ANESTHESIOLOGY

Association of Gestational Age with Postpartum Hemorrhage: An International Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postpartum hemorrhage remains a source of major morbidity among parturients
- Although some risk factors are established, the association between gestational age and postpartum hemorrhage is unclear

What This Article Tells Us That Is New

- In a retrospective analysis of childbirth registries in California and Sweden, the incidence of postpartum hemorrhage varied from 3.2 to 7.1%
- Compared to delivery at a gestational age of 37 to 38 weeks, delivery at 41 to 42 weeks was associated with a doubling of risk among parturients in California and a 62% increase in Swedish women

ABSTRACT

Background: Risk factors for postpartum hemorrhage, such as chorioamnionitis and multiple gestation, have been identified in previous epidemiologic studies. However, existing data describing the association between gestational age at delivery and postpartum hemorrhage are conflicting. The aim of this study was to assess the association between gestational age at delivery and postpartum hemorrhage.

Methods: The authors conducted a population-based retrospective cohort study of women who underwent live birth delivery in Sweden between 2014 and 2017 and in California between 2011 and 2015. The primary exposure was gestational age at delivery. The primary outcome was postpartum hemorrhage, classified using International Classification of Diseases, Ninth Revision—Clinical Modification codes for California births and a blood loss greater than 1,000 ml for Swedish births. The authors accounted for demographic and obstetric factors as potential confounders in the analyses.

Results: The incidences of postpartum hemorrhage in Sweden (23,323/328,729; 7.1%) and in California (66,583/2,079,637; 3.2%) were not comparable. In Sweden and California, the incidence of postpartum hemorrhage was highest for deliveries between 41 and 42 weeks' gestation (7,186/75,539 [9.5%] and 8,921/160,267 [5.6%], respectively). Compared to deliveries between 37 and 38 weeks, deliveries between 41 and 42 weeks had the highest adjusted odds of postpartum hemorrhage (1.62 [95% CI, 1.56 to 1.69] in Sweden and 2.04 [95% CI, 1.98 to 2.09] in California). In both cohorts, the authors observed a nonlinear (J-shaped) association between gestational age and postpartum hemorrhage risk, with 39 weeks as the nadir. In the sensitivity analyses, similar findings were observed among cesarean deliveries only, when postpartum hemorrhage was classified only by International Classification of Diseases, Tenth Revision—Clinical Modification codes, and after excluding women with abnormal placentation disorders.

Conclusions: The postpartum hemorrhage incidence in Sweden and California was not comparable. When assessing a woman's risk for postpartum hemorrhage, clinicians should be aware of the heightened odds in women who deliver between 41 and 42 weeks' gestation.

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Postpartum hemorrhage is one of the leading causes of preventable maternal death and maternal morbidity in developed countries, including the United States.[1–4] In response, maternal safety agencies, such as the National Partnership for Maternal Safety (Council on Patient Safety in Women's Healthcare, Washington, D.C.), recommend that all patients undergo risk assessment for postpartum hemorrhage.[5] This assessment relies on the appraisal of risk factors such as preeclampsia, polyhydramnios, chorioamnionitis, multiple gestation, labor induction, and caesarean delivery.[6–10] However, based on data from a large administrative database, 39% of U.S. women with severe postpartum hemorrhage do not have identifiable risk factors.[7] Therefore, population-wide studies are needed to identify potential clinical risk factors that have not been identified in administrative data.

Gestational age may be an important and underappreciated risk factor for postpartum hemorrhage. Data from *in*

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vitro studies show that there is reduced contractility in myometrium from women with postterm pregnancies compared to term pregnancies,[11] suggesting that these women are at risk for atonic hemorrhage. Other data suggest that, due to impaired placentation, postpartum hemorrhage risk may be higher in women who deliver preterm.[12–14] However, epidemiologic data on the potential association between gestational age and postpartum hemorrhage are conflicting. In two separate Canadian population-based cohorts, a null association was reported between gestational age and postpartum hemorrhage risk.[9,15] In contrast, data from French and U.S. population-based cohorts indicated that women who deliver after 41 weeks have a 1.2-fold greater risk of postpartum hemorrhage compared to women who deliver closer to term.[15,16] These inconsistent findings may be related to geographical differences in maternal and obstetric-related characteristics of women who experienced postpartum hemorrhage.[17] If geographical differences exist in the association between gestational age and postpartum hemorrhage risk, then this has important maternal health implications. For example, national guidelines for postpartum hemorrhage risk assessment would need to account for country-specific gestational age–related risks. Therefore, examining the association between gestational age and postpartum hemorrhage risk in different well-resourced countries should be a research priority.

We hypothesize that a nonlinear association exists between gestational age at birth and the odds of postpartum hemorrhage, with women who deliver before 37 weeks and after 41 weeks having the highest odds. The objective of this investigation was to assess and compare the association between gestational age at delivery and postpartum hemorrhage in large and contemporary delivery cohorts from two different countries—Sweden and the United States. We developed population-based analytic samples for this study using data from the Swedish Pregnancy Register and linked birth certificate and maternal discharge databases in California, United States.

Materials and Methods

We performed a retrospective cohort study of women who underwent delivery hospitalization in California and Sweden. Institutional review board approval for this study was obtained from the Stanford University Institutional Review Board (Stanford, California) and the Regional Ethical Approval Board in Stockholm, Sweden. We adhered to STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) guidelines for these cohort studies.

Information Sources

For California births, we analyzed data from linked hospital discharge data and vital statistics birth data of women who underwent delivery hospitalization. Maternal, obstetric, and delivery data including gestational age at delivery are available in linked maternal discharge and birth certificate datasets. These data were obtained from the California Maternal Quality Care Collaborative Data Center (Stanford, California). Using a modified version of previously published algorithm, maternal and newborn hospital discharge records are probabilistically linked using a matching algorithm with birth certificates,[18,19] with valid linkage for more than 96% of records.[20] For Swedish births, linked population-level databases are available with detailed obstetric and birth data. We analyzed data from the Swedish Pregnancy Register, which comprises electronic medical records linked with maternal sociodemographic information collected by midwives at the first antenatal visit.[21]

We examined data for delivery hospitalizations between 2011 and 2015 in California and between 2014 and 2017 in Sweden. These time periods were selected based on the availability of data with overlapping time periods for analysis. For both cohorts, we included women aged 15 to 50 yr with singleton pregnancies who underwent vaginal or cesarean delivery. We excluded women with missing data for gestational age at delivery, who delivered at less than 22 weeks' gestation or more than 42 weeks' gestation, who had multiple gestation, or who had termination. In the California cohort, we excluded births that occurred at home, in birth centers, and in military hospitals, and with missing data for postpartum hemorrhage. In the Swedish cohort, we excluded births with missing data for blood loss or if the blood loss was less than 50 ml (which was deemed to be clinically implausible). Figure 1 presents flowcharts describing our analytic cohorts, including frequency counts for births with missing data.

