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ORIGINAL RESEARCH

The impact of human immunodeficiency virus infection on obstetric hemorrhage and blood transfusion in South Africa

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BACKGROUND: Globally, as in South Africa, obstetric hemorrhage (OH) remains a leading cause of maternal mortality and morbidity. Although blood transfusion is critical to OH management, the incidence and predictors of transfusion as well as their relation to human immunodeficiency virus (HIV) infection are poorly described.

STUDY DESIGN AND METHODS: A cross-sectional study was conducted of all peripartum patients at four major hospitals in South Africa (April to July 2012). Comprehensive clinical data were collected on patients who sustained OH and/or were transfused. Logistic regression was used to model risk factors for OH and transfusion.

RESULTS: A total of 15,725 peripartum women were evaluated, of whom 3969 (25.2%) were HIV positive. Overall, 387 (2.5%) women sustained OH and 438 (2.8%) received transfusions, including 213 (1.4%) women with both OH and transfusion. There was no significant difference in OH incidence between HIV-positive (2.8%) and HIV-negative (2.3%) patients (adjusted odds ratio [OR], 0.95; 95% confidence interval [CI], 0.72-1.25). In contrast, the incidence of blood transfusion was significantly higher in HIV-positive (3.7%) than in HIV-negative (2.4%) patients (adjusted OR, 1.52; 95% CI, 1.14-2.03). Other risk factors for transfusion included OH, low prenatal hemoglobin, the treating hospital, lack of prenatal care, and gestational age of not more than 34 weeks.

CONCLUSION: In the South African obstetric setting, the incidence of peripartum blood transfusion is significantly higher than in the United States and other high-income countries while OH incidence is similar. While OH and prenatal anemia are major predictors of transfusion, HIV infection is a common and independent contributing factor.

Obstetric hemorrhage (OH) remains a major international public health challenge and is a leading contributor to both obstetric mortality[1-3] and severe acute maternal morbidity.[4] Frequent, unanticipated OH is directly related to absent or deficient obstetric care.[5] Lack of early recognition of risk factors for primary or recurrent OH[3] as well as failure to provide effective pre- and peripartum care contribute

to adverse maternal outcomes.[2] Consequently, morbidity and mortality due to OH are primarily encountered in resource-poor countries; this is the case in South Africa.[6,7]

Studies suggest that lack of blood for transfusion contributes to one-quarter of OH-related deaths and/or "near misses" (severe acute maternal morbidity) in sub-Saharan Africa,[1] underscoring the critical role of blood transfusion in obstetric care. Furthermore, the International Confederation of Midwives and the International Federation of Gynecology and Obstetrics recommend that there be "blood transfusion facilities in all centers that provide comprehensive health care."[2] While the importance of blood transfusion in obstetric practice is widely accepted,[8] published data on the incidence and clinical use of blood transfusion in obstetric settings are lacking. Pertinent to South Africa, where up to 30% of pregnant women are human immunodeficiency virus (HIV) positive,[9,10] the transfusion practices in HIV-positive OH patients have not been studied. Furthermore, blood transfusion reflects a complicated peripartum course,[11,12] and an improved understanding of the risk factors for OH and peripartum transfusion may serve to identify deficiencies in care, thus informing corrective interventions.

Therefore, we conducted a cross-sectional study of all peripartum women who presented to four major obstetric hospitals in South Africa to investigate the risk factors for OH and/or peripartum blood transfusion. In addition, we took advantage of the study to gather contemporary data on HIV prevalence and treatment to ascertain compliance with current HIV treatment guidelines in the South African obstetric population.

MATERIALS AND METHODS

Study design and subjects

A cross-sectional study was conducted over a 4-month period (April to July 2012) on all deliveries at four major hospitals in South Africa: Chris-Hani Baragwanath Hospital (CHB) in Johannesburg, King Edward VIII Hospital (KEH) in Durban, and Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH) in Cape Town. The study received ethical approval from the relevant committees at the participating hospitals in addition to the University of California at San Francisco, the South African National Blood Service (SANBS), and RTI International. Written informed consent was elicited from all women presenting at CHB; a waiver of consent for collection of existing data was granted at the other three hospitals.

The obstetric services at the four sites serve low-income, predominantly black-African and colored women (colored in South Africa denotes a specific mixed-race population group). The four sites have major second-tier or tertiary obstetric services and the patients reflect a generally urban, high-HIV-prevalence population in South Africa. We excluded patients who did not consent (CHB only), who were either transferred or discharged before data could be gathered, or who left prematurely against medical advice.

Trained research personnel enrolled all peripartum obstetric patients with an index hospitalization at any of the four hospitals during the study period. Limited denominator data from all patients were collected on a ledger-style form. The minority of patients who sustained OH and/or were transfused in the peripartum period were identified through daily review of ward admission logs and maternity, delivery, and operating room registers, in combination with direct communication with the blood bank and ward staff. More extensive clinical data were collected on these patients using a newly designed obstetric hemorrhage audit tool. Both machine-readable paper forms (available on request from the authors) were scanned for data entry, and electronic data were transferred to the data-coordinating center for cleaning and analysis. All data were collected either concurrently with the patients' admissions or soon after discharge.

