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Human Papillomavirus, Cervical Intraepithelial Neoplasia, and Quantitative Blood Loss at Delivery

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Abstract: Studies using estimated blood loss show the association of either human papillomavirus (HPV) or cervical intraepithelial neoplasia (CIN) with postpartum hemorrhage (PPH). We study the association of HPV or CIN with either blood loss or PPH as measured by the more precise measure of quantitative blood loss (QBL). We retrospectively studied 2,334 peripartum women with a documented Pap smear prior to delivery. The main predictor variable had categories for HPV and CIN as compared to normal cytology. Covariates included demographics, medical/surgical history, and pregnancy variables. Model 1 included the whole sample. Model 2 included only those with an operative vaginal delivery or a cesarean delivery. Outcome measures were QBL and PPH measured by QBL. We found in model 1 that those HPV positive and those with CIN were each not significantly associated with QBL. In model 2, those HPV positive were significantly associated with increased QBL (B = 0.11, SE = 0.05, p = 0.047), while CIN was not significantly associated with QBL. In model 1, those HPV positive and those with CIN were each not significantly associated with PPH. In model 2, those HPV positive were significantly associated with increased odds for PPH (OR:11.03, 9% CI:1.77, 68.74, p = 0.01) while CIN was not significantly associated with PPH. In conclusion, the presence of HPV was positively associated with an increase in the QBL and PPH at time of delivery for those with operative vaginal and cesarean deliveries. We suggest that clinicians take HPV results of Pap smears into consideration when considering a patient's risk of PPH.

Keywords: human papillomavirus viruses, postpartum hemorrhage, uterine cervical dysplasia.

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Introduction

Human papillomavirus (HPV) prevalence is greater in pregnant women than in non-pregnant women [1]. HPV in pregnancy is associated with various adverse outcomes including miscarriage, preterm delivery, placental abnormalities, and fetal growth restriction [2]. A study reports an increased incidence of postpartum hemorrhage (PPH) among HPV-positive women [3]. Also, among patients with confirmed cervical intraepithelial neoplasia (CIN), there is an increased incidence of PPH among those with cesarean section deliveries as compared to those with vaginal deliveries [4–5].

PPH is the leading cause of maternal mortality worldwide [6]. There has been a changed approach in many healthcare facilities from estimated blood loss (EBL) to the more precise quantitative blood loss (QBL) [7]. QBL measurement improves response time to PPH and has lower maternal morbidity and mortality as compared to EBL measurement [6].

There are a limited number of studies using EBL showing the association of either HPV [3, 5] or CIN [4] with PPH measured by EBL. We are unaware of any literature using the more precise measure of QBL that studies the presence of HPV or CIN with either blood loss or PPH. We study the postpartum experience and compare presence of HPV and CIN without HPV to those with normal cytology using blood loss as measured by QBL. Our primary aim is to study the association of presence of HPV or CIN with QBL. Our secondary aim is to study the association of presence of HPV or CIN with PPH measured by QBL.

Materials and Methods

Setting

We retrospectively studied 2,334 peripartum women delivering at a public safety net hospital located in a Long Island suburb of New York City. We used the timeframe of January 1, 2020 — May 7, 2023 since QBL was consistently used at our hospital after deliveries beginning in January 2020. Inclusion criteria were those between the ages of 21–47 years that had a documented Pap smear prior to delivery of a live neonate. Exclusion criteria were those with confirmed abnormal placentation (i.e., placenta previa, accreta, increta, or percreta) and extramural deliveries. If a patient had multiple deliveries during the study timeframe, we only included the first delivery. Ethical approval was received from the hospital institutional review board. A waiver for informed consent was obtained due to the retrospective nature of the study.