Outcomes

The primary outcome, which was established *a priori*, was postpartum hemorrhage. In the California cohort, postpartum hemorrhage was identified using International Classification of Diseases, Ninth Revision—Clinical Modification (ICD-9-CM) diagnosis codes 666.x. In the Swedish cohort, estimated blood loss data are available in the Swedish Pregnancy Register, and thus we classified postpartum hemorrhage based on an estimated blood loss greater than 1,000 ml in our Swedish cohort. The selected cutpoint was consistent with the postpartum hemorrhage definition used by the Swedish Society for Obstetrics and Gynecology (Stockholm, Sweden).[22] An International Classification of Diseases code was not used to classify postpartum hemorrhage in our main analysis of the Swedish cohort.

Exposure

Information on the main exposure—gestational age at delivery in completed weeks—was obtained through the birth certificate for the California cohort and the Swedish Pregnancy Register for the Swedish cohort. In both cohorts, gestational age was based on best obstetric estimate, which

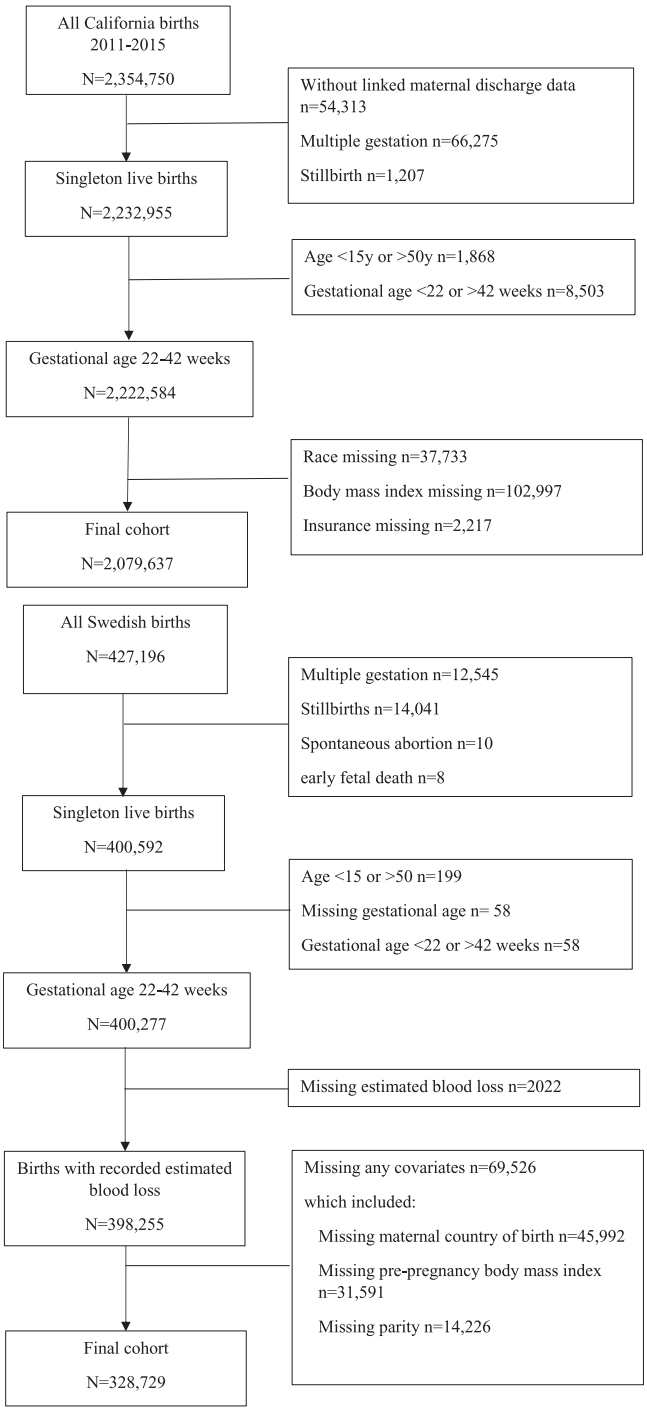

Fig. 1. Study flow charts for the California and Swedish cohorts.

incorporates an estimate from ultrasound findings. The National Center for Health Statistics (Hyattsville, Maryland) has used the obstetric estimate as the standard measure for gestational age dating since 2007,[23] and this approach has better validity than using last menstrual period.[24] Further, joint guidelines from the American College of Obstetricians and Gynecologists (Washington, D.C.), the Society for Maternal-Fetal Medicine (Washington, D.C.), and the American Institute for Ultrasound in Medicine (Laurel, Maryland) state that, for research and surveillance, the best obstetric estimate should be the measure for gestational age.[25] If data for the best obstetric estimates were not

available, we used dating from the last menstrual period for California births and from the date of embryo implantation for *in vitro* pregnancies, last menstrual period, and clinical estimation at birth (in rank descending order) for Swedish births. Gestational age was categorized as less than 28 weeks, 28 to 31 weeks, 32 to 34 weeks, 35 to 36 weeks, 37 to 38 weeks, 39 to 40 weeks, and 41 to 42 weeks, based on review of previously described preterm birth subgroups and definitions for early-term, full-term, and late-term births.[26,27]

Covariates

In both cohorts, based on literature review as well as clinical and biologic plausibility,[7,9,27–38] we selected the following set of covariates as potential confounders of the association between gestational age and postpartum hemorrhage: maternal age, body mass index, parity, hypertensive disease of pregnancy, placenta previa, chorioamnionitis, macrosomia, and polyhydramnios. In the California cohort, other selected covariates were race and ethnicity and insurance type. In the Swedish cohort, an additional covariate was country of birth. Hypertensive disease of pregnancy (hereafter referred to as hypertensive disease) was classified by the presence of one of the following: gestational hypertension, preeclampsia, or eclampsia using ICD-9-CM codes (642.3x; 642.4x; 642.5x; 642.6x) for the California cohort and International Classification of Diseases, Tenth Revision—Clinical Modification (ICD-10-CM) codes (O13.x; O14.x; O15.x) for the Swedish cohort. In the California cohort, maternal race and ethnicity was defined as non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, and other. In the Swedish cohort, maternal country of birth was classified by World Health Organization (Geneva, Switzerland) classification of world regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. In California, data were available for prepregnancy body mass index; in Sweden, data were available for the maternal body mass index from the first prenatal visit (at approximately 10 weeks' gestation). In both cohorts, body mass index was categorized using the World Health Organization Internal Classification,[39] as follows: underweight (less than 18.5 kg/m^2), normal body mass index (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), obese class I (30 to 34.9 kg/m^2), obese class II (35 to 39.9 kg/m^2), and obese class III (greater than or equal to 40 kg/m^2).

