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Medical Complications of Pregnancy: *Original Research*

# Maternal and Perinatal Morbidity and Mortality Associated With Anemia in Pregnancy

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**OBJECTIVE:** To estimate the incidence of anemia in pregnancy and compare the maternal and perinatal outcomes of women with and without anemia.

**METHODS:** We conducted a population-based retrospective cohort study on all pregnant women in British Columbia who had a live birth or stillbirth at or after 20 weeks of gestation between 2004 and 2016. Women were diagnosed with anemia based on two criteria: third-trimester hemoglobin value or a delivery admission diagnosis of anemia (made before delivery). Anemia was categorized into no anemia (hemoglobin 11 g/dL or greater), mild (9–10.9 g/dL), moderate (7–8.9 g/dL), severe (less than 7 g/dL), or anemia of unspecified severity (with diagnosis made before delivery). Logistic regression was used to estimate adjusted odds ratios (aOR) and 95% CIs expressing the association between anemia and maternal and perinatal outcomes.

**RESULTS:** Of 515,270 women in the study population, 65,906 (12.8%) had anemia: 11.8%, 0.43%, and 0.02% had mild, moderate, and severe anemia, respectively, and 0.58% had anemia of unspecified severity. Anemic women had longer hospitalization duration and more antenatal admissions, and rates of preeclampsia, placenta previa and cesarean delivery were higher among women with anemia. The intrapartum–postpartum blood transfusion rate was 5.1 per 1,000 among women without anemia, and higher among women with anemia (aOR 2.45, 95% CI 1.74–3.45 for mild anemia; 21.3, 95% CI 12.2–37.3 for moderate anemia; not analyzable for severe anemia; and 48.3, 95% CI 6.60–353.9 for anemia of unspecified severity). Anemia was associated with preterm birth (mild anemia, aOR 1.09, 95% CI 1.05–1.12; moderate anemia, aOR 2.26, 95% CI 2.02–2.54; anemia of unspecified severity, aOR 2.27, 95% CI 2.06–2.50), small-for-gestational-age live birth, low 5-minute Apgar score, neonatal death, and perinatal death.

**CONCLUSION:** Maternal anemia in pregnancy represents a common and potentially reversible risk factor associated with antepartum, intrapartum, and postpartum maternal morbidity and perinatal morbidity and mortality.

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Anemia affects approximately 40% of pregnant women worldwide and nearly one third of pregnant women in the United States.[1,2] Anemia in pregnancy has been associated with higher rates of maternal death, perinatal death, preterm birth, preeclampsia, low birth weight, small-for-gestational-age (SGA) live birth, and cesarean delivery.[3–9] The risk of these adverse effects may be proportional to the sever-

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**Table 1. Maternal Characteristics Associated With Anemia in Pregnancy, British Columbia, 2004–2016 (N=515,270)***

| Characteristic | 3rd-Trimester Hb Level and Predelivery Admission Diagnosis of Anemia | | | | | P |
|---|---|---|---|---|---|---|
| | No Anemia (Hb 11 g/dL or Greater, No Anemia Diagnosis) (n=449,364) | Mild Anemia (Hb 9–10.9 g/dL) (n=60,590) | Moderate Anemia (Hb 7–8.9 g/dL) (n=2,195) | Severe Anemia (Hb Less Than 7 g/dL) (n=127) | Unspecified (Diagnosis of Anemia) (n=2,994) | |
| Age (y) | | | | | | |
| Younger than 20 | 12,288 (84.7) | 1,977 (13.6) | 122 (0.84) | 6 (0.04) | 110 (0.76) | <.001 |
| 20–24 | 57,402 (86.8) | 7,877 (11.9) | 378 (0.57) | 19 (0.03) | 480 (0.73) | |
| 25–29 | 124,268 (88.1) | 15,452 (11.0) | 564 (0.40) | 39 (0.03) | 789 (0.56) | |
| 30–34 | 152,909 (87.8) | 19,715 (11.3) | 676 (0.39) | 37 (0.02) | 921 (0.53) | |
| 35–39 | 83,677 (86.3) | 12,388 (12.8) | 370 (0.38) | 21 (0.02) | 540 (0.56) | |
| 40 or older | 18,815 (84.6) | 3,181 (14.3) | 85 (0.38) | 5 (0.02) | 154 (0.69) | |
| Parity | | | | | | |
| Nulliparous | 210,026 (87.8) | 26,994 (11.3) | 764 (0.32) | 48 (0.02) | 1,483 (0.62) | <.001 |
| Multiparous | 239,318 (86.7) | 33,594 (12.2) | 1,431 (0.52) | 79 (0.03) | 1,511 (0.55) | |
| Weight (kg) | | | | | | |
| Less than 50 kg | 27,916 (82.1) | 5,545 (16.3) | 297 (0.87) | 15 (0.04) | 243 (0.71) | <.001 |
| 50–59 | 114,468 (85.8) | 17,666 (13.2) | 592 (0.44) | 37 (0.03) | 730 (0.55) | |
| 60–69 | 102,127 (87.7) | 13,252 (11.4) | 404 (0.35) | 24 (0.02) | 633 (0.54) | |
| 70–79 | 56,792 (88.7) | 6,709 (10.5) | 162 (0.25) | 14 (0.02) | 357 (0.56) | |
| 80–89 | 27,020 (89.4) | 2,918 (9.66) | 89 (0.29) | Less than 5 (<0.02) | 189 (0.63) | |
| 90–99 | 13,914 (89.6) | 1,490 (9.59) | 41 (0.26) | 5 (0.03) | 87 (0.56) | |
| 100 or greater | 14,552 (90.0) | 1,467 (9.08) | 38 (0.24) | Less than 5 (<0.03) | 104 (0.64) | |
| Missing | 92,575 (87.9) | 11,543 (11.0) | 572 (0.54) | 28 (0.03) | 651 (0.62) | |
| Smoker | | | | | | |
| No | 373,360 (87.1) | 50,717 (11.8) | 1,878 (0.44) | 106 (0.02) | 2,440 (0.57) | <.001 |
| Past | 36,434 (87.7) | 4,735 (11.4) | 122 (0.29) | 8 (0.02) | 234 (0.56) | |
| Current | 39,570 (87.5) | 5,138 (11.4) | 195 (0.43) | 13 (0.03) | 2,440 (0.57) | |
| History of alcohol use | | | | | | |
| Yes | 4,890 (87.5) | 607 (10.9) | 45 (0.81) | Less than 5 (<0.09) | 47 (0.84) | <.001 |
| No | 444,471 (87.2) | 59,982 (11.8) | 2,150 (0.42) | 126 (0.02) | 2,947 (0.58) | |
| Previous cesarean delivery | | | | | | |
| Yes | 66,182 (86.3) | 9,502 (12.4) | 444 (0.58) | 21 (0.03) | 580 (0.76) | <.001 |
| No | 383,053 (87.4) | 51,078 (11.7) | 1,750 (0.40) | 105 (0.02) | 2,414 (0.55) | |
| Hypertension | | | | | | |
| Yes | 2,898 (84.2) | 481 (14.0) | 26 (0.76) | Less than 5 (<0.15) | 34 (0.99) | <.001 |
| No | 446,463 (87.2) | 60,108 (11.7) | 2,169 (0.42) | 126 (0.02) | 2,960 (0.58) | |
| Chronic disease | | | | | | |
| Yes | 5,451 (83.4) | 937 (14.4) | 57 (0.87) | Less than 5 (<0.08) | 88 (1.35) | <.001 |
| No | 443,912 (87.3) | 59,652 (11.7) | 2,138 (0.42) | 124 (0.02) | 2,906 (0.57) | |
| History of perinatal death | | | | | | |
| Yes | 4,796 (86.1) | 683 (12.3) | 42 (0.75) | 5 (0.09) | 46 (0.83) | <.001 |
| No | 444,568 (87.2) | 59,907 (11.8) | 2,153 (0.42) | 122 (0.02) | 2,948 (0.58) | |
| In vitro fertilization | | | | | | |
| Yes | 7,434 (81.9) | 1,494 (16.5) | 60 (0.66) | Less than 5 (<0.06) | 91 (1.00) | <.001 |
| No | 441,928 (87.3) | 59,095 (11.7) | 2,135 (0.42) | 125 (0.02) | 2,903 (0.57) | |