Variables

The main predictor variable was Pap smear categorized into the following groups: normal cytology, HPV positive, CIN, and HPV positive with CIN. Demographic variables were age (years), race/ethnicity (white, black, Hispanic, Asian, and other), and pre-pregnancy body mass index (BMI; kg/m^2) with categories of normal (18.5–24.9), overweight (25.0–29.9), and obese (30 and greater). Medical and surgical history variables were previous uterine surgery, coagulation defect, chronic or gestational hypertension, pre-eclampsia prior to delivery, pre-gestational or gestational diabetes, cervical diagnostic excisional procedure (i.e., loop electrosurgical excision procedure or cold knife cone surgical biopsy), and cervical insufficiency, all measured as no versus yes. Pregnancy

variables were gravidity (number), parity (number), obstetric anal sphincter injuries (no/yes), and mode of delivery (vaginal, operative vaginal, or cesarean). At our hospital, operative vaginal deliveries are vacuum assisted, and no forceps deliveries are performed.

The primary outcome was QBL. QBL is a quantitative measurement of intrapartum blood loss that is obtained by healthcare personnel. At our institution, QBL is determined by weighing all sources of blood collection and then subtracting the dry weight while assuming one gram is equivalent to one mL of blood loss. The common sources weighed include lap pads, blue towels, and disposable chucks. This weight-based blood loss is then added to the blood loss measured in the under-buttocks drape with collection pouch as well as any suction canisters used. During cesarean section, the quantity of amniotic fluid in the suction canister is subtracted from the total. The secondary outcome was PPH defined as those with 1,000 mL or more of blood loss that was measured by the QBL approach.

Statistical Analysis

Descriptive statistics of mean and standard deviation described the continuous variables, and frequency and percentage described the categorical variables. Analysis of variance compared the groups to the continuous outcome of QBL. The Fisher's exact test compared the groups to the categorical outcome of PPH. Multivariate linear regression and multivariate logistic regression were each conducted for two models. Model 1 included the whole sample. Model 2 included only those with an operative vaginal delivery or a cesarean delivery. Due to the much smaller sample size for the model 2 analyses, only predictor variables statistically significant in model 1 were included in model 2. QBL was logarithmic transformed due to presence of skewness. Analyses for mean values for QBL report non-transformed values for ease of understanding. All p-values were two-tailed. Alpha level for significance was $p < 0.05$. Analyses were conducted with IBM SPSS Statistics Version 29 (IBM Corporation, Armonk, NY, 2022).

Results

Table 1 shows the sample characteristics. The sample had 2,148 with normal cytology (92.0%), 76 who were HPV positive (3.3%), and 110 with CIN (4.7%). No one was both HPV positive and had CIN. For demographics, mean age was slightly above 30 years, more than two thirds were Hispanic race/ethnicity, and 61.3% were obese. For medical and surgical history, percentages ranged from as low as 0.1% for coagulation defect, to as high as 22.2% for previous uterine surgery. For pregnancy variables, mean values for gravidity were 3.0 and for parity were 1.5. There were 6.6% that had an operative vaginal delivery and 7.5% that had a cesarean delivery. There were 1.6% with obstetric anal sphincter injuries.

Univariate analyses were conducted in the whole sample (n = 2,334). Analysis of variance did not show a statistically significant difference ($p = 0.47$) for mean QBL among the groups (normal cytology: M = 364.25, SD = 264.35; HPV positive: M = 351.75, SD = 289.58; CIN: M = 329.99, SD = 221.46). Also, the Fisher's exact test did not show a statistically significant difference ($p = 0.46$) for percentage with PPH (normal cytology: n = 46, 2.1%; HPV positive: n = 3, 3.9%; CIN: n = 2, 1.8%). Univariate analyses were conducted in the subset (n = 328) of those with an operative vaginal delivery or cesarean delivery. Analysis of variance did not show a statistically significant difference ($p = 0.76$) for mean QBL among the groups (normal cytology: n = 304, M = 525.52,

Table 1. Descriptive Statistics of Sample of 2,334 Peripartum Women.