Definitions

"OH" was defined as any obstetric-related hemorrhage occurring in the peripartum period of 48 hours before or after delivery. We used the World Health Organization (WHO) definition of peripartum hemorrhage as at least 500 mL of blood loss for vaginal delivery or at least 1000 mL blood loss for cesarean section. We included live births as well as births associated with stillborn fetuses and early neonatal deaths; however, data collection was restricted to women that were at least 26 weeks' gestation. "Transfusion" was defined as having received any allogeneic blood product, that is, red blood cells (RBCs), platelets (PLTs), plasma, and/or cryoprecipitate, during the peripartum period. "Booked" refers to patients who had had antenatal care during the index pregnancy; in contrast, "unbooked" refers to patients who had not had antenatal care during the index pregnancy. The prenatal hemoglobin (Hb) value that was used was the most recently measured Hb before delivery: 40 and 58% of prenatal Hb values were within 3 and 30 days of delivery, respectively.

At the time of the study the national policy was to administer three-drug antiretroviral therapy (ART) to all HIV-positive pregnant patients with a CD4 count of fewer than 350×10^6 cells/L or with a WHO staging of III or IV. The prevention of mother-to-child transmission (PMTCT) regimen referred to the use of limited monotherapy during the antenatal period and additional ART at the time of delivery and was recommended in HIV-positive patients not fulfilling the criteria for ART, or for patients with HIV presenting for the first time in labor.

TABLE 1. Characteristics of the peripartum women included in the study, overall and by hospital, South Africa, 2012*

Ledger variable	All subjects	CHB	KEH	MMH	GSH
All subjects	15,725	7,548 (48.0)	2,441 (15.5)	4,336 (27.6)	1,400 (8.9)
Age (years)					
≤19	2,067 (13.1)	1,087 (14.4)	357 (14.6)	519 (12.0)	104 (7.4)
20-24	4,402 (28.0)	2,183 (28.9)	747 (30.6)	1,238 (28.6)	234 (16.7)
25-29	4,252 (27.0)	1,898 (25.1)	693 (28.4)	1,245 (28.7)	416 (29.7)
30-34	2,834 (18.0)	1,284 (17.0)	383 (15.7)	813 (18.8)	354 (25.3)
35-39	1,624 (10.3)	812 (10.8)	210 (8.6)	393 (9.1)	209 (14.9)
40+	506 (3.2)	276 (3.7)	46 (1.9)	103 (2.4)	81 (5.8)
Missing	40 (0.3)	8 (0.1)	5 (0.2)	25 (0.6)	2 (0.1)
Race					
Black	10,786 (68.6)	7,470 (99.0)	2,253 (92.3)	854 (19.7)	209 (14.9)
Colored	596 (3.8)	22 (0.3)	32 (1.3)	382 (8.8)	160 (11.4)
Asian	134 (0.9)	3 (0.0)	34 (1.4)	68 (1.6)	29 (2.1)
White	45 (0.3)	1 (0.0)	31 (1.3)	10 (0.2)	3 (0.2)
Missing	4,164 (26.5)	52 (0.7)	91 (3.7)	3,022 (69.7)	999 (71.4)
Prenatal visit					
Booked	15,058 (95.8)	7,291 (96.6)	2,361 (96.7)	4,110 (94.8)	1,296 (92.6)
Unbooked	574 (3.7)	257 (3.4)	65 (2.7)	151 (3.5)	101 (7.2)
Missing	93 (0.6)	0 (0.0)	15 (0.6)	75 (1.7)	3 (0.2)
Type of delivery					
Vaginal	9,117 (58.0)	4,773 (63.2)	1,152 (47.2)	2,567 (59.2)	625 (44.6)
C-section	6,362 (40.5)	2,653 (35.1)	1,220 (50.0)	1,733 (40.0)	756 (54.0)
BBA	191 (1.2)	121 (1.6)	42 (1.7)	16 (0.4)	12 (0.9)
Missing	55 (0.3)	1 (0.0)	27 (1.1)	20 (0.5)	7 (0.5)
Gravidity (includes current pregnancy)					
1	5,215 (33.2)	2,647 (35.1)	717 (29.4)	1,505 (34.7)	346 (24.7)
2	4,738 (30.1)	2,285 (30.3)	766 (31.4)	1,296 (29.9)	391 (27.9)
3	3,198 (20.3)	1,495 (19.8)	563 (23.1)	834 (19.2)	306 (21.9)
4+	2,524 (16.1)	1,120 (14.8)	377 (15.4)	671 (15.5)	356 (25.4)
Missing	50 (0.3)	1 (0.0)	18 (0.7)	30 (0.7)	1 (0.1)
Parity (before current delivery)					
0	5,674 (36.1)	2,949 (39.1)	787 (32.2)	1,533 (35.4)	405 (28.9)
1	5,017 (31.9)	2,355 (31.2)	799 (32.7)	1,406 (32.4)	457 (32.6)
2	3,070 (19.5)	1,398 (18.5)	543 (22.2)	832 (19.2)	297 (21.2)
3	1,239 (7.9)	563 (7.5)	192 (7.9)	341 (7.9)	143 (10.2)
4+	696 (4.4)	282 (3.7)	116 (4.8)	201 (4.6)	97 (6.9)
Missing	29 (0.2)	1 (0.0)	4 (0.2)	23 (0.5)	1 (0.1)
HIV status					
Missing/unknown	130 (0.8)	9 (0.1)	21 (0.9)	96 (2.2)	4 (0.3)
Negative	11,626 (73.9)	5,362 (71.0)	1,517 (62.1)	3,598 (83.0)	1,149 (82.1)
Positive	3,969 (25.2)	2,177 (28.8)	903 (37.0)	642 (14.8)	247 (17.6)
CD4 count (×10⁶/L)					
≥350	1,715 (10.9)	887 (11.8)	393 (16.1)	318 (7.3)	117 (8.4)
<350 and ≥200	1,112 (7.1)	545 (7.2)	312 (12.8)	182 (4.2)	73 (5.2)
<200	663 (4.2)	345 (4.6)	185 (7.6)	89 (2.1)	44 (3.1)
Missing/unknown	479 (3.0)	400 (5.3)	13 (0.5)	53 (1.2)	13 (0.9)

