk associated with preoperative anemia that has been described by others.[8,9]

Clinical implications

Perioperative blood transfusion carries significant morbidity.[26] In women undergoing myomectomy (10% of our cohort) in which the goal is to enhance or preserve future fertility, transfusion can have additional perinatal implications. For example, 8.1% of transfused women develop clinically significant alloantibodies, many of which can result in hemolytic disease of the fetus and newborn.[27]

Our data illustrate that the probability of transfusion is closely related to preoperative hemoglobin. As hemoglobin decreases from 12 to 10 g/dL (mild anemia), the probability of transfusion increases exponentially. Conversely, transfusion probability decreases as hemoglobin levels rise above 12 g/dL. There is almost a 4-fold increase in transfusion probability when hemoglobin decreases from 13 g/dL to 10 g/dL. In light of these findings, it is not surprising that international practice guidelines have set 13 g/dL as the preoperative hemoglobin

TABLE 3
Relative risk of adverse outcomes for anemic compared with nonanemic patients in the propensity-matched cohort stratified by diagnosis and age

	Anemic vs nonanemic patients in groups			
Outcome	AUB/fibroid diagnosis (n = 5486) RR (95% CI)[a]	No AUB/fibroid diagnosis (n = 1036) RR (95% CI)[a]	Age ≤55 y (n = 5786) RR (95% CI)[a]	Age >55 y (n = 736) RR (95% CI)[a]
Primary (death, complication, readmission)	1.12 (1.05–1.19) *P* < .001	1.3 (1.09–1.55) *P* = .003	1.12 (1.05–1.19) *P* < .001	1.4 (1.12–1.76) *P* = .004
Transfusion	3.22 (2.62–3.96) *P* < .001	3.50 (1.86–6.57) *P* < .001	3.21 (2.62–3.92) *P* < .001	4.2 (1.65–10.72) *P* = .003
Surgical site infection	1.02 (0.94–1.11) *P* = .65	1.15 (0.91–1.46) *P* = .25	1.01 (0.93–1.1) *P* = .81	1.35 (1.01–1.81) *P* =0.043
Venothromboembolism	2.00 (0.68–5.85) *P* = .21	—[b]	2.40 (0.85–6.81) *P* = .10	—[b]
Readmission	0.98 (0.87–1.11) *P* = .74	1.40 (1.06–1.85) *P* = .018	0.97 (0.86–1.08) *P* = .55	2.36 (1.54–3.62) *P* < .001

AUB, abnormal uterine bleeding; *CI*, confidence interval; *RR*, relative risk.

[a] Anemia vs no anemia.; [b] Small cell counts (<6) were suppressed to prevent reidentification.