Hb, hemoglobin.
Data are n (%) unless otherwise specified.
* Anemia severity was based on third-trimester Hb level and predelivery admission diagnosis of anemia.

**Table 2. Numbers and Rates of Maternal Outcomes Within Categories of Anemia Severity Based on Third-Trimester Hemoglobin Level and Predelivery Admission Diagnosis of Anemia, British Columbia, 2004–2016 (N=515,270)**

| | 3rd-Trimester Hb Level and Predelivery Admission Diagnosis of Anemia | | | | |
|---|---|---|---|---|---|
| Outcome | No Anemia (Hb 11 g/dL or Greater, No Anemia Diagnosis) | Mild Anemia (Hb 9–10.9 g/dL) | Moderate Anemia (Hb 7–8.9 g/dL) | Severe Anemia (Hb Less Than 7 g/dL) | Unspecified (Predelivery Diagnosis of Anemia) |
| Deliveries | | | | | |
| 2004–2016 | 449,364 (100) | 60,590 (100) | 2,195 (100) | 127 (100) | 2,994 (100) |
| 2008–2016 | 313,104 (100) | 43,265 (100) | 1,583 (100) | 95 (100) | 1,929 (100) |
| Additional care | | | | | |
| Mean LOS (d) | 2.6 | 3.0 | 4.5 | 5.2 | 4.4) |
| Prolonged LOS | 7,201 (1.60) | 1,640 (2.71) | 178 (8.11) | 7 (5.51) | 230 (7.68) |
| Mean no. of antenatal admissions | 0.12 | 0.16 | 0.31 | 0.36 | 0.22) |
| Antenatal admission | 40,241 (8.96) | 7,126 (11.8) | 435 (19.8) | 27 (21.3) | 451 (15.1) |
| Admission to special care unit* | 233 (0.07) | 46 (0.11) | 6 (0.38) | 0 (0) | 17 (0.88) |
| Labor and delivery | | | | | |
| Labor induction | 93,539 (20.8) | 13,156 (21.7) | 462 (21.1) | 26 (20.5) | 696 (23.3) |
| Operative vaginal delivery | 45,283 (10.1) | 6,339 (10.5) | 209 (9.52) | 14 (11.0) | 303 (10.1) |
| Cesarean delivery | 136,853 (30.5) | 19,998 (33.0) | 872 (39.7) | 46 (36.2) | 1,514 (50.6) |
| Obstetric morbidity | | | | | |
| Preeclampsia | 4,714 (1.05) | 715 (1.18) | 48 (2.19) | Less than 5 (<3.93) | 91 (3.04) |
| HELLP syndrome* | 919 (0.29) | 122 (0.28) | Less than 5 (<0.32) | 0 (0) | 22 (1.14) |
| Acute fatty liver* | 22 (0.007) | 6 (0.014) | Less than 5 (<0.32) | 0 (0) | Less than 5 (<0.26) |
| Placenta previa with hemorrhage | 1,403 (0.31) | 343 (0.57) | 36 (1.64) | 5 (3.94) | 68 (2.27) |
| Placental abruption | 4,696 (1.05) | 856 (1.41) | 74 (3.37) | Less than 5 (<3.94) | 136 (4.54) |
| Acute renal failure | 57 (0.013) | 9 (0.015) | Less than 5 (<0.23) | 0 (0) | 8 (0.27) |
| Transfusions and postpartum anemia | | | | | |
| Antepartum transfusion | 34 (0.01) | 18 (0.03) | 28 (1.28) | 9 (7.09) | 32 (1.07) |
| Intrapartum–postpartum transfusion | 2,284 (0.51) | 643 (1.06) | 173 (7.88) | 29 (22.8) | 280 (9.35) |
| Postpartum Hb level (g/dL)* | 1,578 (0.35) | 616 (1.02) | 190 (8.66) | 19 (15.0) | 181 (6.05) |
| Less than 7 | | | | | |
| 7–8.9 | 9,124 (2.03) | 3,955 (6.53) | 478 (21.8) | 16 (12.6) | 493 (16.5) |
| 9–10.9 | 42,722 (9.51) | 8,216 (13.6) | 194 (8.84) | 16 (12.6) | 458 (15.3) |
| 11 or greater | 392,379 (87.3) | 46,718 (77.1) | 1,239 (56.5) | 71 (55.9) | 1,797 (60.0) |
| Postdelivery anemia diagnosis | 3,561 (0.79) | 1,085 (1.79) | 94 (4.28) | 5 (3.94) | 65 (2.17) |
| Infectious morbidity | | | | | |
| Antibiotics in delivery admission | 197,256 (43.9) | 28,552 (47.1) | 1,203 (54.8) | 67 (52.8) | 1,846 (61.7) |
| Prophylactic antibiotics for cesarean delivery* | 75,636 (78.3) | 11,873 (81.9) | 543 (85.4) | 27 (79.4) | 756 (81.8) |

