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Predicting Postpartum Hemorrhage After Vaginal Birth by Labor Phenotype

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Abstract

Introduction: Postpartum hemorrhage (PPH) is an important contributor to maternal morbidity and mortality. Predicting which laboring women are likely to have a PPH is an active area of research and a component of quality improvement bundles. The purpose of this study was to identify phenotypes of labor processes (ie, labors that have similar features, such as duration and type of interventions) in a cohort of women who had vaginal births, estimate the likelihood of PPH by phenotype, and analyze how maternal and fetal characteristics relate to PPH risk by phenotype.

Methods: This study utilized the Consortium for Safe Labor dataset (2002-2008) and examined term, singleton, vaginal births. Using 16 variables describing the labor and birth processes, a latent class analysis was performed to describe distinct labor process phenotypes.

Results: Of 24,729 births, 1167 (4.72%) women experienced PPH. Five phenotypes best fit the data, reflecting labor interventions, duration, and complications. Women who had shorter duration of admission after spontaneous labor onset (admitted in latent or active labor) had the lowest rate of PPH (3.8%-3.9%). The 2 phenotypes of labor progress characterized by women who had complicated prolonged labors (spontaneous or induced) had the highest rate of PPH (8.0% and 12.0%, respectively). However, the majority of PPH (n = 881, 75%) occurred in the phenotypes with fewer complications. Prepregnancy body mass index did not predict PPH. Overall, the odds of PPH were highest among nulliparous women (odds ratio [OR], 1.52; 95% CI, 1.30-1.77), as well as black women (OR, 1.39; 95% CI, 1.13-1.73) and Hispanic women (OR, 1.85; 95% CI, 1.56-2.20). Within phenotypes, maternal race and ethnicity, nulliparity, macrosomia, hypertension, and depression were associated with increased odds of PPH.

Discussion: Women who were classified into a lower-risk labor phenotype and still experienced PPH were more likely to be nulliparous, a person of color, or diagnosed with hypertension.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Keywords

postpartum hemorrhage; health disparity; third-stage labor; obesity

INTRODUCTION

The Centers for Disease Control and Prevention estimate that the incidence of postpartum hemorrhage (PPH) resulting in significant maternal morbidity has increased 3 to 4 times since the early 1990s.[1] All childbearing women are potentially at risk for PPH, but many factors, such as uterine atony, tissue damage, placental complications, and maternal coagulopathy, are known to contribute to PPH.[2,3] Studies that have examined the relationship between obesity and PPH have found conflicting results. Maternal comorbidities associated with obesity may confound this relationship.[4-6] Furthermore, PPH is an example of a maternal health disparity. Non-Hispanic black women have a 26.6% higher risk than white women for severe PPH-related morbidity and about 5 times higher risk for PPH-related mortality, even when accounting for comorbidities.[7]

National safety bundles for PPH risk assessment rely on classification of women by health and pregnancy characteristics that are associated with an increased risk for PPH.[8] Use of these bundles triggers prophylactic and readiness measures at participating institutions. In a recent study of a leading PPH risk assessment tool, 28% of women were classified as having a medium or high risk score, which predicted 60% of PPH cases. However, the remaining 40% of PPH cases in this study occurred among women in the sample who were classified as low risk for PPH according to the assessment tool.[2,9] The study of PPH prediction has proved difficult given the diversity of both birth experiences and women's personal characteristics, in combination with the multiple etiologies of PPH. This is particularly evident among women who may appear at low risk for PPH throughout a labor and birth experience or have different combinations of labor processes, including analgesia, uterotonic medication, fever and/or intraamniotic infection, etc, which may increase their risk of PPH. These processes and events help determine the level of difficulty or complexity of the labor and birth, and a complex birth (vs an uncomplicated birth) prompts more considerations for clinicians to assess at the time of birth. This article presents results of a study designed to identify patterns (phenotypes) of labor processes in a cohort of women with few traditional (overt) risk factors for hemorrhage, using latent class analysis. For each identified labor phenotype, rates of PPH were calculated, and characteristics of women (eg, parity, ethnicity, body mass index [BMI]) in each labor phenotype were described.

METHODS

The Consortium for Safe Labor (CSL) dataset was used for this retrospective cohort analysis. The CSL dataset contains detailed information from 12 clinical centers and includes information about 228,438 births that occurred in the United States between 2002 and 2008. CSL variables include maternal demographic characteristics, health history, reproductive and prenatal history, labor interventions, birth outcomes, and newborn information.[10] CSL data were subjected to cleaning, recoding, logic checking, and validation

studies by the original investigators.[11] Institutional review board approval for this analysis was granted, and standard data use agreements were signed as required.

The California Maternal Quality Care Collaborative assessment tool was used as a guide for defining the labors at lower risk for PPH and identifying variables that are risk factors for PPH.[12] The primary dependent variable, PPH, was defined as a composite of diagnosis from the International Classification of Diseases, Ninth Revision, and reported estimated blood loss of greater than 500 mL after vaginal birth. Although PPH is currently defined as blood loss of at least 1000 mL after vaginal birth,[13] data from births in the CSL database occurred between 2002 and 2008, when the working definition for PPH was greater than or equal to 500 mL estimated blood loss after vaginal birth.[14] A composite PPH outcome variable was used for this study with the rationale that this approach would better identify women who experienced a significant blood loss, regardless of the definition of PPH used at the time. Estimated blood loss by clinicians at the time of birth may underestimate the quantity of blood lost, which also supports the decision to include births with greater than 500 mL estimated blood loss as an measure of PPH.[15]

The sample was limited to women who had term (≥37 0/7 weeks' gestation), vaginal births of a single, live newborn. Women were excluded from the sample who had known complications that were linked to obstetric bleeding prior to birth, including placenta accreta, placenta previa, abruption, and coagulopathy. During the analysis phase, retained placenta and prolonged third stage of labor (>30 minutes) were consistently classified as being highly associated with higher PPH rates but made up less than 2% of the data, which violated the application of the method of analysis (described below) and were therefore excluded. Finally, cases of women with missing information on the primary outcomes (blood loss) or maternal BMI were excluded (see Supporting Information: Figure S1). Some risk factors for PPH, such as intraamniotic infection, magnesium sulfate administration, and instrument-assisted birth, were not excluded, as these factors describe the labor process or phenotype and thus were important to identify latent classes.