* Data are reported as number (%). Column percentages are shown except for the top row.
BBA = born before arrival in hospital; C-section = cesarean section.

Statistical analysis

The descriptive analysis generated counts and percentages for categorical data and distributions for continuous variables. For categorical data, counts and percentages for single variables and combinations of variables were produced, using chi-squared tests of significance. For the continuous data, distributions were examined individually and stratified by covariates, using t tests to test differences between means.

Multivariable modeling was conducted using logistic regression. The primary outcome variables were binary while the predictor variables were categorical or ordinal.

A larger set of variables was initially considered. The model was refined using backward elimination at the $p = 0.05$ level to retain variables. Once a set of variables was identified, interactions were investigated. Computer software (SAS 9.3; TS1M2; SAS Institute, Cary, NC) with enhance analytic product (SAS/STAT 12.1, SAS Institute, Inc., 2011) was used for the data manipulation and analysis; another program (R, version 3.0.1, "Good Sport," R Core Team 2013, http://www.r-project.org/) was used for the data visualization. Finally, the models were tested for calibration using the Hosmer-Lemeshow test for goodness of fit.

TABLE 2. Characteristics of patients with OH and transfusion compared to those without each condition*				
Ledger variable	No hemorrhage	Hemorrhage	No transfusion	Transfusion
Total				
All subjects	15,283 (97.5)	387 (2.5)	15,232 (97.2)	438 (2.8)
Age (years)		(p = 0.0535)		(p = 0.4921)
Missing	27 (73.0)	10 (27.0)	29 (78.4)	8 (21.6)
≤19	2,012 (98.0)	42 (2.0)	1,993 (97.0)	61 (3.0)
20-24	4,305 (98.1)	84 (1.9)	4,286 (97.7)	103 (2.3)
25-29	4,130 (97.4)	109 (2.6)	4,122 (97.2)	117 (2.8)
30-34	2,747 (97.2)	79 (2.8)	2,739 (96.9)	87 (3.1)
35-39	1,572 (97.1)	47 (2.9)	1,572 (97.1)	47 (2.9)
40+	490 (96.8)	16 (3.2)	491 (97.0)	15 (3.0)
Race				
Missing	4,035 (97.5)	102 (2.5)	4,017 (97.1)	120 (2.9)
Asian	129 (96.3)	5 (3.7)	131 (97.8)	3 (2.2)
Black	10,505 (97.6)	253 (2.4)	10,469 (97.3)	289 (2.7)
Colored	569 (95.5)	27 (4.5)	570 (95.6)	26 (4.4)
White	45 (100.0)	0 (0.0)	45 (100.0)	0 (0.0)
Gravidity (including current pregnancy)		(p < 0.0001)		(p = 0.0017)
Missing	48 (100.0)	0 (0.0)	48 (100.0)	0 (0.0)
1	5,100 (98.2)	91 (1.8)	5,063 (97.5)	128 (2.5)
2	4,609 (97.5)	120 (2.5)	4,614 (97.6)	115 (2.4)
3	3,097 (97.1)	91 (2.9)	3,089 (96.9)	99 (3.1)
4+	2,429 (96.6)	85 (3.4)	2,418 (96.2)	96 (3.8)
Parity (before current delivery)		(p = 0.0008)		(p = 0.0222)
Missing	26 (100.0)	0 (0.0)	26 (100.0)	0 (0.0)
0	5,546 (98.1)	105 (1.9)	5,514 (97.6)	137 (2.4)
