Outcomes associated with transfusion in low-risk women with obstetric haemorrhage

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Running Head: Outcomes of obstetric transfusion

Abstract:

Background and objectives: Obstetric haemorrhage is associated with increased blood transfusion, morbidity and health service usage in women. While the use of transfusion in actively bleeding patients is supported, there is little evidence for the use of blood as treatment in the non-bleeding patient following obstetric haemorrhage. Transfusion may expose women to increased morbidity. This study aims to compare outcomes between low-risk women receiving no or 1-2 units of blood in the context of obstetric haemorrhage.

Materials and methods: The study population included women giving birth in hospital in New South Wales, Australia, between July 2006 and December 2010, with a diagnosis of obstetric haemorrhage. Women with medical or obstetric conditions making them high risk were excluded, as were women receiving more than 2 units of blood. Data were obtained from linked hospital, birth and blood bank databases. Propensity score matching was used to compare outcomes between transfused and non-transfused women in order to estimate the impact of the transfusion itself on outcomes.

Results: There were 14989 women with obstetric haemorrhage, of whom, 1702 received a transfusion, including 1069 receiving a transfusion of 1-2 units. Women receiving transfusion were more likely to experience severe maternal morbidity (relative risk 7.0, 95% Confidence interval (2.8,17.8)), be admitted to intensive care (RR 2.1 95% CI(1.2,3.8)), and have a length of stay >5 days (RR 2.0, 95% CI (1.6,2.5)).

Conclusions: Small volume transfusion in the context of obstetric haemorrhage among low-risk women is associated with poorer maternal outcomes and increased healthcare utilisation.

Excessive bleeding around the time of childbirth (including antepartum, intrapartum and postpartum haemorrhage, termed obstetric haemorrhage) is associated with increased morbidity and longer hospital stays compared to women without haemorrhage. Rates of postpartum haemorrhage (5-15% of births) [1], the main contributor to obstetric haemorrhage, are increasing in the United States, Canada, Australia, and elsewhere.[2-5]. Rates of red blood cell (RBC) transfusion in pregnancy and postpartum range from 0.1-2%,[6, 7] however these have also been increasing.[8] There is little evidence guiding transfusion in obstetric patients, with current guidelines based around expert opinion and trials in non-pregnant patients. [9]

There is growing concern that transfused patients have poorer outcomes compared with similar patients not receiving transfusions. Observational studies and randomised trials have found transfusion to be associated with adverse outcomes including increased mortality, wound infection, sepsis, pneumonia, organ failure, and mechanical ventilation. [10-15] However, a Cochrane review of randomised trials comparing liberal and restrictive transfusion strategies reports no difference in mortality and morbidity[16].These findings, in combination with concerns about the decreasing donor base [17] and increasing costs of supplying blood, [17] have led to calls to reduce transfusion, including in obstetrics. It is not clear to what extent findings of studies conducted in surgical, critical care and cardiac patients apply to the generally younger and otherwise healthy obstetric population.

While large volume transfusions reflect management of a massive haemorrhage, small volume transfusions may reflect discretionary transfusions used to treat anaemia and/or symptoms that may be managed conservatively without resorting to blood products. Postpartum anaemia is associated with fatigue, postnatal depression, [18, 19] lower rates of breastfeeding, [20] impaired cognition [21] and poorer maternal-infant bonding [22]. Although transfusion is a common treatment for postpartum anaemia, there is little evidence to support this practice. One trial of restrictive transfusion strategies in obstetric patients, found no clinically relevant difference in fatigue between those transfused and women assigned to non-intervention, and no difference in infection complications and breastfeeding.[23] Current guidelines support the use of transfusion in the actively bleeding obstetric patient and a restrictive approach to transfusion otherwise [9, 24] however the benefits and risks of transfusion following obstetric haemorrhage are largely unknown [9]. Routinely collected administrative data can be used to examine outcomes associated with transfusion, however hospital data usually does not contain detail on number of packs transfused. Linkage to blood issue data provided us an opportunity to examine outcomes following small volume transfusions. This study aimed to compare health and health service utilisation outcomes between low-risk non-transfused women and those receiving 1-2 units of blood in the context of obstetric haemorrhage.