Latent Class Analysis and Labor Process Indicators

The primary independent variable for this analysis was the labor phenotype determined by latent class analysis. Latent class analysis examines a group of related variables (indicators) for the purpose of identifying previously undefined classes, sometimes termed *phenotypes,* within a heterogeneous population.[16] Indicators used for latent class analysis should be components of a behavior, process, or tool. Latent class analysis is a statistical method that concurrently minimizes variance (differences) within classes and maximizes the differences between classes while also quantifying uncertainty in overall classification. This approach places women with the most similar labors together into groups while identifying previously unknown groups from a diverse sample of different labors. This technique has been used to help identify clusters or patterns of behavior, symptoms, or responses on a questionnaire. Latent class analysis can also be used to help predict distal outcomes such as PPH. This approach uses full information maximum likelihood to handle missing data among the indicators, which differs from other cross-sectional analysis types, such as multivariable regression, for which listwise deletion is the default. Full information maximum likelihood

is a strategy by which the missing data are imputed while finding a solution that best fits the available data, thus minimizing loss of overall sample size and power. An assumption of latent class analysis is that missing data are randomly distributed; therefore, CSL medical centers were excluded if they did not report labor process indicators.

To determine labor phenotypes present among women in this sample, variables were included in the latent class analysis that quantified labor events and processes rather than maternal or fetal attributes, such as age, race, weight gain, or gestational age. Five continuous and 11 categorical indicators met these criteria. Another goal of latent class analysis is to arrive at a set number of classes that explains the unique patterns of data in a clinically meaningful manner. Model selection procedures for latent class analysis as detailed by Ram and Grimm[17] were used, sequentially testing the sample by fitting 2 to 7 class solutions and comparing several model fit statistics to identify the best classification. After arriving at a latent class solution, bivariate analyses were performed to compare latent class assignment with the outcome of PPH and with 13 maternal and fetal characteristics that were associated with higher rates of PPH in other studies or are known con-founders for labor outcomes.[18-21] Finally, multivariable logistic regression was used to estimate the odds for the composite PPH outcome based on latent class assignment alone and after adjustments for maternal and fetal characteristics. Covariates included maternal age, gestational age, parity, insurance type, prepregnancy BMI, excess gestational weight gain (using Institute of Medicine gestational weight recommended guidelines), maternal reported race and ethnicity, smoking status, diagnoses of antenatal depression or hypertension, newborn weight (macrosomia, ≥4000 g), and prior uterine incision. In a second regression model, an elective induction of labor variable was included to examine the odds of PPH occurring among women whose labors were induced. Finally, logistic models were built to examine the relationship of each maternal and fetal covariate to PPH within each labor process phenotype. Analyses were conducted using Mplus version 8 (Los Angeles, CA) and Stata version 15.1 (College Station, TX). Because of the large size of the dataset, determined statistical significance was set at .01 or less, unless otherwise noted.

RESULTS

The final analytic sample consisted of data from 24,729 women with singleton vaginal births occurring at a gestational age at least 37 weeks' gestation across 5 data collection sites (see Supporting Information: Figure S1 and Table 1). The overall rate of the PPH was 4.72% (n = 1167). Within the final cohort, 80.5% of women were aged between 20 and 34 years, 47.9% reached 39 0/7 to 40 0/7 weeks' gestation, 57.7% had a parity between 1 and 3, 71.1% had private insurance, 57.6% had a normal prepregnancy BMI, 46.0% gained more than the recommended gestational weight, and 64.5% were white and non-Hispanic. In the latent class analysis, a 5-class (group) solution best fit the labor process indicators (see Supporting Information: Table S1).

Labor Process Phenotypes, PPH, and Maternal and Fetal Characteristics

The 5 labor process phenotypes were labeled to aid model interpretation, reflecting the combinations of labor process indicators included in the latent class model (not the maternal

characteristics). First, the classes were defined by the onset of labor (induced or spontaneous), then by the labor phase at admission (early or active) or a description of the duration of admission or frequency of complications and/or interventions that occurred within the class (prolonged or complicated). Table 2 lists the labor process frequencies and mean durations, which define and organize the phenotypes in more detail. Table 1 lists the frequencies of the maternal and newborn characteristics by class determination, which describes the subgroup of women who experienced the given labor process. All maternal and fetal characteristics (Table 1) included in this study were found to be statistically different across the phenotypes ($P \leq .01$) using chi-square tests. Each phenotype is described below in terms of the rate of PPH, the labor process descriptors, and the characteristics of women represented in the subgroup.

Class 1 was labeled “Spontaneous: Early Admission.” This group was the largest phenotype group (n = 11,168; 45.1% of total sample). Class 1 had the lowest rate of PPH, which occurred among 3.8% of the women in this group. Class 1 describes women with spontaneous onset of labor (97%) who were admitted in latent labor (mean [SD] dilatation on admission of 3.5 [1.3] cm), a majority of whom (66.4%) experienced labor augmentation with oxytocin for a short time (mean [SD] 2.0 [2.5] hours). This group had a high rate of epidural analgesia use (85%), short second stage (mean [SD] 0.6 [0.5] hours), and short mean duration from admission to birth (7.6 [1.6] hours). Women in this class experienced low rates of magnesium sulfate administration, intraamniotic infection, instrument-assisted birth, and shoulder dystocia. In terms of characteristics, women in Class 1 started labor significantly earlier in gestation (38% had labor start between 37 and 38 weeks’ gestation) and low rates of labor starting after 41 weeks’ gestation (1.4%). Additionally, they had the lowest rate of newborn macrosomia (5.6%). Women experiencing their first birth made up 43% of the women in Class 1. Women identified as Hispanic made up 17.4% of Class 1, which is higher than the overall rate in the analytic sample. Rates of hypertensive diagnoses were low at 4.2%.