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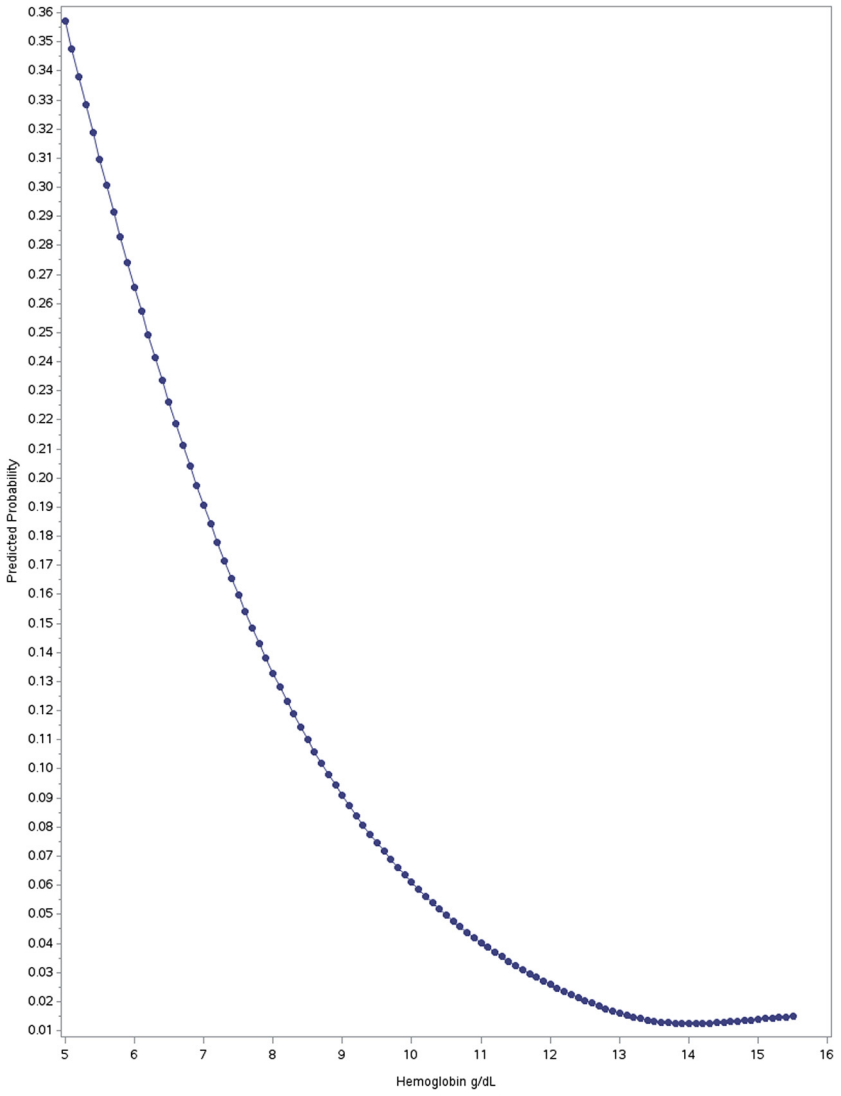
FIGURE 2
Predicted probability of transfusion by preoperative hemoglobin value



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threshold to minimize risk of transfusion and unfavorable outcomes.[28]

Given these findings, surgeons should routinely consider preoperative hemoglobin optimization prior to elective hysterectomy or myomectomy. Anemia is easy to diagnose and simple to treat (for the majority of iron-deficiency anemia), and untreated anemia has consistently been shown to be associated with adverse outcomes. Our results suggest that hemoglobin optimization strategies may differ according to patient age and gynecologic diagnosis.

In situations in which the etiology of preoperative anemia may be AUB/fibroids, hormonal menstrual suppression with gonadotropin-releasing hormone agonists or selective progesterone receptor modulators may be beneficial to correct anemia,[29] whereas in older postmenopausal women, hemoglobin optimization strategies may focus on the investigation of the causes of anemia with targeted treatments (for example, optimizing comorbidities and nutritional status).

Early detection of anemia is the first pillar of patient blood management, an evidence-based bundle of care that has been shown to decrease transfusions, reduce costs, and improve patient outcomes.[30] Our study identifies that timely preoperative diagnosis may be a major barrier to early detection because close to half of patients in the province did not have a complete blood count (CBC) drawn within 2 months of surgery, despite recommendations that patients scheduled for elective surgery should have a CBC a minimum of 30 days before their procedure.[30]

Given that women in Ontario wait an average of 89 days from the decision to operate to hysterectomy,[31] there is adequate time to diagnose and correct anemia. Quality improvement initiatives should focus on understanding why a CBC is not being consistently ordered for women scheduled for hysterectomy/myomectomy, considering their rate of anemia is 6-fold higher than the general population.[32]

Strategies to improve surgeon awareness and education may ensure a timely diagnosis of preoperative anemia. Obstacles to anemia correction must therefore be investigated to understand why 1 in 4 women arrive anemic on the day of surgery (eg, adverse effects of oral iron, ongoing bleeding, cost, and availability of intravenous iron).