Statistical Analyses

A data analysis plan was written after the data were initially accessed. Before primary data analysis, the main aims and analytic plan were reviewed by all study investigators in April 2020. We separately analyzed data from each cohort. In this section, we describe our preplanned analysis. We calculated the overall postpartum hemorrhage incidence in each cohort and the incidence for each completed week of gestation. We used logistic regression to estimate unadjusted and adjusted odds ratios with 95% CI. We also examined the potential for a nonlinear association between gestational age and the odds of postpartum hemorrhage using restricted cubic splines.[40] We used Stata (StataCorp, USA) macro mkspline for this analysis. With this function, a continuous smooth (linear) function is obtained before the first knot, a piecewise cubic polynomial is obtained between adjacent knots, and then a linear function is obtained after the last knot. For the cubic spline structure, we selected the optimal number of knots based on the Akaike information criteria.[41] In both cohorts, the model with three knots had the lowest Akaike information criteria; these knots were generated at 37 (10th centile), 39 (50th centile), and 40 (90th centile) weeks' gestation for the California cohort and at 38 (10th centile), 39 (50th centile), and 40 (90th centile) weeks' gestation for the Swedish cohort.

We did not perform an *a priori* statistical power calculation or estimate a minimum clinically meaningful association. Because we performed analyses of large datasets, we placed less emphasis on statistical hypothesis testing and reporting of *P* values. In line with guidelines from the American Statistical Association (Alexandria, Virginia),[42] our focus was on describing effect estimates (odds ratios) and 95% CI.

A Priori Sensitivity Analyses

We undertook three sensitivity analyses. First, up to 2017, the definition of postpartum hemorrhage in the United States differed according to delivery mode (blood loss greater than 500 ml after vaginal delivery and greater than 1,000 ml after cesarean delivery).[43,44] Given that the blood loss criterion for postpartum hemorrhage after cesarean delivery is identical in the United States and Sweden, we performed additional analyses only in women who underwent cesarean delivery in both countries. Second, women with abnormal placentation, namely placenta previa or accreta, are at very high risk for severe postpartum hemorrhage. For delivery planning, the American College of Obstetricians and Gynecologists recommends cesarean delivery for women with suspected accreta between 34 and 35 weeks and placenta previa between 36 and 37 weeks.[45] To mitigate the potential influence of these conditions on our gestational age–specific risk estimates, we excluded women with placenta previa and accreta from both analytic cohorts. Placenta previa was identified using ICD-9-CM codes 641.0 and 641.1 in the California cohort and ICD-10-CM code O44.x in the Swedish cohort. Women with placenta accreta were identified in an approach using ICD-9-CM codes previously described by Creanga *et al.*[46] for the California cohort and with ICD-10-CM code O43.2x in the Swedish cohort. Third, since 2015, hospitals in California have transitioned to ICD-10-CM codes for maternal discharge data. Given

the recency of this change and the lack of data validating obstetric-related ICD-10-CM codes, we explored the relation between gestational age and postpartum hemorrhage (classified only using ICD-10-CM codes O72.x and O67.8) in California and Sweden for births between January 1, 2016, and December 31, 2017. To ensure that a consistent postpartum hemorrhage definition was applied for both countries, blood loss data were not included in the postpartum hemorrhage definition in the model for Sweden.

A Priori Secondary Analyses

Although uterine atony is recognized as the most common etiology for postpartum hemorrhage,[7] nonatonic etiologies, *e.g.*, retained placenta, may be more common among women who deliver preterm. Therefore, we explored whether differences exist in the association between gestational age and the odds of postpartum hemorrhage by etiology, classified as uterine atony *versus* nonatonic causes. Uterine atony was classified by ICD-9-CM code 666.1x and nonatonic causes by ICD-9-CM codes 666.0x, 666.2x, and 666.3x. We only performed stratified analysis in the California cohort because the Swedish data do not contain ICD-9-CM codes. Further, ICD-10-CM codes do not clearly differentiate uterine atony from nonatonic causes. Because the number of women with postpartum hemorrhage was small among women in California who delivered at less than 31 weeks in each stratified cohort, we performed unadjusted logistic regression only.

Reviewer-requested *Post Hoc* Secondary and Sensitivity Analyses

During the peer review process, several *post hoc* secondary and sensitivity analyses were requested. Because each dataset contains the hospital where women delivered, we used generalized estimating equation models with a binomial family distribution and logit link function to account for within-hospital clustering. For the clustering analyses, we restricted each cohort to hospitals with a mean annual volume of greater than or equal to 100 deliveries.

Because categorization of continuously scaled covariates (maternal age and body mass index) may lead to residual confounding, we initially assessed the relation between maternal age and body mass index using locally weighted scatterplot smoothing curves. Based on this information, in multivariable models for California and Sweden, maternal age was included as a continuous variable and body mass index as a quadratic term.

Finally, we explored whether induction of labor and delivery mode (as interventions for expediting birth) influenced the gestational age–postpartum hemorrhage association by adding these variables to the aforementioned set of covariates in the full multivariable models. All data analyses were performed using Stata version 14.

Results

The final analytic samples consisted of 2,079,637 deliveries in California and 328,729 deliveries in Sweden. We assumed missing data were missing completely at random and, thus, performed complete case analyses. The distribution of baseline characteristics in the final analytic samples and stratified by the presence or absence of postpartum hemorrhage is presented in table 1. In both countries, women with postpartum hemorrhage were more likely to be older than 34 yr, overweight, and nulliparous, and have placenta previa, placenta accreta, hypertensive disease of pregnancy, polyhydramnios, macrosomia, chorioamnionitis, and induction of labor. In California, postpartum hemorrhage was more likely in Asian/Pacific Islanders, those with private insurance, and after vaginal delivery. In Sweden, postpartum hemorrhage was more likely in women from West Pacific regions, in obese women, and after cesarean delivery.