(*continued*)

**Table 2. Numbers and Rates of Maternal Outcomes Within Categories of Anemia Severity Based on Third-Trimester Hemoglobin Level and Predelivery Admission Diagnosis of Anemia, British Columbia, 2004–2016 (N=515,270) (*continued*)**

| | 3rd-Trimester Hb Level and Predelivery Admission Diagnosis of Anemia | | | | |
|---|---|---|---|---|---|
| Outcome | No Anemia (Hb 11 g/dL or Greater, No Anemia Diagnosis) | Mild Anemia (Hb 9–10.9 g/dL) | Moderate Anemia (Hb 7–8.9 g/dL) | Severe Anemia (Hb Less Than 7 g/dL) | Unspecified (Predelivery Diagnosis of Anemia) |
| Chorioamnionitis | 7,049 (1.57) | 1,273 (2.10) | 46 (2.10) | Less than 5 (<3.94) | 76 (2.54) |
| Postpartum wound infection* | 711 (0.23) | 114 (0.26) | 5 (0.32) | Less than 5 (<5.26) | 6 (0.31) |
| Postpartum infection* | 1,790 (0.57) | 298 (0.69) | 20 (1.26) | Less than 5 (<5.26) | 18 (0.93) |
| Postpartum UTI* | 304 (0.10) | 61 (0.14) | Less than 5 (<0.32) | Less than 5 (<5.26) | 7 (0.36) |
| Positive blood culture* | 81 (0.03) | 18 (0.04) | Less than 5 (<0.32) | 0 (0) | 5 (0.26) |

Hb, hemoglobin; LOS, length of stay; HELLP, hemolysis, elevated liver enzymes, and low platelet count; UTI, urinary tract infection.
* Information on these maternal outcomes was available only for deliveries between 2008 and 2016 (n=359,976). Special care unit admissions included admissions to an intensive care unit or high dependency unit.

ity of anemia; preterm birth and low birth weight rates are markedly elevated among women with a hemoglobin level less than 7 g/dL.[10]

The literature on anemia in pregnancy is largely based on studies in African and Asian populations in low-income countries, where the severity and causes of anemia differ from those in high-income countries.[1] Most studies on anemia in pregnancy are set in regions characterized by poor access to antenatal care and where malaria or malnutrition are prevalent.[11,12] It is unclear whether the effects of anemia in the current literature can be generalized to high-income countries where the socioeconomic environment is more affluent, antenatal care services are readily accessible, and risk factors for anemia differ both in type and frequency.

We attempted to estimate the incidence of anemia in pregnancy and to quantify the association of anemia with maternal and perinatal morbidity and mortality in British Columbia, Canada.

## METHODS

We carried out a population-based retrospective cohort study of all pregnant women in British Columbia who had a live birth or stillbirth at or after 20 weeks of gestation between 2004 and 2016. Data on these pregnancies and births were obtained from the British Columbia Perinatal Data Registry,[13] a population-based registry that collects and maintains perinatal data from hospital and home deliveries for surveillance and research purposes. Data from medical records were abstracted by trained heath information management staff using standardized forms. The accuracy of the data was monitored by automated data consistency rules and ad hoc data quality checks; validation studies show the data to be accurate.[14] The British Columbia Perinatal Data Registry included information on more than 99% of births in British Columbia during the study period.

In addition to information on maternal, fetal, and neonatal characteristics, the British Columbia Perinatal Data Registry also included up to 25 diagnosis and 20 procedure codes for each mother and newborn, with diagnoses coded using the International Classification of Diseases, 10th Revision, Canada and procedures coded with the Canadian Classification of Health Interventions. All diagnoses and procedures in the database were based on physician notes, as recorded in the medical chart. The information collected by the data registry was expanded in 2008 to specifically include details regarding hemolysis, elevated liver enzymes, and low platelet count syndrome; acute fatty liver, admission to a special care nursery, postpartum hemoglobin level, and several infectious postpartum illnesses.