Research implications

Our study does not imply a causal link between preoperative anemia and adverse outcomes, nor do our data suggest that correction of anemia will improve patient outcomes, although a reduction in transfusion rate is likely. These are important clinical questions that require further investigation in clinical trials. To our knowledge, there is no prospective study evaluating the effect of preoperative iron therapy or hormonal menstrual suppression to correct anemia on posthysterectomy/myomectomy outcomes. However, results from a randomized control trial of intravenous iron are anticipated.[33]

Strengths and limitations

The use of province-wide administrative data is a major strength of this study because it allowed us to investigate a large cohort and capture readmissions and complications occurring anywhere in the province, regardless of where the

index procedure was performed. The results are highly generalizable to all type and sizes of hospitals. Restricting our cohort to elective procedures for benign indications makes our results generalizable to the vast majority of generalist gynecologists who predominantly operate for benign disease. Furthermore, matching anemic and nonanemic patients on a variety of patient, surgical, and provider characteristics strengthens the findings by accounting for numerous confounding factors.

Our data must be interpreted in the context of the study design. Our outcomes and covariates were limited to those available in the administrative data. We were unable to obtain information on patient ethnicity, etiology of anemia (ferritin levels), hemoglobinopathy status (thalassemia trait), concurrent iron therapy, or other medications such as hormonal menstrual suppression. We also did not have information on the severity of disease or the complexity of the surgical procedure. However, it was reassuring that characteristics such as diagnosis, procedure type, surgical route, and surgery duration were well balanced in the matched cohort.

Whether a patient receives a perioperative transfusion can be subject to a complex decision-making process, taking into account not only the clinical situation but also the hemoglobin level. Some clinicians and institutions have restrictive transfusion practices while others are more liberal. Hence, a patient known to be anemic preoperatively may be more likely to receive a transfusion simply based on local transfusion culture and the knowledge of an anemic hemoglobin level. This source of confounding by indication is unlikely to be significant because we found that patients with unknown hemoglobin level were at similarly higher risk of transfusion. Furthermore, confounding was further reduced by matching for surgeon and institutional characteristics.

Conclusions

Our population-based study of women undergoing elective gynecologic surgery for benign indications confirms the association of anemia with adverse outcomes. Although this was primarily driven by higher rates of transfusion in women with preoperative anemia, some subgroups such as older women and those without a uterine bleeding/fibroid diagnosis experienced other complications, such as increased surgical site infection and readmission rates.

We also found a gap in the quality of care in which about 40% of the women in the province did not have a recent preoperative CBC prior to their elective procedure. These women were at an increased risk of a perioperative transfusion.

Perhaps the reflex treatment for uterine disorders should not be immediate surgery but rather an early detection of preoperative anemia and medical correction of anemia followed by delayed hysterectomy/myomectomy. ■

Acknowledgments

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the author(s) and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Dr Austin is supported by a Mid-Career Investigator award from the Heart and Stroke Foundation. Dr Lipscombe is supported by a Diabetes Investigator award from Diabetes Canada. The authors thank Josie Chundamala, Scientific Grant Editor, funded by the Department of Obstetrics and Gynaecology at Mount Sinai Hospital, for complimentary assistance editing and preparing this manuscript for submission.

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Received March 7, 2019; revised June 7, 2019; accepted July 10, 2019.

This study was supported by the Department of Obstetrics and Gynaecology at Mount Sinai Hospital and the University of Toronto. The sponsors did not have any role in study design, data collection/analysis/interpretation, writing of the manuscript, or decision to submit for publication.

Dr Murji is a member of speaker bureaus and advisory boards for AbbVie, Allergan, Bayer, and Hologic and also a member of the speaker bureau for Medtronic. Dr Callum receives research funding from Canadian Blood Services. The other authors report no conflict of interest.