Variable	Mean (SD) or Frequency (Percentage)
Main Predictor Variable	
Group	
Normal cytology	2,148 (92.0)
HPV positive	76 (3.3)
Cervical intraepithelial neoplasia	110 (4.7)
HPV positive & cervical intraepithelial neoplasia	0 (0.0)
Demographics	
Age (years) [mean]	30.7 (5.65)
Race/ethnicity	
White	128 (5.5)
Black	376 (16.1)
Hispanic	1,599 (68.5)
Asian	74 (3.2)
Other	157 (6.7)
Body mass index (kg/m^2)	
Normal (18.5–24.9)	193 (8.3)
Overweight (25.0–29.9)	710 (30.4)
Obese (30 and greater)	1,431 (61.3)
Medical and Surgical History	
Previous uterine surgery (yes)	518 (22.2)
Coagulation defect (yes)	3 (0.1)
Chronic or gestational hypertension (yes)	63 (2.7)
Pre-eclampsia prior to delivery (yes)	90 (3.9)
Pre-gestational or gestational diabetes (yes)	240 (10.3)
Cervical diagnostic excisional procedure (yes)	28 (1.2)
Cervical insufficiency (yes)	25 (1.1)
Pregnancy	
Gravidity (number) [mean]	3.0 (1.67)
Parity (number) [mean]	1.5 (1.24)
Delivery mode	
Vaginal	2,006 (85.9)
Operative vaginal	154 (6.6)
Cesarean	174 (7.5)
Obstetric anal sphincter injuries (yes)	37 (1.6)
Chorioamnionitis (yes)	0 (0.0)
Outcomes	
Quantitative blood loss (mL) [mean]	362.2 (263.35)
Postpartum hemorrhage (yes)	51 (2.2)

Note: SD — standard deviation, HPV — human papillomavirus. There were no people both positive for HPV and with cervical intraepithelial neoplasia. For body mass index, two people with values of 18.2 and 18.3 were included in normal body mass index. For obstetric anal sphincter injuries, there were 35 people with a third-degree laceration and 2 people with a fourth-degree laceration.

SD = 276.23; HPV positive: n = 14, M = 582.79, SD = 331.64; CIN: n = 10, M = 499.60, SD = 279.69). Also, the Fisher's exact test did not show a statistically significant difference (p = 0.08) for percentage with PPH (normal cytology: n = 7, 2.3%; HPV positive: n = 2, 14.3%; CIN: n = 0, 0.0%).

Table 2 shows the multivariate linear regression analyses for QBL. In model 1, those HPV positive and those with CIN were each not significantly associated with QBL. For demographics, increased age and those obese were each significantly associated with increased QBL. For medical and surgical history, previous uterine surgery, chronic or gestational hypertension, pre-eclampsia prior to delivery, pre-gestational or gestational diabetes, and cervical insufficiency were each significantly associated with increased QBL. For pregnancy, both operative vaginal and cesarean deliveries, and obstetric anal sphincter injuries were each significantly associated with increased QBL. Increased gravidity was significantly associated with decreased QBL. In model 2, those HPV positive were significantly associated with increased QBL. No demographic variables were significantly associated with QBL. For medical and surgical history, previous uterine surgery, chronic or gestational hypertension, pre-eclampsia prior to delivery, and pre-gestational or gestational diabetes were each significantly associated with increased QBL. For pregnancy, only obstetric anal sphincter injuries were significantly associated with increased QBL.

Table 3 shows the multivariate logistic regression analyses for PPH. In model 1, those HPV positive and those with CIN were each not significantly associated with PPH. No demographic variables were significantly associated with PPH. For medical and surgical history, previous uterine surgery, coagulation defect, and pre-eclampsia prior to delivery were each significantly associated with increased odds for PPH. For pregnancy, only increased gravidity was significantly associated with decreased odds for PPH. None of the demographic or pregnancy variables were significantly associated with PPH. In model 2, those HPV positive were significantly associated with increased odds for PPH. For medical and surgical history, previous uterine surgery was significantly associated with increased odds for PPH. No demographic or pregnancy variables were significantly associated with PPH.

Discussion

We found in the whole sample that there was no significant association of either HPV positive or CIN with either QBL or PPH. In the subset of those with operative vaginal and cesarean deliveries, HPV positive was significantly associated with increased QBL and PPH. CIN was not significantly associated with either QBL or PPH. Previous uterine surgery was significantly associated with increased QBL and PPH in both the whole sample and the subset of those with either operative vaginal or cesarean deliveries.