Methods:

Study Population and Data Collection

The study population included all low-risk women giving birth to a singleton infant at term in New South Wales (NSW) hospitals between July 2006 and December 2010, where a diagnosis of obstetric haemorrhage (including antenatal, intrapartum and postpartum haemorrhage) was recorded in hospitalisation data. Postpartum haemorrhage is defined as blood loss of >500mL following vaginal birth and >750mL following Caesarean section. The study population was limited to women receiving no or 1-2 transfusions of RBC, to minimise confounding by indication (i.e. poor outcomes because of the reason or "indication" for the massive transfusion, as opposed to the transfusion itself). Ideally, the study population would have further been restricted to women with anaemia without evidence of active bleeding, however anaemia and timing of bleeding are not well collected. Women with a hospital diagnosis of placental abruption, placenta praevia, morbidly adherent placenta, bleeding or platelet disorders, hypertension, diabetes, other chronic conditions, and those who required a transfusion during pregnancy were considered high risk of adverse outcomes and so excluded. Women receiving other blood products (including platelets and fresh frozen plasma) in addition to RBC were also excluded, as this generally indicates management of a more severe haemorrhage.

This was a retrospective observational study using routinely collected data. Data on maternal characteristics and pregnancy history were obtained from the Perinatal Data Collection, and data on medical diagnoses and procedures, including transfusion, from the Admitted Patients Data Collection. The Perinatal Data Collection is a statutory collection of pregnancy and birth information on all livebirths and stillbirths of at least 400g birthweight or 20 weeks gestation in NSW. The Admitted Patients Data Collection contains data on all NSW hospital admissions, and includes diagnoses coded according to the International Statistical Classification of Diseases 10th Revision-Australian Modification, and procedures coded according to the Australian Classification of Health Interventions. Data on number of transfusions received, and associated pathology tests were obtained from the NSW Clinical Excellence Commission "BloodWatch" Red Cell Utilisation database, and from the Red Cross Blood Bank databases ('Red cell data'). The Red Cell Utilisation database records information on each red cell unit issued to patients in NSW public hospitals, however data were not available for all hospitals for the whole time period. Haemoglobin testing information was available in this database for some women. The Red Cross Blood Bank database contains information on each unit of RBC distributed to NSW hospitals. Registry of Births, Deaths and Marriages data was used to identify out of hospital deaths.

The Centre for Health Record Linkage (CHeReL) undertook probabilistic linkage to link the databases based on personal identifiers. [25] Deidentified data were provided to the researchers. Red cell data were used to identify women with obstetric haemorrhage who received a transfusion of 1-2 units of blood during the hospital admission in which they gave birth; all women birthing in that hospital during the same month who experienced obstetric haemorrhage but did not receive a transfusion were selected for comparison.

Exposure and Outcomes

The exposure of interest was transfusion of 1-2 units of RBC during the birth admission (either prior to or following birth). The primary outcome was severe maternal morbidity, measured by a composite indicator including diagnoses and procedures indicative of severe morbidity (eg cerebral oedema or coma, cardiac arrest, acute renal failure, mechanical ventilation for >8 hours and dialysis).[26] Transfusion-related indicators of morbidity, uterine rupture and procedures known to occur post birth (such as hysterectomy, repair of bladder/intestine) were removed from the original indicator. Secondary outcomes were length of stay >5 days, intensive care unit (ICU) admission, readmission for any reason (within the first 6 weeks), breastfeeding at discharge from the birth admission (any vs none) and all-cause mortality (at 6 weeks and 12 months). Information on potential confounders (listed in Table 1) was obtained from the birth and hospital data, where they are reliably reported. Women were considered at increased PPH risk if they had experienced a PPH or caesarean section in a previous pregnancy. Reason for readmission was determined from the primary diagnosis at readmission.