Class 2, “Spontaneous: Active Admission,” included 12.4% of the total sample (n = 3077), and the rate of PPH in this class was 3.9%. These women are distinct in that they were admitted to the hospital in active, advanced labor with an mean (SD) dilatation of 7.3 (1.6) cm on admission. They had a short duration from admission to birth (mean [SD] 2.8 [2.2] hours) and received a mean (SD) of only 0.3 (1.1) hours exposure to synthetic oxytocin during labor (44.9% had no oxytocin augmentation). Women in Class 2 had the lowest rates of shoulder dystocia (1%), instrument-assisted birth (4%), and magnesium sulfate administration (1%) among all women in the sample. A majority of women in this group labored without regional analgesia (55%). Characteristics of women in Class 2 were notable for having the highest percentage of women aged more than 35 years (12.5%) and the highest proportion of women of parity at least 4 (10.8%). Women identified as white were found in this class at the lowest frequency (61.6%). Hypertension was diagnosed in 3.1% of the class; macrosomia was slightly more common than in Class 1 at 5.9%. Male and female fetal sexes were nearly equal in Classes 1 and 2.

Class 3, “Induction: Moderate Duration Admission,” was the second largest phenotype group (n = 7485, 30.3%); the frequency of PPH in Class 3 was 4.6%. Nearly all women in

this group experienced labor induction with a mean (SD) duration of 10.2 (5.0) hours from admission to birth. They received a mean (SD) of 4.1 (3.0) hours exposure to synthetic oxytocin infusion during labor and had a mean (SD) duration of second-stage labor of 0.5 (0.5) hours. Only 8.37% (n = 566) of the women in this class did not have any oxytocin for labor induction. Few women in Class 3 were administered magnesium sulfate or had intraamniotic infection, instrument-assisted birth, or shoulder dystocia (similar to rates in Class 1). The characteristics of women in Class 3 were notable for relatively older women, although Class 2 was still the oldest. More labors in this class were induced at 40 weeks' gestation and beyond (19.3%) than the first 2 groups. Slightly more women were overweight or obese compared with Classes 1 and 2, and 654 women (9.2%) were diagnosed with hypertension, although, as previously stated, only 152 (2%) had magnesium sulfate administered. This class of women with induced labors had their induction coded as medically indicated 46.8% of the time.

Class 4 (n = 1796, 7.3%), "Spontaneous: Prolonged Second Stage," mostly included women with spontaneous labor (75%), who were admitted in latent labor with a mean (SD) 3.0 (1.7) cm cervical dilatation on admission and had higher rates of complications, including intraamniotic infection (14%), longer mean (SD) second stage (2.9 [0.9] hours), higher rates of instrument-assisted birth (34%), and higher rates of major lacerations with episiotomy (60%) (Table 2). The majority of women in Class 4 received labor augmentation (66% received oxytocin for an average duration of 3.8 hours). The rate of PPH among women in Class 4 was 8.0%. More women in Class 4 were nulliparous (91.1%) than multiparous, more had a later gestational age at onset of labor (28.5% of births occurred after 40 weeks' gestation), and more than 80% had private insurance, higher than any of the other classes. Women in this class more commonly had a normal prepregnancy BMI, and only 10.9% had obesity. This class had the lowest percentage of black and non-Hispanic women (5.3%), the highest proportion of white women, the lowest rate of smoking, the highest percentage of macrosomia (9.9%), and a higher male-to-female newborn ratio. Hypertension was diagnosed in 7.8% of women in Class 4.

Finally, Class 5, "Induction: Prolonged Complicated Admission," was the smallest subgroup at 4.9% of the sample (n = 1203). Women in this group had the highest rates of PPH (12%). Most women in Class 5 had their labor induced with an unfavorable cervix, with a mean (SD) dilatation at admission of 1.3 (0.9) cm. Furthermore, 31% of women in Class 5 required 3 or more cervical ripening or labor induction methods. Women in Class 5 were more likely than women in other groups to experience complications such as intraamniotic infection (15%), long duration from hospital admission until birth (mean [SD] 26.2 [13.1] hours), magnesium sulfate administration (7%), and intrauterine pressure catheter placement (62%). The women represented in Class 5 were more often nulliparous (76.3%) than multiparous, and 12.3% were aged less than 20 years. Labors started at later gestational ages, and 31.6% were more than 40 weeks' gestation. Nearly 50% of the women in Class 5 had a BMI prior to pregnancy of 25.0 kg/m^2 and had the highest rate of exceeding weight gain guidelines (60%). This group also included a higher percentage of black and non-Hispanic women (15.2%). Hypertension was diagnosed in 246 women (23.3%) in Class 5, and newborn macrosomia and male sex were more common as well. Only 20.8% of the induced labors in this class were considered elective.

Likelihood for PPH by Labor Phenotype: Multivariable Regression

Compared with Class 1 (Spontaneous: Early Admission), women in Class 3, Class 4, and Class 5 all had increased odds of PPH (Table 3). The unadjusted odds of PPH occurring (relative to Class 1) were 22%, 121%, and 245% for Classes 3, 4, and 5, respectively. After controlling for demographic characteristics, Classes 3, 4, and 5 compared with Class 1 still predicted increased odds of PPH by 26%, 77%, and 182%, respectively In contrast, women in Class 2 (Spontaneous: Active Admission) did not have higher odds of having a PPH compared with women in Class 1 in adjusted analyses.