We found that those HPV positive were significantly associated with increased QBL and PPH in the subset of operative vaginal and cesarean deliveries while there was no such association in the whole sample. Previous literature with EBL reports that those HPV positive or with CIN are associated with increased risk of PPH [3]. Our findings with QBL and PPH are similar for HPV but different for CIN. As QBL is a more accurate measure of blood loss, this reinforces the important concern that those HPV positive are associated with acute blood loss at the time of delivery. Our lack of a significant association of CIN with increased blood loss, whether for QBL or PPH measurement, is likely due to small sample size. Presence of HPV can be determined for those who received prenatal care that included a Pap smear. For those with an unknown HPV status, this lack of information about HPV would reduce clinician understanding of patient hemorrhage risk.

Table 2. Multivariate Linear Regression Analyses for Quantitative Blood Loss.

Variable	Model 1 B (SE) (n = 2,334)	p-value	Model 2 B (SE) (n = 328)	p-value
Main Predictor Variable				
Group				
Normal cytology	Reference		Reference	
HPV positive	–0.03 (0.03)	0.33	0.11 (0.05)	0.047
Cervical intraepithelial neoplasia	–0.01 (0.02)	0.70	0.02 (0.06)	0.70
Demographics				
Age (years)	0.003 (0.001)	0.01	–0.001 (0.002)	0.54
Race/ethnicity				
White	Reference			
Black	0.04 (0.02)	1.00	—	—
Hispanic	0.03 (0.02)	0.23		
Asian	0.04 (0.03)	0.27		
Other	–0.001 (0.03)	0.98		
Body mass index (kg/m^2)				
Normal (18.5–24.9)	Reference		Reference	
Overweight (25.0–29.9)	0.03 (0.02)	0.09	0.04 (0.05)	0.43
Obese (30 and greater)	0.05 (0.02)	0.01	0.09 (0.05)	0.06
Medical and Surgical History				
Previous uterine surgery (yes)	0.35 (0.01)	<0.001	0.34 (0.03)	<0.001
Coagulation defect (yes)	0.17 (0.14)	0.20	—	—
Chronic or gestational hypertension (yes)	0.09 (0.03)	0.002	0.28 (0.08)	<0.001
Pre-eclampsia prior to delivery (yes)	0.10 (0.03)	<0.001	0.14 (0.07)	0.04
Pre-gestational or gestational diabetes (yes)	0.09 (0.02)	<0.001	0.19 (0.04)	<0.001
Cervical diagnostic excisional procedure (yes)	0.03 (0.05)	0.45	—	—
Cervical insufficiency (yes)	0.11 (0.05)	0.02	0.27 (0.14)	0.06
Pregnancy				
Gravidity (number)	–0.02 (0.004)	<0.001	0.01 (0.01)	0.14
Parity (number)	–0.01 (0.004)	0.20	—	—
Delivery mode				
Vaginal	Reference		—	—
Operative vaginal	0.04 (0.02)	0.04		
Cesarean	0.18 (0.02)	<0.001		
Obstetric anal sphincter injuries (yes)	0.17 (0.04)	<0.001	0.14 (0.07)	0.03
Constant	2.28 (0.04)	<0.001	2.40 (0.07)	<0.001

Note: B — unstandardized beta, SE — standard error, HPV — human papillomavirus. Model 1 included the whole sample. Model 2 included only those with an operative vaginal delivery or a cesarean delivery. The assumptions for linear regression were met, as scatterplots suggested a linear relationship and homoscedasticity, histograms suggested normality, variance inflation factor values indicated no multicollinearity concerns, and Durban–Watson values indicated no autocorrelation concerns. Adjusted R-square: Model 1: 0.35, Model 2: 0.39.

Table 3. Multivariate Logistic Regression Analyses for Postpartum Hemorrhage.