1	4,881 (97.5)	125 (2.5)	4,875 (97.4)	131 (2.6)
2	2,963 (96.8)	97 (3.2)	2,961 (96.8)	99 (3.2)
3	1,197 (97.1)	36 (2.9)	1,186 (96.2)	47 (3.8)
4+	670 (96.5)	24 (3.5)	670 (96.5)	24 (3.5)
Birthweight (g)		(p = 0.0023)		(p < 0.0001)
Missing	11 (91.7)	1 (8.3)	9 (75.0)	3 (25.0)
≤2100	1,590 (96.4)	59 (3.6)	1,539 (93.3)	110 (6.7)
2105-2525	1,505 (97.4)	40 (2.6)	1,501 (97.2)	44 (2.8)
2530-2760	1,536 (98.1)	30 (1.9)	1,522 (97.2)	44 (2.8)
2765-2925	1,548 (98.2)	29 (1.8)	1,538 (97.5)	39 (2.5)
2930-3060	1,517 (98.1)	29 (1.9)	1,526 (98.7)	20 (1.3)
3065-3190	1,563 (97.9)	33 (2.1)	1,565 (98.1)	31 (1.9)
3195-3320	1,510 (98.2)	28 (1.8)	1,507 (98.0)	31 (2.0)
3323-3480	1,532 (97.4)	41 (2.6)	1,535 (97.6)	38 (2.4)
3485-3700	1,518 (97.0)	47 (3.0)	1,525 (97.4)	40 (2.6)
3705+	1,453 (96.7)	50 (3.3)	1,465 (97.5)	38 (2.5)
Gestational age (weeks)		(p < 0.0001)		(p < 0.0001)
Missing	48 (100.0)	0 (0.0)	48 (100.0)	0 (0.0)
≤34	1,860 (96.1)	75 (3.9)	1,804 (93.2)	131 (6.8)
35-36	1,402 (97.0)	43 (3.0)	1,402 (97.0)	43 (3.0)
37	1,498 (97.0)	47 (3.0)	1,497 (96.9)	48 (3.1)
38	2,474 (97.4)	65 (2.6)	2,471 (97.3)	68 (2.7)
39	2,095 (98.1)	41 (1.9)	2,101 (98.4)	35 (1.6)
40	4,237 (98.1)	80 (1.9)	4,235 (98.1)	82 (1.9)
41	1,313 (98.1)	26 (1.9)	1,317 (98.4)	22 (1.6)
42+	356 (97.3)	10 (2.7)	357 (97.5)	9 (2.5)
Hospital		(p < 0.0001)		(p < 0.0001)
CHB	7,332 (97.2)	215 (2.8)	7,357 (97.5)	190 (2.5)
GSH	1,332 (95.6)	61 (4.4)	1,307 (93.8)	86 (6.2)
KEH	2,382 (98.7)	32 (1.3)	2,334 (96.7)	80 (3.3)
MMH	4,237 (98.2)	79 (1.8)	4,234 (98.1)	82 (1.9)
Delivery		(p = 0.2853)		(p = 0.0074)
BBA	186 (97.4)	5 (2.6)	179. (93.7)	12 (6.3)
C-section	6,190 (97.3)	172 (2.7)	6,176 (97.1)	186 (2,9)
Vaginal	8,907 (97.7)	210 (2.3)	8,877 (97.4)	240 (2.6)
Prenatal care		(p < 0.0001)		(p < 0.0001)
Missing	85 (100.0)	0 (0.0)	83 (97.6)	2 (2.4)
Booked	14,664 (97.6)	355 (2.4)	14,639 (97.5)	380 (2.5)
Unbooked	534 (94.3)	32 (5.7)	510 (90.1)	56 (9.9)
HIV status		(p = 0.0776)		(p < 0.0001)
Missing	368 (97.1)	11 (2.9)	363 (95.8)	16 (4.2)
Negative	11,074 (97.7)	264 (2.3)	11,064 (97.6)	274 (2.4)
Positive	3,841 (97.2)	112 (2.8)	3,805 (96.3)	148 (3.7)

Table 2: *Continued*				
Ledger variable	No hemorrhage	Hemorrhage	No transfusion	Transfusion
CD4 category ($\times 10^6$/L)		(p = 0.01350)		(p = 0.6938)
Missing	457 (95.8)	20 (4.2)	459 (96.2)	18 (3.8)
<200	648 (98.3)	11 (1.7)	631 (95.8)	28 (4.2)
200-349	1,072 (96.8)	36 (3.2)	1,066 (96.2)	42 (3.8)
350+	1,664 (97.4)	45 (2.6)	1,649 (96.5)	60 (3.5)

* Data are reported as number (%). Row percentages and chi-squared p values are shown. Fifty-five women without valid data on OH and transfusion were excluded from the table. Chi-square test was not performed due to high proportion of missing data in the race category.
BBA = born before arrival in hospital; C-section = cesarean section.