Among the lowest-risk women in the sample (Classes 1-3), labor induction differentiated women with PPH from similar women who did not experience PPH. For example, women in Class 1 (Spontaneous: Early Admission) and Class 3 (Induction: Moderate Duration Admission) had similar durations of second-stage labor and rates of interventions, including epidural analgesia, magnesium sulfate infusion, instrument-assisted birth, and major perineal laceration or episiotomy. Despite the similarity of these women's labors, after adjustment for maternal and fetal characteristics, women in Class 3 had 26% higher odds of having PPH than women in Class 1 (adjusted odds ratio, 1.26; 95% CI, 1.07-1.47). A key difference between these groups of women appeared to be their duration of exposure to oxytocin during labor (Table 2). Maximum dose of oxytocin infusion was also different in these 2 groups; women in Class 1 had a mean (SD) maximum dose of 5.9 (7.2) mU/min, whereas women (mostly for labor augmentation) in Class 3 had mean (SD) maximum dose of 13.4 (8.6) mU/min (2-sample t test; $P < .001$).

Maternal and Fetal Characteristics Associated with PPH

Using the entire sample of women, after controlling for maternal and fetal characteristics and labor process phenotype, women had increased odds of PPH if they were nulliparous, exceeded weight gain recommendations, or were black or Hispanic ($P < .01$) (Table 3). In addition, a diagnosis of hypertension or preeclampsia during pregnancy and newborn macrosomia also predicted PPH in the adjusted model. Depression during pregnancy and gestational age between 40 1/7 and 41 0/7 weeks' gestation were also associated with higher odds but did not reach statistical significance (data not shown). Women with parity of 4 or more births had lower odds of PPH compared with women with parity of 1 to 3 births. Prepregnancy BMI category did not predict PPH after adjusting for the labor process phenotype and other maternal and fetal characteristics.

When examining only women whose labors were induced (n = 9236) and controlling for all maternal and fetal characteristics as well as elective labor induction, several covariates predicted higher odds of PPH, including nulliparity, black race, Hispanic ethnicity, and the diagnosis of hypertension. Odds for PPH did not differ between women with elective or medically indicated induction of labor. Prepregnancy BMI was also not associated with the PPH outcome for women undergoing an induction of labor.

Different maternal and fetal characteristics changed women's likelihood for PPH *within* each labor process latent class (Table 4). Nulliparous women with labor phenotypes of Class 1 and Class 5 (Spontaneous: Early Admission and Induction: Prolonged Complicated

Admission) had higher odds for PPH compared with women with 1 to 3 prior births. However, nulliparity did not predict PPH in Classes 2 to 4. Grand multiparity was not associated with PPH within each phenotype.

Women of color (particularly black or Hispanic women) within each labor process class were at higher risk odds of PPH than white non-Hispanic women (Table 4). Hispanic women in Classes 1 to 3 (Spontaneous: Early Admission, Spontaneous: Active Admission, and Induction: Moderate Duration Admission) experienced PPH more often than white women did. Similarly, black women in Class 3 (Induction: Moderate Duration Admission) and Class 4 (Spontaneous: Prolonged Second Stage) had higher odds of PPH compared with white women with the same labor phenotype. Black women composed only 5.25% of women in Class 4 but experienced 9.1% of the PPH cases, further highlighting this disparity (Table 3).

Maternal health conditions also predicted risk patterns within the phenotype groups. In the Spontaneous: Early Admission and Induction: Moderate Duration Admission phenotypes (Classes 1 and 3), maternal hypertension was similarly positively associated with PPH, controlling for use of magnesium sulfate. Within the highest PPH frequency classes (Classes 4 and 5), women with a prenatal diagnosis of depression had a higher likelihood of PPH occurring.

Finally, fetal macrosomia and maternal obesity were associated with higher PPH odds within some labor classes. Women with prepregnancy obesity had an increased likelihood of PPH only in Class 2 (Spontaneous: Active Admission). Macrosomia independently predicted PPH among women in Class 4 (Spontaneous: Prolonged Second Stage, which also had long second stages and high rates of instrument-assisted births), but it was also a predictor of PPH among women in Class 1 (Spontaneous: Early Admission).

DISCUSSION

In this study, latent class analysis was used to identify 5 distinct labor process phenotypes and clarify their relationship to PPH in a group of women who had singleton, term vaginal births. Women in this sample did not experience prolonged third stage, placenta previa, abruption, or accreta. As expected, women in this sample of vaginal births with well-documented risks for PPH (Classes 4 and 5, eg, magnesium sulfate, prolonged second stage, instrument-assisted births, intraamniotic infection) experienced PPH more frequently than women without these risk factors. However, women with these associated factors only accounted for 12.1% of the analytic sample and 24.5% of all PPH cases. The preponderance of PPH cases in this study (75.5%) occurred in groups of women who were at overall lower risk for this outcome according to their labor process phenotypes. These findings are supported by existing literature showing that PPH often occurs in women who score as low risk for this outcome when using existing assessment tools.[2,22] This finding highlights the need for continued evaluation of methods to help identify new patterns of risk for PPH.

Also consistent with other literature, maternal obesity was not associated with PPH in this study after controlling for the influence of increased labor complexity among women having vaginal births.[5] Women with obesity are less likely to enter spontaneous labor[23] and more

likely to receive higher amounts of oxytocin and longer labor inductions than women without obesity.[24] Thus, it is unsurprising that women with obesity in this study were more likely to be grouped in Class 5 (Induction: Prolonged Complicated Admission) and to experience increased rates of PPH compared with women with in other classes. However, there did not appear to be an influence of maternal obesity on PPH risk independent of the other known influences of obesity on labor complexity (eg, induction of labor, longer labors). Thus, perinatal care providers caring for women with obesity who have labors that begin spontaneously and proceed without complication can be reassured that these women do not appear to have increased odds of PPH compared with similar women without obesity. The finding of maternal obesity predicting PPH in women presenting to the hospital in advanced labor (Spontaneous: Active Admission) (Table 4) is unknown but may reflect factors associated with precipitous labor or possibly timing for interventions that can mitigate PPH.