Cases of anemia were identified using third-trimester hemoglobin levels of less than 11 g/dL and International Classification of Diseases, 10th Revision, Canada codes for anemia (D50–D64 and O99.0) (Appendix 1, available online at http://links.lww.com/AOG/B612). Cases of anemia that were identified using the O99.0 diagnosis code for anemia were restricted to patients who received the code as a predelivery admission diagnosis (to distinguish anemia in pregnancy from anemia due to intrapartum–postpartum hemorrhage). Cases of anemia included pregnant women with 1) a third-

**Table 3. Unadjusted and Adjusted Odds Ratios Showing the Association Between Anemia Severity and Maternal Outcomes, British Columbia, 2004–2016 (N=515,270)**

| | 3rd-Trimester Hb Level and Preadmission Diagnosis of Anemia | | | |
|---|---|---|---|---|
| | Mild Anemia (Hb 9–10.9 g/dL) | | Moderate Anemia (Hb 7–8.9 g/dL) | |
| Maternal Outcome | OR (95% CI) | aOR (95% CI) | OR (95% CI) | aOR (95% CI) |
| Additional care | | | | |
| Prolonged LOS | **1.67 (1.58–1.76)** | **1.66 (1.57–1.75)** | **5.20 (4.46–6.08)** | **5.41 (4.60–6.35)** |
| Antenatal admission (yes) | **1.35 (1.31–1.39)** | **1.36 (1.32–1.40)** | **2.50 (2.25–2.78)** | **2.42 (2.17–2.69)** |
| Admission to special care unit† | 1.35 (0.99–1.85) | * | **4.83 (2.15–10.9)** | * |
| Labor and delivery | | | | |
| Labor induction | **1.05 (1.03–1.08)** | **1.11 (1.09–1.13)** | 1.01 (0.91–1.12) | **1.22 (1.09–1.35)** |
| Operative vaginal delivery | **1.04 (1.01–1.07)** | **1.05 (1.02–1.08)** | 0.94 (0.81–1.08) | 1.08 (0.93–1.25) |
| Cesarean delivery | **1.12 (1.10–1.14)** | **1.17 (1.14–1.19)** | **1.50 (1.37–1.63)** | **1.86 (1.67–2.08)** |
| Obstetric morbidity | | | | |
| Preeclampsia | **1.11 (1.03–1.21)** | **1.16 (1.07–1.25)** | **2.08 (1.56–2.78)** | * |
| Placenta previa with hemorrhage | **1.75 (1.55–1.96)** | **1.65 (1.47–1.86)** | **5.11 (3.66–7.14)** | * |
| Placental abruption | **1.33 (1.24–1.43)** | **1.30 (1.21–1.40)** | **3.24 (2.56–4.09)** | * |
| Transfusions and postpartum anemia | | | | |
| Antepartum transfusion | **2.17 (1.28–3.66)** | * | **94.2 (60.2–147.5)** | * |
| Intrapartum–postpartum transfusion | **2.53 (1.80–3.56)** | **2.45 (1.74–3.45)** | **22.3 (12.8–38.8)** | **21.3 (12.2–37.3)** |
| Postpartum anemia† | **2.01 (1.97–2.06)** | **2.07 (2.02–2.11)** | **5.23 (4.81–5.70)** | * |
| Infectious morbidity | | | | |
| Antibiotics during delivery admission | **1.13 (1.11–1.15)** | **1.15 (1.13–1.17)** | **1.54 (1.42–1.68)** | **1.68 (1.53–1.83)** |
| Prophylactic antibiotics for cesarean delivery† | **1.25 (1.20–1.31)** | **1.22 (1.17–1.28)** | **1.62 (1.30–2.02)** | **1.57 (1.25–1.96)** |
| Chorioamnionitis | **1.34 (1.26–1.42)** | **1.35 (1.27–1.44)** | 1.34 (1.00–1.79) | **1.61 (1.19–2.16)** |
| Postpartum wound infection† | 1.16 (0.95–1.41) | 1.15 (0.94–1.40) | 1.39 (0.58–3.35) | * |
| Postpartum infection† | **1.20 (1.06–1.36)** | **1.19 (1.05–1.35)** | **2.22 (1.42–3.45)** | * |
| Postpartum UTI† | **1.43 (1.09–1.88)** | * | 2.56 (0.96–6.88) | * |

Hb, hemoglobin; OR, odds ratio; aOR, adjusted odds ratio; UTI, urinary tract infection.

Models adjusted for maternal age, parity, prepregnancy weight, smoking, previous cesarean delivery, alcohol use, preexisting hypertension, chronic diseases and in vitro fertilization (not adjusted for nonindependence of outcomes among deliveries to the same woman. Odds ratios for acute renal failure, acute fatty liver, hemolysis, elevated liver enzymes, and low platelet count syndrome and blood positive culture undefined or could not be estimated. Bold indicates statistically significant ORs.

* Adjusted ORs not estimated because these categories had few events relative to the number of variables in the regression model.

† Information on these maternal outcomes was available only for deliveries between 2008 and 2016 (n=359,976).

trimester hemoglobin level of less than 11 g/dL or 2) a diagnosis of anemia made during the delivery admission but before delivery (referred to as predelivery admission diagnosis of anemia [Appendix 2, available online at http://links.lww.com/AOG/B612]). The reference group (no anemia) included pregnant women who 1) did not have a predelivery admission diagnosis of anemia and 2) had a third-trimester hemoglobin level of 11 g/dL or greater. Anemia severity was categorized into four groups: mild (9–10.9 g/dL), moderate (7–8.9 g/dL), severe (less than 7 g/dL) and unspecified (predelivery admission diagnosis of anemia with third-trimester hemoglobin value missing or at 11 g/dL or greater).

Pregnant women with and without anemia in pregnancy were contrasted in terms of maternal and clinical characteristics such as age, parity, prepregnancy weight, smoking, use of in vitro fertilization, and other factors. Maternal outcomes of interest included indicators of the need for additional care, labor and delivery procedures, obstetric morbidity, blood transfusions, postpartum anemia and infectious morbidity. Perinatal outcomes examined included multiple births, preterm birth, SGA live birth (less than the 10th centile and less than the 3rd centile),[15] low 5-minute Apgar score (less than 7 or less than 4), and neonatal morbidity or perinatal death.