RESULTS

We included 15,725 women over 4 months from April to July 2012. A total of 15,670 patients had valid data for hemorrhage and transfusion. These numbers reflect the exclusion of approximately 12% of peripartum women at one hospital (CHB) due to lack of consent mostly due to inability to contact patients; refusals were rare. The majority of women were aged 20 to 29 and of black race; data on race were not provided on many patients at two hospitals (Table 1). Among all women, 25.2% were HIV positive (prevalence varied by site from 14.8% at MMH to 37% at KEH) and 95.8% had received at least some antenatal care (booked). Fifty-eight percent had vaginal deliveries, 40.5% had cesarean sections, and 1.2% of patients delivered before arrival at the hospital. Mode of delivery differed by HIV status, with cesarean sections performed in 44% of HIV-positive patients compared to 41% of HIV-negative patients (p = 0.0008).

A total of 387 (2.5%) women sustained OH and 438 (2.8%) were transfused; included in these were 213 (1.4%) women with both OH and transfusion (Table 2). The incidence of OH by hospital was 1.3, 1.8, 2.8, and 4.4% at KEH, MMH, CHB, and GSH, respectively. In unadjusted analyses, OH was significantly associated with treating hospital, gestational age, gravidity, parity, prenatal care, and birthweight (Table 2).

The incidences of transfusion were 1.9, 2.5, 3.3, and 6.2% at MMH, CHB, KEH, and GSH, respectively. Transfusion occurred in more HIV-positive (3.7%) than HIV-negative (2.4%) patients. In unadjusted analyses, women aged 20 to 24 years were less likely to receive transfusions compared to other age groups and the incidence of transfusion was positively associated with both parity and HIV infection. Women who received transfusions received a mean of 2.28 RBC, 0.28 plasma, and 0.08 PLT units. No cryoprecipitate was transfused during the study. In those patients who received transfusions, the number of RBC units received did not differ significantly by HIV status.

In the multivariable analysis of risk factors for OH (Table 3), HIV status was not associated with OH (odds ratio [OR], 0.95; Wald 95% CI, 0.72-1.25). The odds of OH were significantly lower in patients who delivered at KEH and MMH compared to CHB. Other risk factors for OH included prenatal Hb less than or equal to 9.2 g/dL, receiving no prenatal care, higher birthweight, low gestational age, and high gravidity. Interestingly, patients who were HIV positive with a CD4 count of fewer than 200 $\times$ 10^6 cells/L were less likely to sustain OH compared to those who were HIV negative (data not shown).

In the multivariable model of risk factors for transfusion, OH was the strongest risk factor for blood transfusion and there was an interaction between OH and prenatal Hb with OH having the most pronounced effect at the lowest levels of antenatal Hb (Table 4 and Fig. 1). In contrast to the findings for OH, HIV status was associated with blood transfusion (adjusted OR, 1.52; 95% CI, 1.14-2.03). Blood transfusion was also significantly more likely to occur at GSH and KEH compared to CHB. Other risk factors significantly associated with blood transfusion included a lack of prenatal care (being unbooked) and low gestational age. Notably, mode of delivery (cesarean section vs. normal vaginal delivery) was not retained as a significant risk factor in the final logistic regression model. Because of the association between HIV infection and transfusion, we explored models with other HIV variables. A model substituting HIV treatment found an association between transfusion and combination ART (but not short-course PMTCT) when compared to no-therapy or HIV-negative patients.

The mean Hb on hospital admission or at the last prenatal visit was 11.4 g/dL in HIV-negative and 11.0 g/dL in HIV-positive patients (p < 0.0001; Fig. 2). This small difference in means translated to significant differences in the proportion of anemic patients using the cutoff of 11g/dL: 36% for HIV-negative and 47% for HIV-positive patients (p < 0.0001). Mean Hb increased slightly with age and differed by hospital: 10.6, 11.3, 11.4, and 11.5 g/dL at KEH, GSH, MMH, and CHB, respectively. In contrast, the respective mean pretransfusion (posttransfusion) Hb values were 7.8 (10.3), 7.5 (9.1), 7.0 (9.0), and 7.7 (8.8) g/dL. The difference in pre- and posttransfusion Hb was associated with hospital (highest at KEH) and age (a linear decrease was observed with advancing age; data not shown).