This study adds to extant literature by quantifying a specific duration of oxytocin infusion that was associated with PPH outcomes during vaginal birth. Many authors have found positive associations between PPH and use of oxytocin during labor.[18,20,25-32] However, in the existing PPH risk assessment tools, prolonged oxytocin exposure is mentioned as a risk factor for hemorrhage.[12] Women in the current study experienced an increased odds of PPH after mean (SD) of 4 (3.0) hours (Induction: Moderate Duration Admission). Oxytocin infusion during labor may diminish uterine response via oxytocin receptor downregulation. Balki et al showed that when pretreating myometrial strips with oxytocin, the dose, duration, and manner of administration (intermittent vs continuous) all contributed to subsequent uterine responsivity.[33-35]

Women of color, relative to white women, were more likely to have PPH after controlling for comorbidities, maternal and fetal characteristics, and labor phenotypes. This finding is corroborated by other studies that have found racial and/or ethnic disparities in adverse labor outcomes and PPH morbidity in particular.[7] Racial disparities in perinatal health in general are multifactorial and may be related to differences in access to or engagement in care,[36] disparate hospital care practices,[37,38] racism and segregation,[39,40] pervasive stress,[41-43] or epigenetic effects.[44-46] Race and ethnicity are not included as part of published PPH risk scoring tools.[12] Further research that may validate this independent link between race and ethnicity and PPH is needed to explore root causes to improve health disparities. If this link is replicated, race and ethnicity could be included in revised risk assessment tools to ensure that even among low-risk women or labors that are not overtly complicated, a lived experience of racial inequity might be considered an important predictor for PPH.

Another key finding of this analysis is the increased odds of PPH among women who were nulliparous, compared with women having 1 to 3 previous births. Nulliparous women tend to have relatively longer labor durations and are more vulnerable to genital tract trauma compared with multiparous women,[11,47] which may explain some of this associated risk for PPH. However, most nulliparas do not have prolonged labors by definition and would not receive added risk assessment points. Currently, grand multiparity is considered a risk factor for PPH by established tools,[12] a relationship that was not supported by this analysis.

The association of depression and PPH, which has been examined in other studies,[48,49] may be linked to use of antidepressant medication use for treatment of depression in pregnancy. The mechanism for this association is proposed as a lowered concentration of platelet serotonin, which aids normally aids in platelet aggregation.[48] However, other authors have reported a positive influence of serotonin on myometrial contractility, possibly helping avoid uterine atony.[50,51] These competing physiologic effects may explain why both treated and untreated depression in pregnancy have been associated with a risk for PPH.[52] Furthermore, a recent study of serum levels of antidepressant medication in pregnant women found that women with levels below therapeutic thresholds experienced more PPH than those with levels in a therapeutic range.[51] The data used for the present study did not detail treated versus untreated depression, and the results showed an association between depression and PPH only for women in the longer or more complicated labor phenotypes. The possibility that depression is associated with other unmeasured comorbidities, which influence labor complexity and PPH, therefore remains a possibility. However, the association between depression (and/or treatment) during pregnancy and PPH deserves more research given the importance of maternal mental health on many perinatal outcomes and the growing use of selective serotonin reuptake inhibitors during pregnancy.

Clinical and Research Implications

When caring for women with established PPH risk factors such as long labor induction processes, prolonged second stage, and/or suspected intraamniotic infection, perinatal care providers should be prepared for PPH, as this study supports previous literature in identifying these factors as key predictors of PPH. However, based on these results, birth care providers should also remain vigilant for PPH when caring for women who score as low risk on current assessment tools if they are nulliparous, women of color, or have uncomplicated labor induction with even short periods of oxytocin infusion. Evidence-based screening tools that are validated specifically for nulliparous versus multiparous women may be one way to develop a more personalized clinical rating system. More research is needed on groups of women who are considered to be at lower risk for PPH to validate any newly identified risk factors or develop prevention strategies specific to the labor phenotype. Finally, further research on prenatal depression and/or treatment for depression may be another opportunity to advance risk assessment accuracy.

Strengths and Limitations

This study had several strengths. First, it included a large sample of women who had vaginal births and few overt risk factors for obstetric bleeding, thus providing much-needed information on PPH in a lower-risk population. Second, this study grouped women for their PPH risks according to their labor processes—thus making these findings more easily translatable to practicing clinicians. Considering labor with a phenotype classification helps provide insight into the contributions to PPH in a clinically meaningful manner, as the phenotype helps provide a picture of many labor events and process that occur simultaneously.[16] In contrast, multivariable regression models allow for consideration of a single indicator (independent variable) while holding constant (*ceteris paribus*) other independent variables. In effect, regression methods help answer the question of how a one variable performs in spite of the effect all other variables, whereas latent class analysis

considers the relationship among multiple indicators to the outcome because all the variables determine the class membership. The ability to have more detailed information about the processes of labor (labor induction methods, oxytocin duration) in this dataset provided more granularity in understanding risks associated with complex birth processes.

This study also had several limitations. First, the CSL dataset used for this analysis lacked information on some important known predictors of PPH that are included in PPH risk factor tools, including large uterine fibroids, history of PPH, blood counts (admission hemoglobin, platelet count), and use of prophylactic oxytocin after birth. In addition, several CSL medical centers were excluded from this analysis because of missing information on key variables. Although this study includes a nationally representative set of medical centers, these were primarily teaching institutions. Results may therefore not be generalizable to all settings. The age of the CSL dataset is also a limitation of this study. Since the mid-2000s, when births included in the CSL dataset occurred, updates on PPH prevention and treatment have been issued, including an emphasis on uterotonic prophylaxis.[13,53] Finally, there may be unmeasured differences in diagnosis of PPH or estimation of blood loss. Although the CSL data were collected using a standardized protocol,[10] human error or institutional differences remain a possibility.