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Appendix A: code lists

Variables	Code	Definition
Study population		
Total hysterectomy		
CCI	1RM89AA	Excision total, uterus and surrounding structures using combined laparoscopic and vaginal approach
	1RM89CA	Excision total, uterus and surrounding structures using vaginal approach
	1RM89DA	Excision total, uterus and surrounding structures using endoscopic (laparoscopic) approach
	1RM89LA	Excision total, uterus and surrounding structures using open approach
Radical hysterectomy		
CCI		
	1RM91AA	Excision radical, uterus and surrounding structures, using combined laparoscopic and vaginal approach (includes laparoscopic radical vaginal hysterectomy)
	1RM91CA	Excision radical, uterus and surrounding structure, using vaginal approach
	1RM91DA	Excision radical, uterus and surrounding structures, using endoscopic (laparoscopic) approach
	1RM91LA	Excision radical, uterus and surrounding structures, using abdominal approach (eg, Wertheim operation) (includes modified radical hysterectomy)
Subtotal hysterectomy		
CCI	1RM87	Excision partial uterus and surrounding structures
OHIP fee code		
	S757	Corpus uteri-inc/exc.-hysterectomy-total abd./vag.
	S758	Corpus uteri-inc/exc.-hysterectomy-total-ant.+post.rep.
	S759	Corpus uteri-inc/exc.-hysterectomy-total-ant.orpost.rep
	S763	Corpus uteri inc.exc.hysterectomy-radical(wertheims)
	S810	Laparoscopic vaginal hysterectomy
	S816	Hysterectomy—vaginal
Myomectomy		
CCI	1RM87	Excision partial uterus and surrounding structures
OHIP fee code	S764	Corpus uteri inc. exc. myomectomy
Outcomes		
Transfusion		
DAD	BTANY=1	Transfusion

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Appendix A: code lists *(continued)*

Variables	Code	Definition
Hemorrhage		
ICD-10	T810	Hemorrhage and hematoma complicating a procedure, not elsewhere classified
	T811	Shock during or resulting from a procedure, not elsewhere classified
	R571	Hypovolemic shock
	R58	Haemorrhage, not elsewhere classified
CCI	1LZ19	Transfusion, circulatory system NEC
	1PM13	Control of bleeding, bladder
	1RM13	Control of bleeding, uterus and surrounding structures
	1RN13	Control of bleeding, cervix
	1RS13	Control of bleeding, vagina
	1RW13	Control of bleeding, vulva
Surgical site infection		
ICD-10	K630	Intestine abscess
	K750	Liver abscess
	L0331	Cellulitis of abdominal wall
	L0332	Celluliits of umbilicus
	L0333	Cellulitis of groin
	N151	Renal and perinephric abscess
	N730	Acute parametritis and pelvic cellulitis
	K65	Peritonitis
	N71	Inflammatory disease of uterus, except cervix
	T813	Disruption of operation wound, NEC
	T814	Infection following procedure
	T857	Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts
	T86842	Infection of soft tissue (skin, muscle, fascia, tendon, mucosa) graft/flap
	T86822	Infection of bone graft/flap
	T86882	Infection of other transplanted tissue
CCI	1YZ52JA	Drainage, skin NEC using external manual expression (or separation of infected wound)
	1YS52JA	Drainage, skin of abdomen and trunk using external manual expression (or separation of infected wound)
	1OT52LA	Drainage, abdominal cavity using open approach
	1OT52HA	Drainage, abdominal cavity using percutaneous (needle) approach
	1OT52HHD1	Drainage, abdominal cavity using percutaneous transcatheter approach and antiinfective irrigating solution
	1OT52HHD2	Drainage, abdominal cavity using percutaneous transcatheter approach and salt irrigating solution
	1OT52HHD3	Drainage, abdominal cavity using percutaneous transcatheter approach and other irrigating solution

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Appendix A: code lists *(continued)*