TABLE 3. Multivariable logistic regression model of OH*		
Variable	OR	95% CI
Hospital (< 0.0001)		
CHB	1.00	
GSH	1.19	0.84-1.67
KEH	0.38	0.25-0.56
MMH	0.68	0.51-0.91
Age, years (0.9620)		
≤19	1.00	
20-24	0.90	0.59-1.36
25-29	1.02	0.66-1.60
30-34	0.95	0.58-1.55
35-39	0.89	0.51-1.54
40+	0.98	0.48-1.97
Hb, g/dL (<0.0001)		
≤9.2	3.16	2.03-4.90
9.3-10.0	1.49	0.91-2.44
10.1-10.5	1.39	0.83-2.34
10.6-11.0	1.00	
11.1-11.4	0.96	0.55-1.69
11.5-11.8	1.16	0.69-1.97
11.9-12.2	1.21	0.73-2.01
12.3-12.6	1.06	0.61-1.84
12.7-13.3	1.24	0.75-2.06
13.4+	0.75	0.42-1.35
Prenatal care (<0.0001)		
Booked	1.00	
Unbooked	2.56	1.59-4.10
Birthweight, g (0.0008)		
≤2100	1.00	
2105-2525	1.19	0.73-1.94
2530-2760	0.99	0.56-1.75
2765-2925	1.11	0.62-1.98
2930-3060	1.03	0.56-1.90
3065-3190	1.21	0.67-2.20
3195-3320	1.15	0.62-2.13
3323-3480	1.83	1.04-3.23
3485-3700	2.06	1.17-3.62
3705+	2.57	1.47-4.47
Gestational age, weeks (0.0030)		
≤34	2.37	1.47-3.84
35-36	1.54	0.97-2.44
37	1.75	1.16-2.66
38	1.25	0.86-1.82
39	0.86	0.57-1.32
40	1.00	
41	0.88	0.54-1.43
42+	1.31	0.64-2.68
HIV status (0.7233)		
No	1.00	
Yes	0.95	0.72-1.25
Gravidity (0.0493)		
1	1.00	
2	1.25	0.89-1.74
3	1.41	0.96-2.07
4+	1.79	1.19-2.70

* ORs with 95% CI are shown, and the p value for association of each variable with OH is shown in the left-hand column.

| TABLE 4. Multivariable logistic regression model of risk factors for blood transfusion with an interaction between OH and Hb*		
Variable	OR	95% CI
Hospital (0.0064)		
CHB	1.00	
GSH	1.84	1.24-2.72
KEH	1.50	1.03-2.17
MMH	1.03	0.73-1.45
Age, years (0.8026)		
≤19	1.00	
20-24	0.74	0.49-1.12
25-29	0.79	0.52-1.20
30-34	0.88	0.56-1.37
35-39	0.79	0.47-1.33
40+	0.80	0.37-1.75
Gestational age, weeks (<0.0001)		
≤34	2.90	1.98-4.25
35-36	1.07	0.64-1.79
37	1.53	0.95-2.45
38	1.36	0.89-2.08
39	0.75	0.44-1.27
40	1.00	
41	1.19	0.67-2.12
42+	1.30	0.52-3.26
HIV status (0.0046)		
Negative	1.00	
Positive	1.52	1.14-2.03
Prenatal care (<0.0001)		
Booked	1.00	
Unbooked	2.77	1.68-4.56
Hb, g/dL (p < 0.0001), by hemorrhage (p < 0.0001) interaction (p = 0.0198)		
With OH: Hb (g/dL)		
≤9.2	467.0	200.1->999.9
9.3-10.0	928.2	317.1->999.9
10.1-10.5	217.6	79.8-593.1
10.6-11.0	264.7	95.2-736.1
11.1-11.4	163.3	54.0-493.8
11.5-11.8	150.8	53.7-423.6
11.9-12.2	287.4	106.3-777.1
12.3-12.6	160.9	53.9-480.1
12.7-13.3	94.1	34.6-256.0
13.4+	158.9	50.0-505.1
Without OH: Hb (g/dL)		
≤9.2	9.3	4.6-18.8
9.3-10.0	2.9	1.3-6.3
10.1-10.5	2.4	1.0-5.6
10.6-11.0 (ref. cell)	1.0	
11.1-11.4	1.6	0.6-4.0
11.5-11.8	2.5	1.1-5.7
11.9-12.2	1.6	0.7-3.8
12.3-12.6	1.4	0.5-3.7
12.7-13.3	1.8	0.8-4.4
13.4+	1.9	0.8-4.7

* ORs with 95% CIs are shown, and the p value for association of each variable with transfusion is shown in the left-hand column.

Among HIV-positive patients, 50.9% had a CD4 count of fewer than 350×10^6 cells/L. Of these, 81.2% received ART and an additional 14.5% received PMTCT. Among all HIV-positive women, ART or PMTCT was administered in 93.1% of cases. Women who failed to access antenatal care were less likely to have received (necessary) ART, although similar rates of PMTCT were observed.

DISCUSSION

These findings show that the incidence of OH in South Africa is similar to that reported in the United States (2.3%-2.9%)[13] and is not associated with HIV status. In contrast, the incidence of blood transfusion is up to 10-
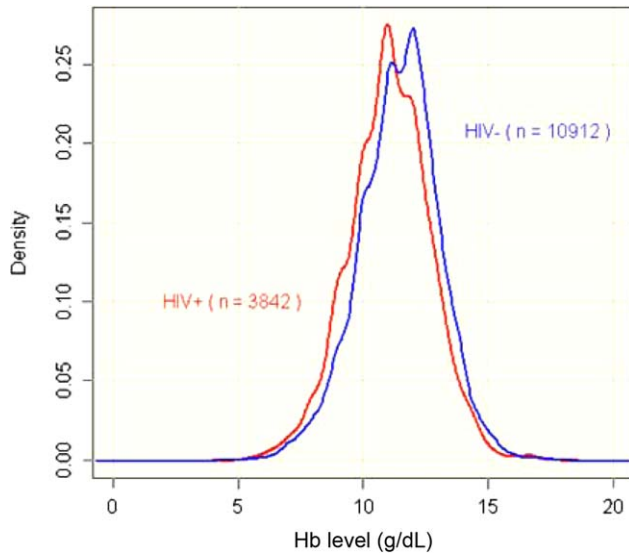
Fig. 1. Prenatal Hb by HIV status. The proportion of each subgroup with each value of Hb is indicated on the Y axis. Mean Hb was 11.4 g/dL among HIV-negative and 11.0 g/dL among HIV-positive peripartum women.