The incidence of postpartum hemorrhage in California was 66,583/2,079,637 (3.2%). The incidence in Sweden based on estimated blood loss criteria was 23,323/328,729 (7.1%) and using ICD-10-CM codes only was 23,838/328,729 (7.3%). The incidences by completed week of gestation for California and Sweden are presented in figures 2 and 3. In both cohorts, the incidence of postpartum hemorrhage had a bimodal distribution according to gestational age, with peaks at 22 and 42 weeks in California and 26 and 42 weeks in Sweden. Unadjusted and adjusted curves for the relations between gestational age and postpartum hemorrhage using restricted cubic spline are presented in Supplemental Digital Content 1 (http://links.lww.com/ALN/C550), Supplemental Digital Content 2 (http://links.lww.com/ALN/C551), Supplemental Digital Content 3 (http://links.lww.com/ALN/C552), and Supplemental Digital Content 4 (http://links.lww.com/ALN/C553). Unadjusted and adjusted splines modeled an area of inflection around 39 weeks in California and Sweden, with the odds of postpartum hemorrhage steadily decreasing from 22 to 39 weeks, then increasing rapidly afterward up to 42 weeks. The shape of the curves for the unadjusted models were similar (J-shaped) for Sweden and California; however, after adjustment, the curve between 22 and 39 weeks was flatter (more attenuated) in Sweden.

For our preselected gestational age categories, the incidence of postpartum hemorrhage is presented in table 2. In California and Sweden, the incidence was highest for deliveries between 41 and 42 weeks (8,921/160,267 [5.6%] and 7,186/75,539 [9.5%], respectively). Compared to women who delivered between 37 and 38 weeks (the reference group), the adjusted odds of postpartum hemorrhage for women who delivered between 41 and 42 weeks was highest in California (adjusted odds ratio, 2.04; 95% CI, 1.98 to 2.09) and in Sweden (adjusted odds ratio, 1.62; 95% CI, 1.56 to 1.69). Before 37 weeks, women who delivered between 22 and 27 weeks in California had the highest odds of postpartum hemorrhage (adjusted odds ratio, 1.48;

Table 1. Patient Characteristics

Characteristic	California			Sweden		
	All Women (N = 2,079,637)	No Postpartum Hemorrhage (N = 2,013,054)	Postpartum Hemorrhage (N = 66,583)	All Women (N = 328,729)	No Postpartum Hemorrhage (N = 305,406)	Postpartum Hemorrhage (N = 23,323)
Age (yr)						
< 20	135,821 (6.5%)	131,341 (6.5%)	4,480 (6.7%)	3,105 (0.9%)	2,962 (1.0%)	143 (0.6%)
20–34	1,546,493 (74.4%)	1,498,058 (74.4%)	48,435 (72.8%)	253,645 (77.2%)	236,461 (77.4%)	17,184 (73.7%)
35–39	315,854 (15.2%)	305,203 (15.2%)	10,651 (16.0%)	58,203 (17.7%)	53,510 (17.5%)	4,693 (20.1%)
≥ 40	81,469 (3.9%)	78,452 (3.9%)	3,017 (4.5%)	13,776 (4.2%)	12,473 (4.1%)	1,303 (5.6%)
Race						
White non-Hispanic	558,344 (26.8%)	541,703 (26.9%)	16,641 (25.0%)	Not applicable	Not applicable	Not applicable
Black non-Hispanic	103,359 (5.0%)	100,225 (5.0%)	3,134 (4.7%)	Not applicable	Not applicable	Not applicable
Asian/Pacific Islander non-Hispanic	276,583 (13.3%)	265,417 (13.2%)	11,166 (16.8%)	Not applicable	Not applicable	Not applicable
Hispanic	1,037,314 (49.9%)	1,005,228 (49.9%)	32,086 (48.2%)	Not applicable	Not applicable	Not applicable
American Indian/ Alaska Native	6,087 (0.3%)	5,866 (0.3%)	221 (0.3%)	Not applicable	Not applicable	Not applicable
Other	97,950 (4.7%)	94,615 (4.7%)	3,335 (5.0%)	Not applicable	Not applicable	Not applicable
Insurance type				Not applicable	Not applicable	Not applicable
Government	1,007,580 (48.4%)	979,220 (48.7%)	28,360 (42.6%)	Not applicable	Not applicable	Not applicable
Private	999,536 (48.1%)	962,766 (47.8%)	36,770 (55.2%)	Not applicable	Not applicable	Not applicable
Other/unknown	72,521 (3.5%)	71,068 (3.5%)	1,453 (2.2%)	Not applicable	Not applicable	Not applicable
Maternal country of birth						
Africa	Not applicable	Not applicable	Not applicable	17,548 (5.3%)	16,284 (5.3%)	1,264 (5.4%)
Americas	Not applicable	Not applicable	Not applicable	4,072 (1.3%)	3,713 (1.2%)	359 (1.6%)
South-East Asia	Not applicable	Not applicable	Not applicable	4,647 (1.5%)	405 (1.7%)	4,647 (1.5%)
Europe	Not applicable	Not applicable	Not applicable	269,789 (82.1%)	250,548 (82.1%)	19,241 (82.5%)
East Mediterranean	Not applicable	Not applicable	Not applicable	27,007 (8.2%)	25,555 (8.4%)	1,452 (6.2%)
West Pacific	Not applicable	Not applicable	Not applicable	5,261 (1.6%)	4,659 (1.5%)	602 (2.6%)
Body mass index*						
Underweight	82,313 (4.0%)	80,044 (4.0%)	2,269 (3.4%)	8,563 (2.6%)	8,077 (2.6%)	486 (2.1%)
Normal weight	996,021 (47.9%)	964,396 (47.9%)	31,625 (47.5%)	191,341 (58.2%)	178,533 (58.4%)	12,808 (54.9%)
Overweight	541,244 (26.0%)	523,373 (26.0%)	17,871 (26.8%)	84,181 (25.6%)	77,806 (25.5%)	6,375 (27.3%)
Obese I	272,760 (13.1%)	263,934 (13.1%)	8,826 (13.3%)	31,411 (9.6%)	28,889 (9.5%)	2,522 (10.8%)
Obese II	117,062 (5.6%)	113,385 (5.6%)	3,677 (5.5%)	9,998 (3.0%)	9,161 (3.0%)	837 (3.6%)
Obese III	70,237 (3.4%)	67,922 (3.4%)	2,315 (3.5%)	3,235 (1.0%)	2,940 (1.0%)	295 (1.3%)
Parity						
Nulliparous	822,863 (39.6%)	790,637 (39.3%)	32,226 (48.4%)	138,900 (42.3%)	127,209 (41.6%)	11,691 (50.1%)
Multiparous	1,256,774 (60.4%)	1,222,417 (60.7%)	34,357 (51.6%)	189,829 (57.8%)	178,197 (58.4%)	11,632 (49.9%)
Placenta previa	14,320 (0.7%)	12,821 (0.6%)	1,499 (2.3%)	1,774 (0.5%)	1,236 (0.4%)	538 (2.3%)
Placenta accreta	850 (0%)	358 (0%)	492 (0.7%)	149 (0.1%)	43 (0%)	106 (0.5%)
Hypertensive disease of pregnancy†	116,673 (5.6%)	109,058 (5.4%)	7,615 (11.4%)	15,910 (4.8%)	14,183 (4.6%)	1,727 (7.4%)
Polyhydramnios	11,298 (0.5%)	10,836 (0.5%)	462 (0.7%)	1,513 (0.5%)	1,307 (0.4%)	206 (0.9%)
Macrosomia	49,700 (2.4%)	47,351 (2.4%)	2,349 (3.5%)	6,198 (1.9%)	5,214 (1.7%)	984 (4.2%)
Chorioamnionitis	55,683 (2.7%)	50,152 (2.5%)	5,531 (8.3%)	1,024 (0.3%)	861 (0.3%)	163 (0.7%)
Induction of labor	317,983 (15.3%)	303,269 (15.1%)	14,714 (22.1%)	30,454 (9.3%)	27,379 (9.0%)	3,075 (13.2%)
Mode of delivery						
Vaginal	1,409,901 (67.8%)	1,361,194 (67.6%)	48,707 (73.2%)	274,160 (83.4%)	257,723 (84.4%)	16,437 (70.5%)
Cesarean	669,736 (32.2%)	651,860 (32.4%)	17,876 (26.8%)	54,569 (16.6%)	47,683 (15.6%)	6,886 (29.5%)