Logistic regression was used to quantify unadjusted odds ratios (ORs) and adjusted odds ratios (aORs) and 95% CIs expressing the association between anemia in pregnancy and maternal and perinatal morbidity and mortality. Variables included in the regression analysis included age, parity, prepregnancy weight, smoking, alcohol use, previous cesarean delivery, hypertension, chronic disease (including preexisting diabetes mellitus, chronic renal disease due to hypertension, liver disease, other renal disease, and diseases of the circulatory system), history of perinatal death, and in vitro fertilization in the current pregnancy. Event frequencies in some categories of anemia were too small to permit fitting regression models with the covariates mentioned

| Maternal Outcome | 3rd-Trimester Hb Level and Preadmission Diagnosis of Anemia | | | |
|---|---|---|---|---|
| | Severe Anemia (Hb Less Than 7 g/dL) | | Unspecified (Predelivery Diagnosis of Anemia) | |
| | OR (95% CI) | aOR (95% CI) | OR (95% CI) | aOR (95% CI) |
| Additional care | | | | |
| Prolonged LOS | **3.47 (1.62–7.44)** | * | **5.16 (2.24–11.9)** | **4.72 (2.00–11.1)** |
| Antenatal admission (yes) | **2.73 (1.79–4.18)** | * | 1.06 (0.49–2.30) | 0.96 (0.44–2.11) |
| Admission to special care unit† | — | * | **55.2 (13.3–228.5)** | * |
| Labor and delivery | | | | |
| Labor induction | 0.98 (0.91–1.12) | * | 0.74 (0.40–1.37) | 0.70 (0.37–1.31) |
| Operative vaginal delivery | 1.11 (0.63–1.93) | * | 1.40 (0.72–2.72) | 1.41 (0.71–2.80) |
| Cesarean delivery | 1.29 (0.90–1.85) | * | **1.83 (1.16–2.89)** | **2.43 (1.42–4.18)** |
| Obstetric morbidity | | | | |
| Preeclampsia | **3.03 (1.12–8.21)** | * | **5.33 (1.94–14.6)** | * |
| Placenta previa with hemorrhage | **12.6 (5.17–30.9)** | * | 4.20 (0.58–30.2) | * |
| Placental abruption | 2.24 (0.71–7.05) | * | **8.18 (3.55–18.9)** | **8.03 (3.47–18.6)** |
| Transfusions and postpartum anemia | | | | |
| Antepartum transfusion | **556.3 (270.2–999.9)** | * | **416.8 (147.6–999.9)** | * |
| Intrapartum–postpartum transfusion | **84.1 (26.4–267.9)** | * | **47.6 (6.57–345.4)** | **48.3 (6.60–353.9)** |
| Postpartum anemia† | **5.35 (3.77–7.59)** | * | **5.77 (3.65–9.11)** | * |
| Infectious morbidity | | | | |
| Antibiotics during delivery admission | **1.42 (1.00–2.01)** | * | 1.02 (0.65–1.62) | 1.05 (0.65–1.70) |
| Prophylactic antibiotics for cesarean delivery† | 1.07 (0.47–2.46) | * | 0.94 (0.35–2.56) | 0.93 (0.34–2.54) |
| Chorioamnionitis | 1.00 (0.24–4.04) | * | * | * |
| Postpartum wound infection† | 4.66 (0.65–33.5) | * | * | * |
| Postpartum infection† | 3.73 (0.92–15.1) | * | * | * |
| Postpartum UTI† | **10.8 (1.50–77.5)** | * | * | * |

above.[16] Therefore, adjusted models were estimated if the anemia severity category included at least 100 women with the event of interest.

Some women contributed more than one delivery to the study population and such deliveries (which represented nonindependent observations because of potential correlation in maternal–perinatal outcome rates) would have affected the precision of the estimates of effect. We were unable to address this problem directly because our data did not include identifiers permitting linkage of women across deliveries, and, hence, we carried out additional analyses restricted to nulliparous women. This issue of nonindependence of observations also affected analyses of perinatal outcomes involving twins and triplets; this problem was addressed by using generalized estimating equations and cluster-specific regression models.[17,18]

Population attributable fractions associated with anemia (which depend on anemia frequency and effect, and express the proportion of an outcome that could be prevented if anemia in pregnancy was avoided) were estimated using the formula for a multicategory exposure.[19]

Analyses were carried out using SAS 9.4, and the study received ethics approval from the University of British Columbia's Children's and Women's Health Center Research Ethics Board (IRB number H17-01524).

## RESULTS

The study population included 515,270 pregnant women, of whom 364,422 (70.7%) had a documented maternal third-trimester hemoglobin value. Overall, 65,906 (12.8%, 95% CI 12.8–12.8) women had anemia in the antenatal period: 11.8% had mild anemia, 0.43% had moderate anemia, 0.02% had severe anemia and 0.58% had anemia of unspecified severity (Appendix 3 available online at http://links.lww.com/AOG/B612). Among women with an anemia diagnosis, 98.4% received a (etiologically) nonspecific diagnosis of anemia (Appendix 4, available online at http://links.lww.com/AOG/B612).

Rates of anemia were significantly higher among women at the extremes of reproductive age (younger than 20 years and 40 years or older); multiparous women; women with prepregnancy weight less than 50 kg; nonsmokers; women with a previous cesarean delivery, hypertension, chronic disease, or history of perinatal death; and women with in vitro fertilization in the current pregnancy (Table 1).

**Table 4. Numbers and Rates of Fetal and Neonatal Outcomes Associated With Maternal Anemia, British Columbia, 2004–2016 (n=523,669)***