Variables	Code	Definition
	1RM52	Drainage, uterus and surrounding structures
	1ZZ35HAK4	Pharmacotherapy, total body general antiinfective agents percutaneous approach (intramuscular, intravenous, subcutaneous, intradermal) cephalosporin and related substance
OHIP diagnosis code	682	Cellulitis, abscess
	998	Surgical site infection
	614	Acute or chronic salpingitis or oophoritis or abscess, pelvic inflammatory disease
	567	Peritonitis, with or without abscess
	709	Other disorders of skin and subcutaneous tissue
OHIP fee code	J149	Diagnostic ultrasound guide
	Z101	Subcutaneous abscess—local anesthesia
	S314	Abdomen (including peritoneal)—abscess
	S313	abdomen—including peritoneal abscess-subphrenic
	Z574	Remove sutures and reexplore abdominal wound under general anaesthesia
	Z569	Pelvic abscess I&D rectal or vaginal approach
	Z594	Percutaneous abdominal abscess drain including daily supervision
	Z595	Replace drain catheter abdominal abscess
	Z153	Skin debride and dressing major
	Z102	Skin incision abscess/hematoma general anaesthesia
	Z172	I&D abscess/hematoma
	Z173	I&D abscess/hematoma
	Z174	I&D abscess/hematoma
	Z227	Skin incision intramuscular abscess/hematoma
	S343	Secondary closure for evisceration
	Z080	Debridement of wound(s) and/or ulcer(s) extending into subcutaneous tissue—1
	Z081	Debridement of wound(s) and/or ulcer(s) extending into subcutaneous tissue—2
	Z082	Debridement of wound(s) and/or ulcer(s) extending into subcutaneous tissue—3
	Z083	Debridement of wound(s) and/or ulcer(s) extending into subcutaneous tissue—4 or more
Venothromboembolism		
ICD-10	I80	Phlebitis and thrombophlebitis
	I82	Other venous embolism and thrombosis
	I26	Pulmonary embolism

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Appendix A: code lists *(continued)*

Variables	Code	Definition
Sepsis		
ICD-10	A41	Other sepsis (includes sepsis, SIRS, septic shock)
	A40	Streptococcal sepsis
	A021	Salmonella sepsis
	A227	Anthrax sepsis
	A267	Erysipelothrix sepsis
	A327	Listerial sepsis
	A427	Actinomycotic sepsis
	A5486	Gonococcal sepsis
	B377	Candidal sepsis
	R650	Systemic inflammatory response syndrome of infectious origin without organ failure
	R651	Systemic inflammatory response syndrome of infectious origin with acute organ failure
Shock		
ICD-10	R57	Shock, not elsewhere classified
Myocardial infarction		
ICD-10	I21	Acute myocardial infarction
	I22	Subsequent myocardial infarction
	I23	Certain current complications following acute myocardial infarction
Cardiac arrest		
ICD-10	R092	Respiratory arrest
	I46	Cardiac arrest
OHIP FEECODE	G395	Cardiac Arrest with CPR
	G391	Amount payable per physician per patient for the fourth and subsequent physician's
	G521	first hour (or part thereof)
	G523	Second hour (or part thereof)
	G522	After first ó hour, per hour
Pneumonia		
ICD-10	J12	Viral pneumonia, not elsewhere classified
	J13	Pneumonia due to *Streptococcus pneumoniae*
	J14	Pneumonia due to *Haemophilus influenzae*
	J15	Bacterial pneumonia, not elsewhere classified
	J16	Pneumonia due to other infectious organisms, not elsewhere classified
	J17	Pneumonia in diseases classified elsewhere
	J18	Pneumonia, organism unspecified
	J690	Pneumonitis due to food and vomit
OHIP diagnosis code	486	Pneumonia all types

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Appendix A: code lists *(continued)*