CONCLUSION

In summary, this study shows evidence of 5 distinct phenotypes that describe the labor process and are associated with differing likelihood of PPH. Although women with more complex labor processes had the highest odds of PPH, women who experienced few labor complications nevertheless accounted for the large majority of PPH cases in this sample. Women of color were more likely to have PPH across all phenotypes, regardless of their labor process, comorbidities, or other maternal and fetal characteristics. In addition, nulliparous women were more likely to experience PPH than parous women. Short duration of oxytocin exposure for an uncomplicated labor induction also increased the odds of PPH. This study also supports findings of emerging research examining how PPH may be influenced by perinatal depression. Finally, maternal BMI prior to pregnancy, in agreement with other literature, is not a risk factor for PPH. The authors propose that future PPH analyses explicitly describe subgroup patterns to identify precision approaches for preventing and treating hemorrhage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Quick Points

- Women with labor complications such as prolonged second stage, magnesium sulfate use, and intraamniotic infection were more likely to experience postpartum hemorrhage (PPH) than women with uncomplicated labors. However, the preponderance of PPH cases occurred in women who were at lower risk for that outcome according to their labor processes.
- Women with prepregnancy obesity were more likely to have complicated induced labors but were not more likely to experience PPH than women who were not obese and had similar labor complexity.
- Women with term vaginal births were more likely to experience PPH when they were nulliparous, had pregnancy weight gain greater than guidelines, were black or Hispanic, had fetal macrosomia, or had hypertensive complications.
- Prenatal depression was a predictor of hemorrhage among the groups of women with more difficult labors.

Table 1.

Sample Description of Maternal and Fetal Characteristics in National Multisite DataSet from 2002 to 2008 (N = 24,729)

Maternal and Fetal Characteristics	Total sample[a] (N = 24,729)	Labor Phenotype Class				
		Class 1 Spontaneous: Early Admission (n = 11,168)	Class 2 Spontaneous: Active Admission (n = 3077)	Class 3 Induction: Moderate Duration Admission (n = 7485)	Class 4 Spontaneous: Prolonged Second Stage (n = 1796)	Class 5 Induction: Prolonged Complicated Admission (n = 1203)
Maternal age, n (%), y						
<20	2248 (9.1)	1197 (10.7)	205 (6.6)	496 (6.6)	203 (11.3)	147 (12.3)
20-34	19,901 (80.5)	8909 (79.8)	2489 (80.9)	611 (81.7)	1445 (80.5)	947 (78.9)
35-39	2168 (8.8)	889 (7.9)	319 (10.4)	745 (9.9)	131 (7.3)	84 (7.0)
≥40	400 (1.6)	170 (1.5)	64 (2.1)	129 (1.7)	16 (0.9)	21 (1.8)
Gestational age, n (%), wk						
37.0-38.9	8283 (33.5)	4282 (38.3)	1018 (33.1)	2115 (28.3)	464 (25.8)	404 (33.6)
39.0-40.0	11,868 (47.9)	5073 (45.4)	1650 (53.6)	3918 (52.3)	820 (45.7)	407 (33.8)
40.1-41.0	3994 (16.2)	1662 (14.8)	368 (11.9)	1195 (15.9)	458 (25.5)	311 (25.9)
>41.0	584 (2.36)	151 (1.4)	41 (1.3)	257 (3.4)	54 (3.0)	81 (6.7)
Parity, n (%)						
Nulliparous	10,453 (42.3)	4807 (43.0)	463 (24.8)	2329 (31.1)	1636 (91.1)	918 (76.3)
Para 1-3	12,793 (51.7)	5695 (50.9)	1981 (64.4)	4700 (62.8)	155 (8.6)	262 (21.8)
Para ≥4	1483 (6.0)	666 (5.9)	333 (10.8)	456 (6.1)	5 (0.3)	23 (1.9)
Insurance, n (%)						
Private	17,413 (71.1)					
Public	7081 (28.9)	3385 (30.6)	824 (27.2)	2077 (28.0)	297 (22.2)	298 (33.4)
Prepregnancy BMI, n (%), kg/m^2						
Underweight (BMI <18.5)	1519 (6.1)	2311 (6.8)	227 (7.4)	382 (5.1)	116 (6.5)	40 (3.3)
Normal (BMI 18.5 to <25.0)	14,241 (57.6)	6609 (59.2)	1858 (60.4)	4074 (54.4)	1126 (62.7)	574 (47.7)
Overweight (BMI 25.0 to <30)	5357 (21.7)	2311 (20.7)	636 (20.4)	1743 (23.3)	357 (19.9)	310 (25.8)
Obese (BMI ≥30)	3612 (14.6)	1494 (13.4)	356 (11.6)	1286 (17.2)	197 (10.9)	279 (23.2)
Institute of Medicine weight gain guidelines by BMI, n (%)						
Met guidelines	7918 (32.0)	3626 (32.5)	1062 (34.5)	2385 (31.9)	547 (30.5)	298 (24.8)
Over guidelines	11,379 (46.0)	4992 (44.7)	1179 (38.3)	3513 (46.9)	977 (54.4)	728 (59.7)
Under guidelines	5432 (21.9)	2550 (22.8)	836 (27.2)	1587 (21.2)	272 (15.1)	187 (15.5)