fold higher than that reported in the United States (0.24%-0.46%)[14] and is also high as compared to several other high-middle-income countries.[11,15] While high rates of transfusion were observed in all patients, transfusion incidence was significantly higher in HIV-positive patients after controlling for potential confounders such as age, parity, hospital, and mode of delivery. The study also demonstrated good compliance with the current South African obstetric HIV management guidelines whereby the overwhelming majority of HIV positive patients received either therapeutic ART and/or PMTCT.

In South Africa, OH is the third leading cause of maternal death, and mortality rates associated with OH have escalated over the past decade.[16] From 2008 to 2010, there were 688 deaths attributable to OH in South Africa, representing an increase of 32.4% (18.82–24.91/100,000 live births) compared with 2005 to 2007. The majority of deaths were deemed to have been avoidable and 13.2% were attributed to lack of adequate blood transfusion. This spurred efforts to improve access to blood transfusion in the obstetric setting, such as placement of emergency group O blood in refrigerators at district hospitals where more than one-third of OH-related deaths reportedly occur.[16] While this has helped to improve availability of blood, obstetric blood utilization continues to place a significant demand on the South African blood transfusion services.

Mortality ascribed to OH in high resource settings is comparatively low and has been relatively static over recent decades.[17] For example, OH mortality in Australia during 2003 to 2005 was 8.4 per 100,000 live births.[3] In contrast, morbidity due to OH, which is estimated to be

100-fold more common than OH-associated death,[13,17] may be increasing.[12,18,19] However, data on nonfatal OH and consequent morbidity are sparse and impeded by variability in the definition of OH and measurement of peripartum blood loss. Reliable international and regional data are needed to inform public health intervention, particularly in Africa.[20]

In contrast to our a priori expectations, the study found that the incidence of OH in South Africa either approximates or is lower than rates reported from high-income countries.[18,20,21] For example, the OH incidence in the United States was 2.3% in 1994 and 2.9% in 2006,[22] which is similar to the rates observed in our study. In contrast, the rates of blood transfusion in South Africa were found to be 5- to 10-fold higher than that reported from the United States, despite US rates having increased from 2.38 to 4.58 per 1000 deliveries between 1998 to 1999 and 2004 to 2005, which was ascribed to a general increase in US blood utilization over a similar time period.[23] More than half of women with OH in our study were transfused; by comparison, only 11.7% of women with OH in Australia are transfused.[21]

A major finding of this study was the significantly higher risk of peripartum transfusion in HIV-positive patients after controlling for known confounders. We postulate that this association may reflect a high prevalence of unaddressed antenatal anemia as evidenced by significant differences in mean prenatal Hb and proportion anemic between HIV-positive and -negative patients. The association between HIV and anemia is well described[24-26] and has a multitude of causes, which includes direct effects of the virus itself, infection,
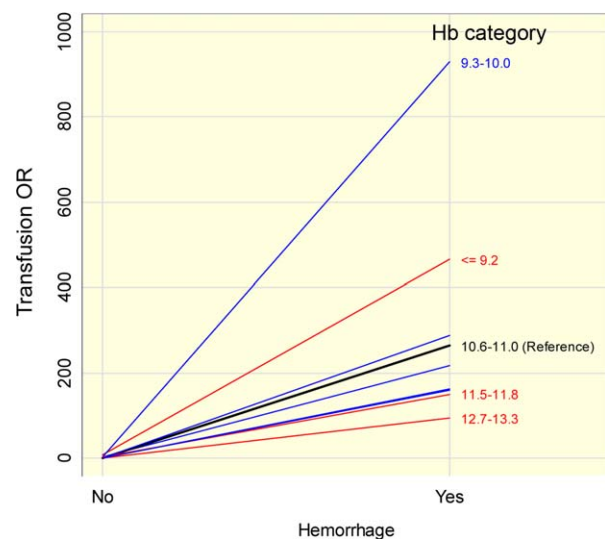
Fig. 2. OR for blood transfusion, according to OH status and prenatal Hb level. OH carries a very strong odds of transfusion, especially in women in the two lowest categories of prenatal Hb.

neoplasia, and therapy (e.g., ART). While severe anemia is an indication for blood transfusion, it also renders patients less likely to tolerate bleeding at time of delivery and may exacerbate bleeding once initiated due to the adverse rheologic effects of a low hematocrit on hemostasis.[27] This hypothesis is supported by the observed interaction between prenatal Hb and OH in relation to transfusion: women with the lowest prenatal Hb showed the greatest impact of OH on their risk of receiving a transfusion. South African maternal mortality reports also show that more than one-third of OH-related deaths have underlying anemia.[16] Thus, anemia due to HIV disease itself or to ART seems the likely reason for the higher rates of transfusion in HIV-positive patients. HIV-related coagulopathy and institutional or physician-specific variability in transfusion practice for HIV-positive versus -negative patients are other plausible explanations that warrant future evaluation.