Data presented as n (%).

*Prepregnancy body mass index for California; body mass index at the first prenatal visit in Sweden. †Includes gestational hypertension, preeclampsia, and eclampsia.

95% CI, 1.33 to 1.65). In contrast, a null association was observed for women who delivered in Sweden between 22 and 27 weeks (adjusted odds ratio, 1.01; 95% CI, 0.75 to 1.38). In adjusted models for California and Sweden, women who delivered between 28 and 31 weeks, 32 and 34 weeks, and 35 and 36 weeks had either slightly or no higher odds of postpartum hemorrhage relative to the reference group. Point estimates for all covariates included in our final models are presented in Supplemental Digital Content 5 (http://links.lww.com/ALN/C554).

A Priori Sensitivity Analyses

Adjusted odds ratios in models examining only cesarean deliveries and excluding women with placenta previa

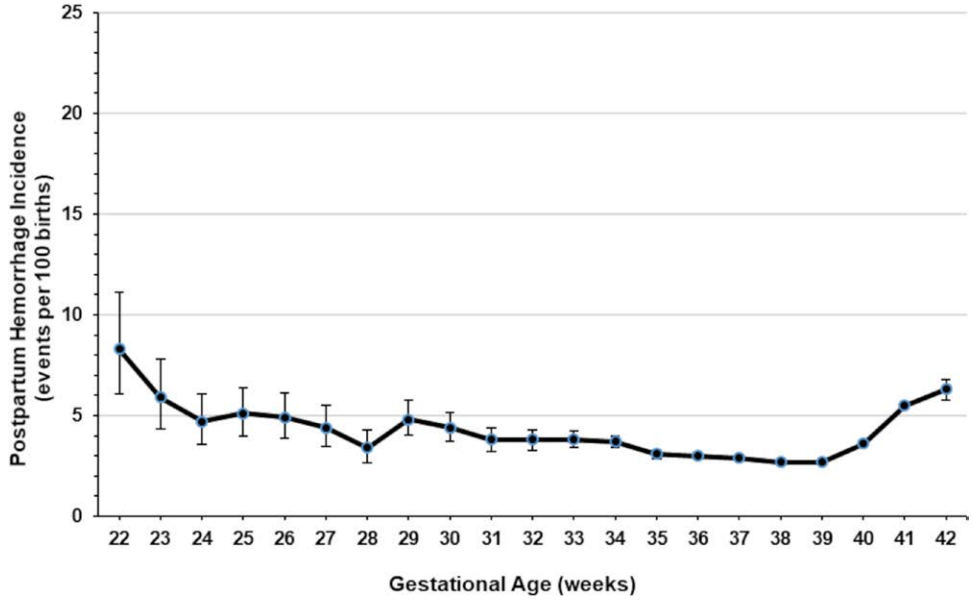

Fig. 2. Gestational age–specific incidence of postpartum hemorrhage in California.