Maternal and Fetal Characteristics	Total sample[a] (N = 24,729)	Labor Phenotype Class				
		Class 1 Spontaneous: Early Admission (n = 11,168)	Class 2 Spontaneous: Active Admission (n = 3077)	Class 3 Induction: Moderate Duration Admission (n = 7485)	Class 4 Spontaneous: Prolonged Second Stage (n = 1796)	Class 5 Induction: Prolonged Complicated Admission (n = 1203)
Race and ethnicity, n (%)						
White and non-Hispanic	15,942 (64.5)	6991 (65.4)	1828 (61.6)	5105 (70.4)	1269 (75.8)	749 (65.9)
Black and non-Hispanic	3094 (12.5)	1377 (12.9)	422 (14.2)	1034 (14.3)	88 (5.3)	173 (15.2)
Hispanic	3677 (14.9)	1862 (17.4)	532 (17.9)	882 (12.2)	230 (13.7)	171 (15.1)
Asian or Pacific Islander	1015 (4.1)	468 (4.4)	184 (6.2)	233 (3.2)	88 (5.3)	42 (3.7)
Smoking, n (%)	1490 (6.0)	758 (6.8)	196 (6.4)	370 (4.9)	68 (3.8)	98 (8.2)
Depression (prenatal), n (%)	1404 (5.7)	692 (6.2)	130 (4.2)	433 (5.8)	82 (4.6)	67 (5.6)
Hypertension, n (%)	1553 (6.8)	431 (4.2)	89 (3.1)	654 (9.2)	133 (7.8)	246 (23.3)
Newborn macrosomia (≥4000 g), n (%)	1613 (6.6)	619 (5.6)	179 (5.9)	527 (7.1)	176 (9.9)	112 (9.4)
Female fetal sex, n (%)	12,412 (50.2)	5649 (50.6)	1511 (49.1)	3832 (51.2)	852 (47.5)	568 (47.3)
Uterine scar, n (%)	803 (3.3)	463 (5.2)	138 (4.5)	127 (1.7)	50 (2.8)	25 (2.1)
Indication labor induction, n (%)	9236 (100)					
Indicated	4916 (53.2)	300 (91.2)	41 (95.4)	3499 (46.8)	347 (75.6)	729 (79.2)
Elective	4320 (46.8)	29 (8.8)	2 (4.7)	3986 (53.3)	112 (24.4)	191 (20.8)

Abbreviation: BMI, body mass index.

[a]Missing data: Maternal age (n = 12), insurance (n = 235), race and ethnicity (n = 1001), hypertension diagnosis (1707), macrosomia (n = 255), fetal sex (n = 22).

Table 2.

Labor Process Variables Describing the Sample of 24,729 Vaginal Births and the Composition of Each Labor Phenotype Class and Rate of Postpartum Hemorrhage

	Analytic Sample[a]	Class 1 Spontaneous: Early Admission	Class 2 Spontaneous: Active Admission	Class 3 Induction: Moderate Duration Admission	Class 4 Spontaneous: Prolonged Second Stage	Class 5 Induction: Prolonged Complicated Admission
Distribution of class membership, n (%)	24,729 (100)	11,168 (45.1)	3077 (12.4)	7485 (30.3)	1796 (7.3)	1203 (4.9)
Postpartum hemorrhage rate,[b] n (%)	1,167 (4.7)	420 (3.8)	120 (3.9)	341 (4.6)	143 (8.0)	143 (11.9)
Labor process variables						
Spontaneous labor, n (%)	15,493 (62.6)	10,902 (97)	2983 (99)	0 (0)	1324 (75)	284 (24)
≥3 methods needed for labor induction,[c] n (%)	882 (5.2)	0 (0)	0 (0)	514 (7)	51 (3)	317 (31)
Neuroaxial analgesia, n (%)	20,087 (82.2)	9488 (85)	1272 (45)	6479 (86)	1700 (96)	1148 (96)
Intrauterine pressure catheter, n (%)	4770 (19.3)	1783 (16)	17 (1)	1645 (22)	572 (32)	753 (62)
Artificial rupture of membranes, n (%)	16,416 (66.4)	6378 (58)	1571 (59)	6577 (89)	960 (56)	930 (78)
Fever and/or intraamniotic infection, n (%)	819 (3.3)	298 (3)	17 (1)	64 (1)	253 (14)	187 (15)
Magnesium sulfate use, n (%)	404 (1.6)	124 (1)	15 (1)	152 (2)	31 (2)	82 (7)
Having both episiotomy and lacerations, n (%)	7925 (32.0)	3429 (31)	677 (22)	2225 (30)	1072 (60)	522 (43)
Instrument-assisted vaginal birth, n (%)	2096 (8.5)	679 (6)	113 (4)	475 (6)	599 (34)	230 (19)
Shoulder dystocia, n (%)	423 (1.7)	172 (2)	19 (1)	127 (2)	55 (3)	50 (4)
Admission until birth, mean (SD), h	9.2 (6.9)	7.5 (1.6)	2.8 (2.2)	10.2 (5.0)	13.3 (5.2)	26.2 (13.1)
Cervical dilatation on admission, mean (SD), cm	3.5 (2.1)	3.5 (1.3)	7.3 (1.6)	2.4 (1.2)	3.0 (1.7)	1.3 (0.9)
Oxytocin duration, mean (SD), h	3.7 (4.5)	2.0 (2.5)	0.3 (1.1)	4.1 (3.0)	3.9 (4.2)	13.1 (8.4)
Number of cervical examinations, mean (SD)	7.5 (3.0)	7.5 (2.6)	4.8 (1.6)	7.5 (2.4)	9.3 (3.2)	12.6 (3.9)
Full dilation duration, mean (SD), h	0.8 (0.9)	0.6 (0.5)	0.5 (0.6)	0.5 (0.5)	2.9 (0.9)	1.3 (0.9)
Third stage of labor, mean (SD), min	5.4 (3.9)	5.3 (3.6)	5.1 (4.2)	5.1 (3.6)	6.4 (4.8)	6.2 (4.5)

[a]Missing data: duration of admission (n = 102), cervical dilatation on admission (n = 758), duration of oxytocin (n = 433), duration of second stage (n = 2021), number of cervical examinations (n = 489), artificial rupture of membranes (n = 704), instrument-assisted vaginal birth (n = 803), medications for labor induction (n = 121), laceration or episiotomy (n = 1).