Variables	Code	Definition
Ventilator use		
ICD-10	J952	Acute pulmonary insufficiency following nonthoracic surgery
	J953	Chronic pulmonary insufficiency following surgery
	J960	Acute respiratory failure
OHIP Fee code	G405	Critical care ventilation support—intensice care—physician in charge first day
	G557	Comprehensive intense critical ventilation support, phyician in charge, first day
	G406	Critical care ventilation support, intensive care, physician in charge, second to 10th day
	G558	Comprehensive intensive critical ventilation, physician in charge, second to10th day
Stroke		
ICD-10	H34	Retinal vascular occlusions
	I63	Cerebral infarction
	I64	Stroke, not specified as hemorrhage or infarction
	I61	Intracerebral hemorrhage
	I60	Subarachnoid hemorrhage
	G45	Transient cerebral ischemic attacks and related syndromes
OHIP diagnosis code	432	Intracranial hemorrhage
	435	Transient cerebral ischemia
	436	Acute cerebrovascular accident, CVA, stroke
	437	Chronic arteriosclerotic cerebrovascular disease, hypertensive encephalopathy
Coma		
ICD-10	R402	Coma, unspecified, or persistent vegetative state
Acute renal failure		
ICD-10	N17	Acute renal failure
OHIP diagnosis code	584	Acute renal failure
Unplanned return to the operating room		
DAD	INUNPL1-INUNPL20 NE	Unplanned return to OR

CCI, Canadian Classification of Health Interventions; *CPR*, cardiopulmonary resuscitation; *CVA*, cardiovascular accident; *DAD*, Discharge Abstract Database; *ICD-10*, *International Classification of Diseases*, 10th revision; *I&D*, incision & drainage; *NEC*, necrotizing enterocolitis; *OHIP*, Ontario Health Insurance Plan; *OR*, operating room; *SIRS*, systemic inflammatory response syndrome.

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Appendix B: Additional analyses

TABLE 1
Baseline characteristics for propensity-matched cohort for not anemic and unknown anemia groups

Variables	Not anemic (n = 12,994)	Unknown (n = 12,994)	Standardized differences
Demographics			
Age at index date			
Mean (SD)	51.77 ± 12.24	51.75 ± 12.62	0
Median (IQR)	49 (43–60)	49 (43–61)	
Charlson index			
0, n, %	4441 (34.2%)	4449 (34.2%)	0
1, n, %	336 (2.6%)	335 (2.6%)	0
2, n, %	544 (4.2%)	545 (4.2%)	0
≥3, n, %	190 (1.5%)	196 (1.5%)	0
No hospitalizations	7483 (57.6%)	7469 (57.5%)	0
Comorbidities			
Diabetes, n, %	1785 (13.7%)	1780 (13.7%)	0
Coronary artery disease, n, %	600 (4.6%)	604 (4.6%)	0
Stroke, n, %	30 (0.2%)	35 (0.3%)	0.01
COPD, n, %	999 (7.7%)	1009 (7.8%)	0
Previous VTE, n, %	67 (0.5%)	60 (0.5%)	0.01
Chronic kidney disease, n, %	249 (1.9%)	264 (2.0%)	0.01
Previous cancer diagnosis, n, %	3965 (30.5%)	3929 (30.2%)	0.01
Transfusion within 6 months prior, n, %	103 (0.8%)	110 (0.8%)	0.01
Income qunitile			
First quintile, n, %	2188 (16.8%)	2244 (17.3%)	0.01
Second quintile, n, %	2479 (19.1%)	2482 (19.1%)	0
Third quintile, n, %	2726 (21.0%)	2671 (20.6%)	0.01
Fourth quintile, n, %	2908 (22.4%)	2922 (22.5%)	0
Fifth quintile, n, %	2693 (20.7%)	2675 (20.6%)	0
Rurality			
Rural, n, %	1628 (12.5%)	1673 (12.9%)	0.01
Urban, n, %	11,366 (87.5%)	11,321 (87.1%)	0.01
Surgical characterisitics			
Procedure type			
Hysterectomy, n, %	12,516 (96.3%)	12,495 (96.2%)	0.01
Myomectomy, n, %	478 (3.7%)	499 (3.8%)	0.01
Hysterectomy type			
Total hysterectomy, n, %	11,563 (89.0%)	11,660 (89.7%)	0.02
Subtotal hysterectomy, n, %	725 (5.6%)	708 (5.4%)	0.01
Radical hysterectomy, n, %	228 (1.8%)	127 (1.0%)	0.07