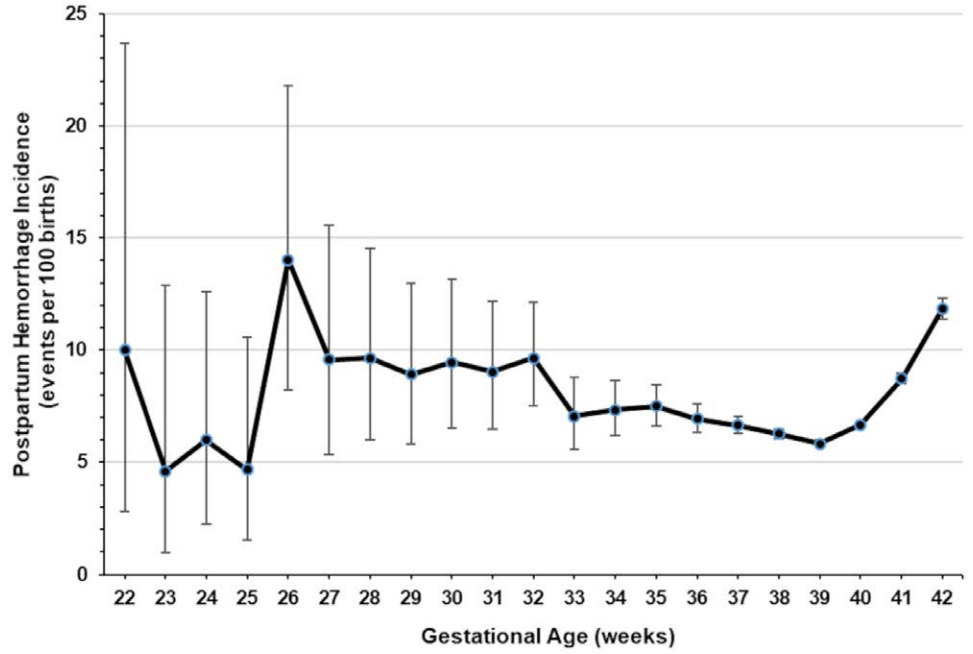

Fig. 3. Gestational age–specific incidence of postpartum hemorrhage in Sweden.

and accreta for the California and Swedish cohorts were consistent with those of our main analyses (table 3). For deliveries between 2016 and 2017, in both cohorts, women who delivered in any preterm subgroup were not at higher odds of postpartum hemorrhage compared to our reference group. However, in both cohorts, point estimates for women who delivered between 39 and 40 weeks and 41 and 42 weeks were significantly higher than the reference

Table 2. Univariable and Multivariable Models for the Risk of Postpartum Hemorrhage according to Gestational Age in California and Sweden

	California			Sweden		
	Postpartum Hemorrhage Incidence	Univariable Model	Multivariable Model*	Postpartum Hemorrhage Incidence	Univariable Model	Multivariable Model†
Gestational Age (Weeks)	n/N (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	n/N (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
22–27	365/7,099 (5.1%)	1.91 (1.72–2.13)	1.48 (1.33–1.65)	48/572 (8.4%)	1.35 (1.00–1.81)	1.01 (0.75–1.38)
28–31	477/11,650 (4.1%)	1.51 (1.37–1.65)	1.12 (1.02–1.24)	113/1,225 (9.2%)	1.49 (1.23–1.82)	1.14 (0.93–1.39)
32–34	1,196/32,059 (3.7%)	1.37 (1.29–1.45)	1.10 (1.04–1.17)	276/3,588 (7.7%)	1.23 (1.08–1.39)	0.99 (0.87–1.13)
35–36	2,658/87,929 (3.0%)	1.10 (1.05–1.15)	0.98 (0.94–1.02)	692/9,697 (7.1%)	1.13 (1.04–1.23)	0.97 (0.89–1.06)
37–38	13,949/506,079 (2.8%)	Reference group	Reference group	4,167/65,435 (6.4%)	Reference group	Reference group
39–40	39,017/1,274,554 (3.1%)	1.11 (1.09–1.14)	1.17 (1.15–1.20)	10,841/172,673 (6.3%)	0.98 (0.95–1.02)	1.07 (1.03–1.11)
41–42	8,921/160,267 (5.6%)	2.08 (2.02–2.14)	2.04 (1.98–2.09)	7,186/75,539 (9.5%)	1.55 (1.49–1.61)	1.62 (1.56–1.69)

*Adjusted for maternal age, race/ethnicity, insurance type, prepregnancy body mass index, parity, hypertensive disorder of pregnancy, placenta previa, macrosomia, chorioamnionitis, and polyhydramnios. †Adjusted for maternal age, country of birth (world region), body mass index at first antenatal visit, parity, hypertensive disorder of pregnancy, placenta previa, macrosomia, chorioamnionitis, and polyhydramnios.

group, with the highest odds for women who delivered between 41 and 42 weeks (California: adjusted odds ratio, 1.94; 95% CI, 1.86 to 2.02; Sweden: adjusted odds ratio, 1.64; 95% CI, 1.55 to 1.74).

A Priori Secondary Analysis

Results of our models stratified according to etiology of postpartum hemorrhage (uterine atony *vs.* nonatonic causes) for California are presented in Supplemental Digital Content 6 (http://links.lww.com/ALN/C555). In the univariable models, the unadjusted odds of postpartum hemorrhage from nonatonic causes increased as the gestational age decreased in women who delivered preterm. Among women who delivered after 38 weeks, the odds of postpartum hemorrhage from nonatonic causes were only higher in women who delivered between 41 and 42 weeks (unadjusted odds ratio, 1.52; 95% CI, 1.43 to 1.61). We observed no statistically significant associations between gestational age and the odds of postpartum hemorrhage from uterine atony in any preterm group relative to the reference group. The odds of postpartum hemorrhage were 1.1- and 2.2-fold higher in women who delivered between 39 and 40 weeks (unadjusted odds ratio, 1.15; 95% CI, 1.13 to 1.18) and between 41 and 42 weeks (unadjusted odds ratio, 2.23; 95% CI, 2.16 to 2.30).

Reviewer-requested *Post Hoc* Secondary and Sensitivity Analyses

We performed additional modeling accounting for within-hospital clustering for 252 and 39 hospitals in California and Sweden, respectively. Due to the limit in matrix sizes computed with this approach, we used a 20% random sample from each analytic sample then applied a generalized estimating equation approach. Data are presented in Supplemental Digital Content 7 (http://links.lww.com/ALN/C556). Apart from women who delivered between 21 and 27 weeks, we observed modest attenuation of the point estimates for odds of postpartum hemorrhage in all other gestational age subgroups relative to our main analyses. Women who delivered between 41 and 42 weeks still had the highest odds of postpartum hemorrhage in both cohorts (California: adjusted odds ratio, 1.64; 95% CI, 1.53 to 1.76; Sweden: adjusted odd ratio, 1.57; 95% CI, 1.41 to 1.75).

In additional sensitivity analyses, in multivariable models for California and Sweden, we accounted for maternal age as a continuous variable and body mass index with a quadratic term. In models for both regions, we observed similar point estimates to those of our main analyses (Supplemental Digital Content 8, http://links.lww.com/ALN/C557). The adjusted odds ratios for postpartum hemorrhage for women who delivered between 41 and 42 weeks in California and Sweden were 2.03 (95% CI, 1.97 to 2.09) and 1.61 (95% CI, 1.55 to 1.68), nearly identical to the primary analysis (table 2).