| Outcome | 3rd-Trimester Hb Level and Predelivery Admission Diagnosis of Anemia | | | | |
|---|---|---|---|---|---|
| | No Anemia (Hb 11 g/dL or Greater, and No Anemia Diagnosis) | Mild Anemia (Hb 9–10.9 g/dL) | Moderate Anemia (Hb 7–8.9 g/dL) | Severe Anemia (Hb Less Than 7 g/dL) | Unspecified (Predelivery Diagnosis of Anemia) |
| Multiple births | 13,102 (2.87) | 3,078 (4.95) | 230 (9.96) | 16 (11.9) | 283 (9.03) |
| Preterm birth (less than 37 wk) | 42,507 (9.38) | 6,745 (10.9) | 470 (20.6) | 29 (22.1) | 654 (21.2) |
| Very preterm birth (less than 32 wk) | 6,680 (1.47) | 1,247 (2.01) | 134 (5.86) | 11 (8.40) | 191 (6.20) |
| SGA live birth | | | | | |
| Less than 10th centile | 31,329 (6.92) | 3,860 (6.24) | 190 (8.34) | 21 (16.0) | 228 (7.43) |
| Less than 3rd centile | 7,618 (1.68) | 890 (1.44) | 67 (2.94) | 6 (4.58) | 63 (2.05) |
| 5-min Apgar score | | | | | |
| Less than 7 | 8,592 (1.90) | 1,204 (1.95) | 82 (3.59) | 11 (8.53) | 132 (4.32) |
| Less than 4 | 1,429 (0.32) | 188 (0.30) | 22 (0.96) | Less than 5 (<3.88) | 45 (1.47) |
| Special care nursery admission | 31,884 (7.03) | 5,336 (8.61) | 372 (16.2) | 29 (22.0) | 470 (15.2) |
| Respiratory distress syndrome | 4,577 (1.01) | 873 (1.41) | 71 (3.10) | 8 (6.06) | 135 (4.37) |
| Fetal asphyxia | 2,406 (0.53) | 333 (0.54) | 16 (0.69) | Less than 5 (<3.70) | 25 (0.80) |
| Birth asphyxia | 678 (0.15) | 88 (0.14) | Less than 5 (<0.22) | Less than 5 (<3.70) | 11 (0.35) |
| Convulsions | 573 (0.13) | 70 (0.11) | 6 (0.26) | 0 (0) | 12 (0.38) |
| HIE | 304 (0.07) | 50 (0.08) | Less than 5 (<0.22) | Less than 5 (<3.70) | Less than 5 (<0.16) |
| Bacterial sepsis | 1,567 (0.35) | 263 (0.42) | 18 (0.78) | 0 (0) | 25 (0.80) |
| Congenital anomalies | 23,115 (5.07) | 3,226 (5.19) | 163 (7.06) | 16 (11.9) | 233 (7.43) |
| Stillbirth | 2,241 (0.49) | 162 (0.26) | 18 (0.78) | Less than 5 (<3.70) | 49 (1.56) |
| Neonatal death | 835 (0.18) | 105 (0.17) | 13 (0.57) | Less than 5 (<3.79) | 26 (0.84) |
| Perinatal death | 3,076 (0.67) | 267 (0.43) | 31 (1.34) | 5 (3.70) | 75 (2.39) |

Hb, hemoglobin; SGA, small for gestational age; HIE, hypoxic ischemic encephalopathy.
Total births served as the denominator for rates of multiple birth, fetal asphyxia, congenital anomalies, stillbirth, and perinatal death rates, and live births served as the denominator for all other rates.
* Anemia severity was based on third-trimester Hb level and predelivery admission diagnosis of anemia.

Additional care increased with the severity of anemia as reflected in the higher rate of women requiring an antenatal admission and admission to a special care unit (Table 2). The mean length of postpartum stay was 2.6 days for women without anemia and 3.0, 4.5, 5.2 and 4.4 days for women with mild, moderate, severe and unspecified anemia in pregnancy, respectively.

Women with anemia had significantly higher odds of prolonged hospital stay (less than 7 days) compared with nonanemic women (Table 3). The unadjusted ORs between mild, moderate, and severe anemia and antenatal admission were all significantly elevated and increased with anemia severity; women with anemia of moderate and unspecified severity also had significantly higher unadjusted ORs for admission to a special care unit. Adjusted ORs for these outcomes were not significantly different from unadjusted ORs.

Unadjusted and adjusted ORs for labor induction, operative vaginal delivery, and cesarean delivery were significantly higher among women with mild anemia (compared with nonanemic women); unadjusted and adjusted ORs for cesarean delivery were significantly higher among women with moderate and unspecified anemia. Unadjusted ORs between preeclampsia and mild, moderate and severe anemia increased with anemia severity and were highest among women with unspecified anemia. Odds ratios also were significantly higher between specific

categories of anemia and placenta previa with hemorrhage and placental abruption (Table 3).

Unadjusted ORs for intrapartum–postpartum blood transfusion were significantly elevated for women with anemia, with ORs being 2.53, 95% CI 1.80–3.56 for mild anemia, 22.3, 95% CI 12.8–38.8 for moderate anemia, 84.1, 95% CI 26.4–267.9 for severe anemia and 47.6, 95% CI 6.56–345.4 for anemia of unspecified severity. Adjusted ORs were similar to unadjusted ORs. Odds ratios for indices of infectious morbidity were variable, being significantly higher among women with mild and moderate anemia for antibiotic use, postpartum infection, chorioamnionitis and postpartum urinary tract infection (Table 3).

The unadjusted OR for preterm birth was 1.12 (95% CI 1.09–1.16) for mild anemia, 2.38 (95% CI 2.13–2.65) for moderate anemia, 2.58 (95% CI 1.65–4.02) for severe anemia and 2.44 (95% CI 2.22–2.68) for anemia of unspecified severity (Table 4). Adjusted odds ratios between anemia and preterm birth were slightly attenuated but significant (when estimable; Table 5). Other perinatal outcomes with significantly higher ORs included multiple birth, very preterm birth, respiratory distress syndrome, special care unit admission, and bacterial sepsis. Odds ratios for congenital anomalies, SGA birth, stillbirth, and perinatal death were significantly lower among women with mild anemia; the ORs for these outcomes were significantly higher among women with moderate, severe, and unspecified anemia. For instance, the unadjusted OR for perinatal death among women with mild anemia was 0.61 (95% CI 0.53–0.69), whereas the unadjusted ORs for perinatal death among women with moderate anemia, severe anemia, and anemia of unspecified severity were 1.99 (95% CI 1.99–2.88), 5.69 (95% CI 2.28–14.2), and 3.65 (95% CI 2.88–4.64), respectively.