[b]Postpartum hemorrhage rate is a composite of diagnosis code from the *International Classification of Diseases, Ninth Revision* and estimated blood loss over 500 mL on birth record.

[C]Methods and procedures included any of the following within cases coded for induced labor only: artificial rupture of membranes, misoprostol or prostaglandin El agonist, mechanical dilator, prostaglandin E2 agonist synthetic oxytocin.

Table 3.

Risk for Postpartum Hemorrhage by Labor Process Phenotype and Maternal and Fetal Characteristics

	Risk for Postpartum Hemorrhage		
	Entire Sample (N = 24,729)		Women with Labor Induction (n = 8223)
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Adjusted[a] OR (95% CI)
Labor process phenotype			
Class 1 (Spontaneous: Early Admission)	Reference	Reference	Reference
Class 2 (Spontaneous: Active Admission)	1.03 (0.84-1.27)	1.17 (0.93-1.46)	—
Class 3 (Induction: Moderate Duration Admission)	1.22 (1.05-1.42)[b]	1.26 (1.07-1.47)[b]	1.56 (0.79-3.11)
Class 4 (Spontaneous: Prolonged Second Stage)	2.21 (1.82-2.70)[c]	1.77 (1.42-2.21)[c]	2.63 (1.23-5.60)[b]
Class 5 (Induction: Prolonged Complicated Admission)	3.45 (2.82-4.21)[c]	2.82 (2.24-3.54)[c]	3.89 (1.91-7.89)[c]
Parity			
Nulliparous	1.72 (1.52-1.94)[c]	1.52 (1.30-1.77)[c]	1.47 (1.17-1.87)[c]
Para 1-3	Reference	Reference	Reference
Para 4+	0.72 (0.52-0.99)[b]	0.69 (0.49-0.99)[b]	0.62 (0.34-1.11)
Pregnancy weight gain guidelines[d]			
Met guidelines	Reference	Reference	Reference
Over guidelines	1.34 (1.17-1.54)[c]	1.22 (1.05-1.43)[b]	1.18 (0.93-1.49)
Race and ethnicity			
White and non-Hispanic	Reference	Reference	Reference
Black and non-Hispanic	1.38 (1.16-1.64)[c]	1.39 (1.13-1.73)[b]	1.61 (1.18-2.19)[b]
Hispanic	1.77 (1.53-2.06)[c]	1.85 (1.56-2.20)[c]	1.96 (1.48-2.59)[c]
Asian or Pacific Islander	1.21 (0.89-1.62)	1.22 (0.89-1.67)	1.58 (0.98-2.57)
Hypertension	2.15 (1.79-2.56)[c]	1.63 (1.33-2.00)[c]	1.72 (1.31-2.26)[c]
Macrosomia (≥4000 g)	1.53 (1.25-1.87)[c]	1.54 (1.23-1.94)[c]	1.50 (0.80-1.67)
Indication IOL (n = 9236) elective	0.65 (0.54-0.78)[c]	NA	1.04 (0.82-1.31)

Abbreviations: IOL, induction of labor; NA, not analyzed; OR, odds ratio.

[a]Adjusted for history of prior cesarean birth, fetal sex, prenatal depression, gestational weight gain under recommended guidelines, public versus private insurance, maternal age, smoking status, gestational age at birth, and prepregnancy body mass index.

[b]$P \leq .01$.

[c]$P \leq .001$.

[d]Institute of Medicine guidelines based on prepregnancy body mass index.

Table 4.

Maternal and Fetal Characteristics Significantly Associated with Postpartum Hemorrhage Risk Within Members of Each Labor Process Latent Class[a]

Variables Significantly Associated with PPH	OR (95% CI)	*P* Value
Class 1: Spontaneous: Early Admission		
Nulliparous	1.75 (1.38-2.29)	<.001
Exceeded weight gain guidelines	1.29 (0.99-1.66)	.052
Hispanic	1.88 (1.43-2.48)	<.001
Hypertension	1.68 (1.10-2.56)	.016
Macrosomia (≥4000 grams)	1.89 (1.30-2.74)	.001
Class 2: Spontaneous: Active Admission		
Obesity (BMI ≥30 kg/m^2)	1.83 (1.07-3.12)	.028
Hispanic	1.78 (1.07-2.96)	.023
Class 3: Induction: Moderate Duration Admission[b]		
Black and non-Hispanic	1.54 (1.07-2.23)	.02
Hispanic	1.91 (1.36-2.67)	<.001
Asian or Pacific Islander	1.98 (1.15-3.39)	.014
Smoker	0.38 (0.15-0.93)	.030
Hypertension	1.83 (1.29-2.58)	.001
Class 4: Spontaneous: Prolonged Second Stage		
Gestational age (40.1-41 wk)	1.68 (1.08-2.62)	.021
Black and non-Hispanic	2.51 (1.23-5.70)	.019
Depressed	2.17 (1.01-4.66)	.046
Macrosomia	2.44 (1.47-4.05)	.001
Class 5: Induction: Prolonged Complicated Admission		
Nulliparous	4.36 (2.11-9.03)	<.001
Hispanic	1.75 (1.01-3.05)	.047
Depressed	2.61 (1.07-6.26)	.034

Abbreviations: BMI, body mass index; OR, odds ratio; PPH, postpartum hemorrhage.

[a]Each model controls for maternal age, gestational age, parity, insurance, weight gain guidelines, maternal race and ethnicity, smoking, depression, hypertension, newborn macrosomia, fetal sex, and uterine scar.

[b]Indication for induced labor also included in model (for Class 3 only).