To explore whether induction of labor and delivery mode potentially alter the direction and statistical significance of the associations in our main analyses, we included both variables as covariates to the full model in each cohort. Data are presented in Supplemental Digital Content 9 (http://links.lww.com/ALN/C558). The adjusted odds ratios for postpartum hemorrhage for women who delivered between 41 and 42 weeks in California and Sweden were 1.92

Table 3. Sensitivity Analyses Focused on Cesarean Deliveries, Deliveries Excluding Placenta Previa or Accreta, and Deliveries in 2016 and 2017

	California			Sweden		
	Postpartum Hemorrhage Incidence	Univariable Model	Multivariable Model	Postpartum Hemorrhage Incidence	Univariable Model	Multivariable Model
Gestational Age (weeks)	n/N (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	n/N (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Cesarean deliveries only (N = 669,736 for California and N = 54,569 for Sweden)*						
22–27	154/4,156 (3.7%)	1.61 (1.37–1.90)	1.21 (1.02–1.43)	37/339 (10.9%)	1.03 (0.73–1.45)	0.97 (0.68–1.38)
28–31	299/7,372 (4.1%)	1.77 (1.57–2.00)	1.30 (1.15–1.47)	99/810 (12.2%)	1.17 (0.94–1.45)	1.13 (0.90–1.41)
32–34	648/16,271 (4.0%)	1.74 (1.60–1.90)	1.35 (1.24–1.47)	179/1,655 (10.8%)	1.02 (0.86–1.19)	0.91 (0.77–1.08)
35–36	1,054/34,862 (3.0%)	1.31 (1.22–1.40)	1.08 (1.01–1.16)	350/2,727 (12.8%)	1.23 (1.09–1.39)	1.01 (0.89–1.15)
37–38	3,655/157,038 (2.3%)	Reference group	Reference group	2,095/19,632 (10.7%)	Reference group	Reference group
39–40	9,762/405,184 (2.4%)	1.04 (1.00–1.08)	1.13 (1.08–1.17)	2,427/19,678 (12.3%)	1.18 (1.11–1.25)	1.26 (1.18–1.34)
41–42	2,304/44,853 (5.1%)	2.27 (2.15–2.40)	2.06 (1.94–2.18)	1,699/9,728 (17.5%)	1.77 (1.65–1.90)	1.89 (1.76–2.04)
Deliveries excluding placenta previa and accreta (N = 2,065,235 for California and N = 326,863 for Sweden)†						
22–27	326/6,835 (4.8%)	1.81 (1.62–2.03)	1.47 (1.32–1.65)	40/548 (7.3%)	1.23 (0.89–1.70)	0.99 (0.71–1.37)
28–31	374/11,085 (3.4%)	1.26 (1.14–1.40)	1.01 (0.91–1.12)	104/1,170 (8.9%)	1.52 (1.24–1.87)	1.26 (1.02–1.54)
32–34	955/30,647 (3.1%)	1.16 (1.09–1.24)	1.00 (0.94–1.07)	225/3,446 (6.5%)	1.09 (0.95–1.25)	0.95 (0.83–1.10)
35–36	2,337/85,043 (2.7%)	1.02 (0.98–1.07)	0.96 (0.92–1.00)	556/9,366 (5.9%)	0.99 (0.90–1.08)	0.91 (0.83–1.00)
37–38	13,478/501,191 (2.7%)	Reference group	Reference group	3,890/64,622 (6.0%)	Reference group	Reference group
39–40	38,721/1,270,491 (3.0%)	1.14 (1.12–1.16)	1.18 (1.16–1.20)	10,754/172,285 (6.2%)	1.04 (1.00–1.08)	1.08 (1.04–1.12)
41–42	8,888/159,943 (5.6%)	2.13 (2.07–2.19)	2.04 (1.98–2.10)	7,156/75,426 (9.5%)	1.64 (1.57–1.70)	1.65 (1.58–1.72)
Deliveries between 2016 and 2017 (N = 850,549 for California and N = 168,983 for Sweden)*						
22–27	135/2,808 (4.8%)	1.43 (1.20–1.70)	1.13 (0.95–1.35)	24/300 (8.0%)	1.27 (0.83–1.93)	1.03 (0.67–1.57)
28–31	203/4,792 (4.2%)	1.25 (1.08–1.44)	0.97 (0.84–1.12)	52/638 (8.2%)	1.29 (0.97–1.72)	1.01 (0.76–1.36)
32–34	587/13,920 (4.2%)	1.24 (1.14–1.36)	1.04 (0.95–1.14)	129/1,805 (7.2%)	1.12 (0.93–1.35)	0.93 (0.77–1.12)
35–36	1,404/37,373 (3.8%)	1.10 (1.04–1.17)	1.00 (0.95–1.06)	343/4,939 (6.9%)	1.09 (0.97–1.23)	0.93 (0.83–1.05)
37–38	7,085/207,273 (3.4%)	Reference group	Reference group	2,185/34,061 (6.4%)	Reference group	Reference group
39–40	19,323/518,351 (3.7%)	1.17 (1.06–1.13)	1.19 (1.14–1.21)	5,952/88,805 (6.7%)	1.05 (1.00–1.10)	1.13 (1.07–1.19)
41–42	4,329/66,032 (6.6%)	1.98 (1.91–2.06)	1.94 (1.86–2.02)	3,701/38,435 (9.6%)	1.55 (1.47–1.64)	1.64 (1.55–1.74)

*Multivariable model for California adjusted for maternal age, race/ethnicity, insurance type, prepregnancy body mass index, hypertensive disorder of pregnancy, parity, placenta previa, macrosomia, chorioamnionitis, and polyhydramnios. Multivariable model for Sweden adjusted for maternal age, country of birth (world region), body mass index at first antenatal visit, parity, hypertensive disorder of pregnancy, placenta previa, macrosomia, chorioamnionitis, and polyhydramnios. †Multivariable model for California adjusted for maternal age, race/ethnicity, insurance type, prepregnancy body mass index, hypertensive disorder of pregnancy, parity, macrosomia, chorioamnionitis, and polyhydramnios. Multivariable model for Sweden adjusted for maternal age, country of birth (world region), body mass index at first antenatal visit, parity, hypertensive disorder of pregnancy, macrosomia, chorioamnionitis, and polyhydramnios.

(95% CI, 1.86 to 1.97) and 1.83 (95% CI, 1.75 to 1.91). In both cohorts, addition of these covariates did not alter the direction of any association or markedly shift confidence intervals around the point estimates toward or away from the null.