Results of analyses restricted to nulliparous women, which were based on 239,315 women, showed that variance estimates were generally similar to those from results of analyses based on all women with some notable differences (Appendices 5–8, available online at http://links.lww.com/AOG/B612). For instance, the aOR for mild anemia and prolonged hospital stay was 1.45 (95% CI 1.34–1.57) among deliveries to nulliparous women and 1.66 (95% CI 1.57–1.75) among all deliveries, whereas the aOR for multiple birth was 1.65 (95% 1.52–1.80) among deliveries to nulliparous women and 1.69 (95% CI 1.59–1.79) among all deliveries. The population attributable fractions based on unadjusted ORs for anemia in pregnancy were generally small (2.0% for cesarean delivery, 3.1% for preeclampsia, 2.8% for preterm birth), except for maternal blood transfusion (25.1% for intrapartum–postpartum transfusion).

## DISCUSSION

In this large, retrospective, population-based cohort study examining the association between anemia and a broad range of maternal morbidity and perinatal morbidity and mortality in Canada, anemia was associated with several types of morbidity and resulted in the need for increased health care requirements, including intensive care for both the mother and neonate. In addition to a higher burden of illness, anemic women had higher rates of placentally mediated antepartum morbidity such as preeclampsia. During the intrapartum period, anemia was associated with higher rates of induction of labor, cesarean delivery, and blood transfusion, and rates of infectious morbidity were significantly higher among anemic women in the intrapartum and postpartum periods. Moderate and severe anemia in pregnancy were associated with significantly higher rates of preterm and SGA live birth, and perinatal mortality and morbidity.

Our study showed higher rates of postpartum urinary tract infection and other postpartum infections among women with anemia and also higher rates of antibiotic use during the delivery admission. Neonates of anemic women also had higher rates of bacterial sepsis after delivery. Both anemia and receipt of allogenic blood transfusions have been associated with higher rates of infection in trauma, as well as noncardiac and gynecologic surgical patients.[20–22]

The frequency of neonatal morbidity and mortality varied with the degree of maternal anemia. The unexpected negative association between mild anemia and perinatal morbidity and mortality, which has not been reported previously, may represent a heightened maternal physiologic response to pregnancy: physiologic adaptation to pregnancy in many healthy women likely leads to a significantly expanded blood volume, which manifests as mild anemia and results in optimal perinatal outcomes. On the other hand, moderate and severe maternal anemia confer a physiologic burden on the mother, placenta and fetus, and this results in less optimal maternal and neonatal outcomes. Interestingly, mild anemia, which was associated with lower rates of several adverse pregnancy outcomes, was associated with higher rates of infectious morbidity such as bacterial sepsis (suggesting that women diagnosed with mild anemia include some who have an optimal physiologic response to pregnancy and others with true anemia of mild severity).

**Table 5. Unadjusted and Adjusted Odds Ratios Showing the Association Between Anemia Severity and Fetal and Neonatal Outcomes, British Columbia, 2004–2016 (n=523,669)***

| | 3rd-Trimester Hb Level and Preadmission Diagnosis of Anemia | | | |
|---|---|---|---|---|
| | Mild Anemia (Hb 9–10.9 g/dL) | | Moderate Anemia (Hb 7–8.9 g/dL) | |
| Outcome | OR (95% CI) | aOR (95% CI) | OR (95% CI) | aOR (95% CI) |
| Multiple births | **1.76 (1.66–1.86)** | **1.69 (1.59–1.79)** | **3.76 (3.11–4.54)** | **4.11 (3.36–5.01)** |
| Preterm birth (less than 37 wk) | **1.12 (1.09–1.16)** | **1.09 (1.05–1.12)** | **2.38 (2.13–2.65)** | **2.26 (2.02–2.54)** |
| Very preterm birth (less than 32 wk) | **1.33 (1.24–1.42)** | **1.30 (1.21–1.39)** | **4.23 (3.50–5.12)** | **3.95 (3.23–4.83)** |
| SGA live birth | | | | |
| Less than 10th centile | **0.88 (0.85–0.91)** | **0.83 (0.80–0.86)** | **1.17 (1.01–1.37)** | 1.13 (0.97–1.33) |
| Less than 3rd centile | **0.84 (0.78–0.90)** | **0.80 (0.75–0.86)** | **1.67 (1.30–2.16)** | † |
| 5-min Apgar score | | | | |
| Less than 7 | **1.01 (0.95–1.07)** | **1.03 (0.97–1.10)** | **1.84 (1.46–2.32)** | † |
| Less than 4 | 0.95 (0.81–1.11) | 0.97 (0.83–1.14) | **2.80 (1.80–4.37)** | † |
| Special care nursery admission | **1.21 (1.17–1.25)** | **1.21 (1.17–1.25)** | **2.47 (2.19–2.78)** | **2.52 (2.22–2.85)** |
| Respiratory distress syndrome | **1.36 (1.26–1.47)** | **1.35 (1.24–1.46)** | **2.98 (2.30–3.86)** | † |
| Fetal asphyxia | 1.02 (0.91–1.14) | 1.03 (0.92–1.16) | 1.32 (0.81–2.16) | † |
| Birth asphyxia | 0.94 (0.75–1.18) | † | 1.13 (0.42–3.03) | † |
| Convulsions‡ | 0.90 (0.70–1.15) | † | 2.07 (0.93–4.63) | † |
| HIE | 0.94 (0.75–1.18) | † | 1.13 (0.42–3.03) | † |
| Bacterial sepsis‡ | **1.23 (1.08–1.40)** | **1.24 (1.08–1.41)** | **2.27 (1.43–3.62)** | † |
| Congenital anomalies‡ | 1.03 (0.99–1.07) | 1.00 (0.96–1.04) | **1.42 (1.21–1.67)** | **1.41 (1.20–1.66)** |
| Stillbirth | **0.51 (0.43–0.60)** | **0.50 (0.42–0.59)** | **1.62 (1.01–2.61)** | † |
| Neonatal death | 0.89 (0.72–1.10) | 0.90 (0.72–1.11) | **2.96 (1.65–5.30)** | † |
| Perinatal death | **0.61 (0.53–0.69)** | **0.61 (0.53–0.70)** | **1.99 (1.37–2.88)** | † |