Variability in transfusion practice may be contributing to the high rates of transfusion. While not unique to South Africa, the decision to transfuse is informed both by laboratory variables (primarily the Hb) as well as the patient's symptoms and signs (presence of symptomatic anemia). Although South Africa has national transfusion guidelines, they do not establish specific thresholds for transfusion, instead suggesting that "patients with a Hb level below 7g/dl often require a transfusion." In the context of OH, the guidelines recommend that patient's Hb values be "maintained between 6 and 10g/dl during the resuscitation phase."[28] Our study did not evaluate compliance with guidelines directly; however, the observed pretransfusion Hb values and transfusion delta (post- minus pretransfusion Hb) do suggest that there is general compliance with those guidelines. Differences in pre- and posttransfusion Hb levels between hospitals show some variability in transfusion practice that may benefit from targeted blood management interventions such as the use of 1-unit versus 2-unit blood orders. Importantly, the observed high rates of transfusion in our study are notable for having occurred in a setting where blood inventories are constantly strained: during the study period, SANBS operated on an average blood reserve of 3.88 days (2.2-6.5 days; M. Vermeulen, SANBS, personal communication, 2014).

Obstetric transfusion was also associated with the treating hospital, lower gestational age, and the absence of prenatal care. The comparatively high rate of transfusion at GSH may be consistent with this hospital's status as a high-risk obstetric referral unit, as we were unable to fully adjust for comorbidity in our multivariable model. Reasons for higher adjusted odds of transfusion at KEH are less clear and may be attributable to a high prevalence of HIV and anemia in the hospital's population. Lack of prenatal care is a recognized risk factor for complications during pregnancy and delivery,[16,29] whereby the absence of prenatal care precludes timely diagnosis and intervention of complicating conditions (e.g., multiple pregnancy, placenta previa, anemia), several of which could require transfusion if neglected.

This study used the opportunity to gather contemporary data on HIV prevalence and treatment in the obstetric setting. HIV/AIDS is currently the leading cause of peripartum mortality in South Africa.[30] Twenty-five percent of patients in our study were HIV positive and the observed differences by hospital (Table 1) mirror regional differences in national HIV surveillances.[31] Effective management of HIV in pregnancy with three-drug ART significantly reduces the rate of mother to child transmission of HIV to under 2%.[32] However, South Africa was relatively late in adopting the WHO recommendations on initiation of ART at a CD4 count of not more than $350 \times 10^6/L$[33] and, as of 2010, there were an estimated 213,800 HIV-infected mothers still in need of PMTCT,[33] in addition to 1,584,000 adult infections that require ART. Nevertheless, our 2012 data demonstrate good ARV and PMTCT penetrance in the obstetric setting, consistent with recent public health priorities in South Africa.[31,34] Fully 81% of women with a CD4 count of fewer than 350×10^6 cells/L were on ARV therapy and almost all of those not on routine therapeutic ARVs received PMTCT.

Despite its contributions, there are several limitations to our study. First, data sources in the hospitals were often incomplete leading to missing data and there was variability as to when prenatal Hb levels were measured. The prenatal Hb values were used as a substitute for the pretransfusion Hb values, when the latter had not been obtained; a proportion of the prenatal Hb values had been collected over 30 days before delivery. Second, while we adhered to a standard definition of OH, we did not assess compliance with the WHO definition and recognize that the estimation of blood loss is often inaccurate and nonreproducible.[2,35-38] Third, our four large urban hospitals allowed efficient capture of data on a large number of deliveries, but do not represent the full spectrum of obstetric care in South Africa, in particular, more rural, underresourced settings. Our focus on secondary- and tertiary-level hospitals may also account for the comparatively high rate of cesarean sections; in contrast to our study, the rate of cesarean section in district hospitals is approximately 18.8%. Finally, we restricted the study to OH in the context of viable pregnancies around time of delivery and did not capture data on maternal hemorrhage that occurs in nonviable pregnancies, for example, spontaneous abortions and ectopic pregnancies.

In conclusion, this study has demonstrated similar rates of OH but disproportionately high rates of transfusion in peripartum patients in South Africa relative to developed countries and identified HIV as a risk factor for transfusion. While the findings suggest that antenatal anemia may underlie the high risk of transfusion,

coagulopathy and variation in transfusion practice in care of HIV-positive patients also warrant investigation. The findings also show good compliance with HIV prescribing guidelines despite earlier delays in implementation. Future directions include the application of this study's approach to other settings, allowing validation and extension of our findings. If replicated, the study's findings suggest that systematic treatment of prenatal anemia may be a viable intervention to prevent peripartum blood transfusion.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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