Variable	Model 1 OR (95% CI) (n = 2,334)	p-value	Model 2 OR (95% CI) (n = 328)	p-value
Main Predictor Variable				
Group				
Normal cytology	1.00		1.00	
HPV positive	1.27 (0.35, 4.62)	0.71	11.03 (1.77, 68.74)	0.01
Cervical intraepithelial neoplasia	0.86 (0.19, 3.78)	0.84	<0.001 (<0.001, —)	1.00
Demographics				
Age (years)	1.04 (0.98, 1.10)	0.22	—	—
Race/ethnicity				
White	1.00			
Black	1.82 (0.39, 8.49)	0.45	—	—
Hispanic	1.35 (0.31, 5.88)	0.69		
Asian	<0.001 (<0.001, —)	1.00		
Other	0.38 (0.03, 4.43)	0.44		
Body mass index (kg/m^2)				
Normal (18.5–24.9)	1.00		—	—
Overweight (25.0–29.9)	0.62 (0.19, 2.03)	0.43		
Obese (30 and greater)	1.09 (0.37, 3.18)	0.88		
Medical and Surgical History				
Previous uterine surgery (yes)	5.57 (2.67, 11.62)	<0.001	9.87 (1.12, 86.98)	0.04
Coagulation defect (yes)	73.87 (5.51, 990.92)	0.001	—	—
Chronic or gestational hypertension (yes)	3.14 (0.68, 14.63)	0.14	—	—
Pre-eclampsia prior to delivery (yes)	4.61 (1.42, 15.02)	0.01	<0.001 (<0.001, —)	1.00
Pre-gestational or gestational diabetes (yes)	1.47 (0.40, 5.34)	0.56	—	—
Cervical diagnostic excisional procedure (yes)	3.86 (0.45, 33.38)	0.22	—	—
Cervical insufficiency (yes)	<0.001 (<0.001, —)	1.00	—	—
Pregnancy				
Gravidity (number)	0.75 (0.59, 0.95)	0.02	1.04 (0.75, 1.43)	0.82
Parity (number)	1.15 (0.90, 1.47)	0.26	—	—
Delivery mode				
Vaginal	1.00		—	—
Operative vaginal	<0.001 (<0.001, —)	1.00		
Cesarean	1.12 (0.50, 2.51)	0.78		
Obstetric anal sphincter injuries (yes)	1.80 (0.22, 14.76)	0.59	—	—

Note: OR — odds ratio, CI — confidence interval, HPV — human papillomavirus. Model 1 included the whole sample. Model 2 included only those with an operative vaginal delivery or a cesarean delivery. Model 2 did not include the variable of coagulation as there were no people with "yes" for the variable. The assumptions for logistic regression assumptions were met, as variance inflation factor values indicated no multicollinearity concerns and the Box–Tidwell test indicated linearity of the continuous independent variables with its log odds value. Nagelkerke R-square: Model 1: 0.14, Model 2: 0.17.

Also, HPV excision procedures have a potential postoperative complication of cervical stenosis. If cervical stenosis is present, it may negatively impact cervical dilation during labor due to altered integrity and pliability of the tissue and is harder to achieve hemostasis secondary to scar formation [8]. In such a situation, a cesarean delivery may be the preferred delivery method. This can be the reason that this association of HPV positive with increased QBL and PPH occurred in the subset of operative vaginal and cesarean deliveries but not in the whole sample.

We found in the whole sample that age and obesity were each significantly associated with increased QBL but not PPH while no association occurred for age and obesity with QBL and PPH in the subset of those with operative vaginal and cesarean deliveries. Maternal age is a risk factor for PPH among those greater than 40 years old [9, 10]. Also, those with obesity are at increased risk for PPH [11]. It is possible that we did not find any association between age and PPH in the whole sample or with either QBL or PPH in the subset of those with operative vaginal and cesarean deliveries due to the average age in our study being of relatively younger patients and not of the older ages reported in previous research. We suggest that we did not find any association of obesity with PPH because of the prophylactic uterine atony prevention approach used at our hospital for those pregnant women who are obese. Administration of uterotonic agents actively combats uterine atony which is the leading cause of PPH.