Hb, hemoglobin; OR, odds ratio; aOR, adjusted odds ratio; SGA, small for gestational age; HIE, hypoxic ischemic encephalopathy.
All models included adjustment for maternal age, parity, prepregnancy weight, smoking, previous cesarean delivery, alcohol use, preexisting hypertension, chronic diseases and in vitro fertilization and multiple birth. All models adjusted for nonindependence of twin and triplet gestations (except as indicated). Adjusted models included variables for maternal age, parity, prepregnancy weight, smoking, previous cesarean delivery, alcohol use, preexisting hypertension, chronic diseases and in vitro fertilization. Odds ratios for acute renal failure, acute fatty liver, hemolysis, elevated liver enzymes, and low platelet count syndrome and blood positive culture undefined or could not be estimated. Bold indicates Statistically significant ORs.
* Anemia severity was based on third-trimester Hb level and predelivery admission diagnosis of anemia.
† Not adjusted for the nonindependence of births after multifetal gestation (owing to model fitting constraints).
‡ Adjusted ORs not estimated as these categories had few events relative to the number of variables in the regression model.

Our findings are consistent with the literature with regard to higher rates of SGA live birth, preterm birth, and perinatal death associated with moderate and severe anemia.[3–7] The findings with regard to maternal and perinatal morbidity and mortality vary slightly from prior studies.[6–10] This may be a result of different causes of anemia in Asian and African countries and challenges accessing health care during pregnancy in lower resource countries. We found a lower incidence of all severities of anemia in comparison with lower resource countries.[1]

If our findings represent causal associations between anemia status and adverse outcomes, treating iron deficiency before conception or early in the antenatal period may help reduce maternal morbidity and perinatal morbidity and mortality.[11] Although the population attributable fraction associated with anemia and each specific adverse outcome was small, the large number of adverse outcomes associated with anemia and the high effect on blood transfusions suggests that anemia is a condition worth preventing.

There were a few limitations that may have affected the findings of our retrospective cohort study. The third-trimester hemoglobin value was missing in a significant fraction of our study participants; for these participants, we relied solely on predelivery admission diagnosis of anemia. We were also limited in our ability to assess the association between severe anemia and relatively rare outcomes owing to the small number of such cases. Analysis of outcomes by type of anemia was also limited by the low frequency of anemia and its types (Appendix 4, http://links.lww.com/AOG/B612); differences in anemia types may have resulted in different maternal and fetal responses. Other limitations included the potential for reverse causality (eg, some of the association between anemia and placenta previa or abruption may have been because of antepartum hemorrhage leading to anemia) and the lack of individual-level information on maternal ethnicity, education, and household income. Information on gestational age at

| | 3rd-Trimester Hb Level and Preadmission Diagnosis of Anemia | | | |
|---|---|---|---|---|
| | Severe Anemia (Hb Less Than 7 g/dL) | | Unspecified (Predelivery Diagnosis of Anemia) | |
| Outcome | OR (95% CI) | aOR (95% CI) | OR (95% CI) | aOR (95% CI) |
| Multiple births | **4.57 (2.23–9.35)** | † | **3.38 (2.85–4.01)** | **3.15 (2.62–3.79)** |
| Preterm birth (less than 37 wk) | **2.58 (1.65–4.02)** | † | **2.44 (2.22–2.68)** | **2.27 (2.06–2.50)** |
| Very preterm birth (less than 32 wk) | **6.03 (3.06–11.9)** | † | **4.30 (3.66–5.06)** | **3.86 (3.25–4.59)** |
| SGA live birth | | | | |
| Less than 10th centile | **2.33 (1.44–3.76)** | † | 1.04 (0.91–1.20) | 0.98 (0.85–1.14) |
| Less than 3rd centile | **3.00 (1.32–6.81)** | † | 1.23 (0.95–1.58) | † |
| 5-min Apgar score | | | | |
| Less than 7 | **4.72 (2.47–9.01)** | † | **2.33 (1.94–2.79)** | **2.12 (1.76–2.56)** |
| Less than 4 | 4.05 (0.93–17.6) | † | **4.75 (3.49–6.45)** | † |
| Special care nursery admission | **3.86 (2.52–5.91)** | † | **2.25 (2.03–2.50)** | **2.08 (1.87–2.32)** |
| Respiratory distress syndrome | **6.57 (3.16–13.7)** | † | **4.31 (3.56–5.21)** | **3.83 (3.13–4.67)** |
| Fetal asphyxia | 1.41 (0.20–10.1) | † | **1.52 (1.02–2.25)** | † |
| Birth asphyxia | 5.28 (0.74–37.8) | † | **2.17 (1.16–4.07)** | † |
| Convulsions‡ | — | † | **3.05 (1.72–5.42)** | † |
| HIE | 5.28 (0.74–37.8) | † | **2.17 (1.16–4.07)** | † |
| Bacterial sepsis‡ | — | † | **2.33 (1.56–3.46)** | † |
| Congenital anomalies‡ | **2.52 (1.50–4.25)** | † | **1.50 (1.32–1.72)** | **1.38 (1.20–1.58)** |
| Stillbirth | **5.08 (1.62–16.0)** | † | **3.21 (2.39–4.30)** | † |
| Neonatal death | **7.14 (1.64–31.0)** | † | **4.88 (3.28–7.26)** | † |
| Perinatal death | **5.69 (2.28–14.2)** | † | **3.65 (2.88–4.64)** | † |

diagnosis of anemia and gestational age at diagnosis of placental complications would have provided better insight into potential cause-effect relationships and information on socioeconomic status would have provided insight into the social determinants of perinatal health. Finally, we did not have access to treatments that may have been provided when anemia was diagnosed.

In summary, our study shows that anemia in pregnancy, especially moderate and severe anemia, is associated with several different types of maternal morbidity and perinatal morbidity and mortality even in a high-income country. Prepregnancy and antenatal treatment of anemia has the potential to improve outcomes for affected women and their fetuses and neonates and minimize the illness burden and cost due to this common disease.

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