Discussion

In our analyses of population-based cohorts from California and Sweden, women who delivered between 41 and 42 weeks had the highest incidence (5.6% in California and 9.5% in Sweden) and the highest adjusted odds of postpartum hemorrhage. Adjustments for demographic and obstetric factors only modestly attenuated these associations. Because current risk assessment tools do not include gestational age–related risks, inclusion of delivery between 41 and 42 weeks as a risk factor in these tools may be warranted. Findings from our analysis also suggest that, among women in California, an inverse relation exists between gestational age and the odds of hemorrhage among women who deliver preterm (before 37 weeks' gestation). However, due to sparsity of data in both cohorts, we were unable to obtain precise and consistent estimates of the odds of postpartum hemorrhage among women who delivered before 31 weeks.

A key finding from our analysis is that, despite between-group differences in baseline maternal characteristics in the California and Swedish cohorts, the highest incidence and adjusted odds of postpartum hemorrhage occurred between 41 and 42 weeks in both regions. Developers of hemorrhage risk assessment tools and public health researchers may wish to focus on women who deliver at a gestational age away from the nadir (39 weeks), specifically between 41 and 42 weeks and women in California who deliver between 22 and 27 weeks. Although the associations

were statistically nonsignificant, we did observe a higher incidence and adjusted odds of postpartum hemorrhage in Swedish women who delivered between 28 and 31 weeks relative to women who delivered between 37 and 38 weeks. Data sparsity may explain why the confidence intervals overlapped the null within these gestational age subgroups.

The higher odds of postpartum hemorrhage after 38 weeks (especially between 41 and 42 weeks) across two geographically distinct delivery populations suggest that biologic or pathologic connections may explain this association. Previous studies have observed reduced contractility in myometrial samples from postterm pregnancies,[11] which may mean that these women are at risk for atonic hemorrhage. Other biologic factors may explain the inverse association between gestational age and hemorrhage risk before 37 weeks. For example, studies have reported that retained placenta is associated with preterm birth,[12–14] with defective or impaired placentation considered a potential mechanism.[47] Also, findings from our secondary analyses suggest that the association between gestational age at birth and the odds of postpartum hemorrhage may vary according to hemorrhage etiology. Further research is needed to examine the intersection between gestational age at delivery, myometrial contractility (including the contractile response of exogenous oxytocin), altered placentation, and other etiologies with hemorrhage risk. From a clinical standpoint, we acknowledge that women who deliver at these extremes of gestational age cannot simply be funneled to deliver at 39 weeks to reduce their hemorrhage risk. However, understanding potential causal mechanisms may lessen the risk of hemorrhage for women with gestational ages distributed toward the extremes of the curve.

In our analysis, the overall incidences of postpartum hemorrhage in California and Sweden were markedly different (3.2% and 7.1%). There may be several reasons for these findings. Between-country differences may exist in the modalities used for measuring blood loss as well as in the approaches used in the diagnosis, reporting, and coding of postpartum hemorrhage. In Sweden, standardized electronic birth records include data for the estimates of blood loss after delivery in all patients. Equivalent data were not available for California births. However, differences in incidence between the two regions were still observed even when postpartum hemorrhage was classified using ICD-10-CM codes for births between 2016 and 2017. It is also possible that differences in intrapartum practices may in part explain the different incidences in Sweden and California. Although the overall incidence of postpartum hemorrhage in each region is quite different, this observation should not affect overall measures of association as we used consistent definitions for postpartum hemorrhage in each cohort.

Our study has several strengths. Access to population-level data from large delivery cohorts drawn from two well-resourced countries enabled detailed examination of our primary association of interest. The availability of gestational age and maternal data in both the Swedish Pregnancy Register and linked birth certificate–maternal discharge data for California births overcomes the limitations of administrative datasets, such as the Nationwide Inpatient Sample, that lacked data on gestational age.[7,48,49]

We acknowledge several study limitations. First, the database for California deliveries does not contain blood loss data. Although we classified postpartum hemorrhage in California using ICD-9-CM or ICD-10-CM codes, validation studies report high positive predictive values (greater than 73% for ICD-9-CM and 92% for ICD-10-CM codes) and moderate to high negative predictive values (81% for ICD-9-CM and 98 to 99% for ICD-10-CM codes).[50–53] Despite the availability of blood loss data for the Swedish cohort, the measurement modality used to quantify blood loss across Swedish hospitals is not recorded in the pregnancy register. Visual estimation typically underestimates actual blood loss volumes,[54] which may mean that the hemorrhage incidence in Sweden was underestimated. Further, we do not have information on how obstetric care providers detected or diagnosed postpartum hemorrhage in each region. If we assume nondifferential outcome misclassification, our point estimates may be biased toward the null. Second, postpartum hemorrhage definitions over the study period differed in Sweden and the United States.[22,43] To help overcome this limitation, we performed a sensitivity analysis of only cesarean deliveries because the definitions for postpartum hemorrhage are identical for this delivery mode in both countries. We performed additional sensitivity analyses of deliveries between 2016 and 2017 in both regions using ICD-10-CM codes. Results of these sensitivity analyses indicated modest variability in the point estimates for women who delivered preterm in the California cohort. However, in all sensitivity analyses in both cohorts, women who delivered between 41 and 42 weeks consistently had the highest odds of postpartum hemorrhage. Third, confounders used for adjustment differed in both cohorts. However, these confounders were selected based on available data in both datasets to generate minimally biased estimates of risk. Residual confounding may partially explain the observed associations in our study, especially in women who delivered after 38 weeks. Fourth, in our sensitivity analyses, we excluded women with placenta previa or accreta. However, ICD-9-CM codes for placenta accreta are not available, and ICD-10-CM codes have not been validated. Because women with these disorders are at high risk for severe postpartum hemorrhage and are likely to be delivered before 37 weeks,[55] this would explain why point estimates in this range moved toward the null. Fifth, all datasets lacked nuanced clinical data related to hemorrhage management, such as the use of uterotonic therapies or antifibrinolytics.

In summary, our findings indicate that the gestational age at delivery influences the maternal risk of postpartum hemorrhage. Clinicians should be aware of the heightened

odds of postpartum hemorrhage in women who deliver between 41 and 42 weeks. These findings should also serve to inform future guidelines for postpartum hemorrhage risk assessment.

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Competing Interests

The authors declare no competing interests.

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