Medical and surgical history variables of previous uterine surgery, chronic or gestational hypertension, pre-eclampsia, pre-gestational or gestational diabetes, and cervical insufficiency were associated with increased QBL in the whole sample while only previous uterine surgery, coagulation defect, and pre-eclampsia were associated with increased PPH in the whole sample. It is well known that previous uterine surgery is associated with increased blood loss and PPH [1]. Our findings are consistent with this pattern. Hypertensive disorders including chronic or gestational hypertension and pre-eclampsia are causes of PPH [12]. Our findings are not consistent with this pattern, as we only found an association for chronic or gestational hypertension with increased QBL but not with PPH. Our hospital follows American College of Obstetrics and Gynecology guidelines for early induction of labor for those with hypertensive disorders of pregnancy [13]. We suggest that the uterotonic agents used as part of this active management throughout induction of labor can lessen the incidence of PPH.

Increased weight of the neonate in women with diabetes leads to uterine over-distension or genital tract lacerations [14]. This can lead to increased QBL but is not a risk factor for PPH. A possible reason for the association of cervical insufficiency with increased QBL but not with PPH is because our sample size for cervical insufficiency was small and could only detect an association for the QBL continuum but not the dichotomous higher risk concern of PPH. Coagulation defect is associated with increased PPH [12]. Our findings are similar to this pattern. A possible reason for the lack of association with increased QBL is due to the very small number of only three patients with coagulation defect.

We found conflicting patterns in that increased gravidity was associated with decreased QBL, while increased gravidity was also associated with increased PPH within the whole sample. We did not find any association with parity. Previous literature does not discuss gravidity and only mentions that increased parity is a risk factor for increased PPH [9]. We suggest that the reason we did not find any association with parity is because our mean parity was low at only 1.5 and there was limited variability while other studies that have a higher mean parity have greater variability. We found conflicting findings with gravidity because PPH due to multiparity is most often associated with uterine atony [15]. If the uterus has good tone and involutes after delivery the QBL is decreased, however, if atony does occur, there is increased risk of PPH.

Obstetric anal sphincter injuries were associated with QBL in the whole sample and in the subset but not associated with PPH in either the whole sample or subset. This finding highlights the current understanding that the most common complication following perineal laceration is bleeding [16]. We suggest that the reason for an association with QBL but not PPH is because the necessary interventions including expedited repair were done to prevent PPH.

Our study has several limitations. First, only high-risk strains of HPV are collected during Pap smears and therefore no conclusions can be made on whether the presence of a low-risk HPV strain could impact QBL or PPH. Second, specific HPV strains were not collected among many patients due to an initial laboratory not providing such information. Third, we only collected Pap smears as indicated by American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines which is once every 3 or 5 years, with or without HPV, depending on the patient's age [17]. Because of this time interval, the Pap smear used in the study may not be most representative of the HPV status at delivery if such guidelines are followed. It is possible that patients with negative HPV at time of Pap smear may have acquired HPV by time of delivery.

An area of future study might include determining if QBL is associated with a particular strain of HPV. As HPV genotyping becomes more available, future research might include particular HPV strain infections as an independent risk factor for adverse pregnancy outcomes including PPH. The clinical significance of understanding such a relationship could lead to HPV status or strain being included in current risk calculation tools such as the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) hemorrhage risk-prediction tool [18, 19]. By improving the hemorrhage prediction tool, we can continue to decrease the rate of morbidity and mortality associated with PPH.

Conclusion

In conclusion, the presence of HPV was positively associated with an increase in the QBL and PPH at time of delivery for those with operative vaginal and cesarean deliveries. We suggest that clinicians take HPV results of Pap smears into consideration when considering a patient's risk of PPH.

Author contribution ctatement

M.M. — study design, data interpretation, drafting manuscript, final approval of manuscript; J.F. — study design, data analysis, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript; P.I. — study design, data acquisition, data interpretation, critically revising manuscript for important intellectual content, final approval of manuscript. All authors accept responsibility for the paper as published.

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Conflict of interest

None declared.

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