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TABLE 1
Baseline characteristics for propensity-matched cohort for not anemic and unknown anemia groups *(continued)*

Variables	Not anemic (n = 12,994)	Unknown (n = 12,994)	Standardized differences
Route of hysterectomy			
Minimally invasive, n, %	7329 (56.4%)	7338 (56.5%)	0
Open, n, %	5187 (39.9%)	5157 (39.7%)	0
Surgery duration			
First quintile, n, %	2566 (19.7%)	2715 (20.9%)	0.03
Second quintile, n, %	2573 (19.8%)	2785 (21.4%)	0.04
Third quintile, n, %	2611 (20.1%)	2648 (20.4%)	0.01
Fourth quintile, n, %	2445 (18.8%)	2452 (18.9%)	0
Fifth quintile, n, %	2535 (19.5%)	2093 (16.1%)	0.09
Diagnosis related to index procedure			
AUB, n, %	3915 (30.1%)	4013 (30.9%)	0.02
Prolapse, n, %	3407 (26.2%)	3387 (26.1%)	0
Pain/endometriosis, n, %	2948 (22.7%)	2905 (22.4%)	0.01
Postmenopausal issues, n, %	298 (2.3%)	280 (2.2%)	0.01
Fibroids, n, %	5007 (38.5%)	4978 (38.3%)	0
Mass/dysplasia, n, %	1274 (9.8%)	1273 (9.8%)	0
Other, n, %	1672 (12.9%)	1661 (12.8%)	0
Bleeding/fibroid diagnosis			
AUB/fibroid, n, %	7141 (55.0%)	7141 (55.0%)	0
Other, n, %	5853 (45.0%)	5853 (45.0%)	0
Provider-related characteristics			
Surgeon age			
Mean (SD)	50.88 ± 9.88	50.80 ± 9.67	0.01
Surgeon years in practice			
Mean (SD)	25.53 ± 10.19	25.46 ± 10.11	0.01
Surgeon volume for hysterectomy			
Mean (SD)	48.25 ± 29.66	48.07 ± 29.70	0.01
Duration of patient-specialist relationship			
Mean (SD)	5.55 ± 5.58	6.01 ± 5.53	0.08
Institution-related characteristics			
Teaching hospital			
Yes, n, %	4086 (31.4%)	4025 (31.0%)	0.01
Hospital volume for hysterectomy			
First quintile, n, %	267 (2.1%)	276 (2.1%)	0
Second quintile, n, %	998 (7.7%)	966 (7.4%)	0.01
Third quintile, n, %	2480 (19.1%)	2484 (19.1%)	0
Fourth quintile, n, %	3218 (24.8%)	3217 (24.8%)	0
Fifth quintile, n, %	6031 (46.4%)	6051 (46.6%)	0

AUB, abnormal uterine bleeding; *COPD*, chronic obstructive pulmonary disease; *IQR*, interquartile range; *VTE*, venothromboembolism.
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TABLE 2
Distribution of timing of preoperative hemoglobin result in relation to surgery for the matched cohort

Days	Entire cohort, %	Anemic, n, %	Nonanemic, n, %
0	34 (0.52%)	≤35	≤5
1–15	4012 (61.51%)	1974 (60.53%)	2038 (62.5%)
16–30	1564 (23.98%)	731 (22.42%)	833 (25.54%)
31–45	494 (7.57%)	276 (8.46%)	218 (6.69%)
46–60	418 (6.41%)	≤250	≤170

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