Pre-transfusion haemoglobin was calculated as the minimum haemoglobin recorded on or in the two days prior to the transfusion. Post-transfusion haemoglobin was the maximum haemoglobin in the two days following transfusion. The percentage change in haemoglobin was calculated where both pre-and post-transfusion measures were available.

Statistical Analysis

Unadjusted comparisons between transfused and non-transfused women were made using Chi-square tests and relative risks for categorical variables, and the Wilcoxon test for length of stay. To try to isolate the effect of transfusion on adverse outcomes, propensity score matching was used to create two groups of women with similar characteristics and risk factors, who differed on whether they received a transfusion. A logistic regression model was built using the maternal and pregnancy characteristics listed in Table 1 to predict the probability of transfusion. Nearest neighbour propensity score matching with exact matching on hospital type, and a caliper of 0.1 standard deviations of the logit of the propensity score was then used to find non-transfused women who most closely resembled the transfused women across all characteristics considered. The average standardised absolute mean distance was used as a measure of balance between the two groups. Modified Poisson regression models were then used to determine the relationship between each adverse outcome and transfusion within the matched sample, additionally adjusting for the propensity score. [27]

As haemoglobin results were only available for transfused women, and haemoglobin levels were the only reliable measure of anaemia, it was not possible to adjust for anaemia. To assess the potential effect of anaemia, a probabilistic bias analysis was performed.[28] Probabilistic bias analysis gives an indication of the expected change in risk associated with transfusion, had we been able to additionally adjust for anaemia. For this analysis a prevalence of 80% (range 70%-90%) for anaemia in transfused women (based on available data) and 30% in non-transfused women (range 5%-60%) was used. The rate in non-transfused women was selected to reflect rates reported in other studies, which ranged from 13%[29] to around 50%.[30] The risk of severe morbidity associated with anaemia in a postpartum

population is unknown, however a review by Shander et al reports relative risks of around 1.5 to 2.5 across a range of patient populations, [31] so a relative risk of 2.5 was used as a conservative estimate (range 1.2-3.0).

To address the concern that women receiving blood were a sicker or more anaemic population, a sensitivity analysis was performed comparing women with a pre-transfusion haemoglobin ≥70g/L to non-transfused women.

This study was approved by the NSW Population and Health Services Research Ethics Committee. Analyses were performed in SAS 9.4 and R 3.3.1. Probabilistic bias analysis was conducted in Microsoft Excel.

Results

There were 218,324 births in participating hospitals, of which 165,529 (75.8%) were to women considered low-risk. Among the low-risk women, the obstetric haemorrhage rate was 9.1% (N=14989), and 1702 (1.1%) were transfused (1-2 units N=1069, 3+ units N=633). Ninety-five women received a single unit of blood. Women with obstetric haemorrhage receiving no or 1-2 units of blood were retained for analysis (N=14356) (Supp Figure 1).

Transfused women were more likely to be primiparous, have an instrumental delivery and give birth outside of a tertiary centre (Table 1). In unadjusted analysis, transfused women were more likely to experience severe morbidity, ICU admission, organ failure, readmission and longer hospital stays. Their infants were less likely to be receiving any breastmilk on hospital discharge (Table 2). There were 575 (4%) women readmitted within 6 weeks. The primary reason for readmission in both transfused and non-transfused women was bleeding related (including delayed post-partum haemorrhage and retained placenta), with higher rates amongst transfused women (Table 3).

The median pre-transfusion haemoglobin was 76g/L (Interquartile range 69,90, n=720), and 527 (73%) had a pre-transfusion haemoglobin ≥ 70g/L. The median post-transfusion haemoglobin was 89 g/L (IQR 83,96, n=651). Among the 631 (59%) transfused women with pre- and post-transfusion haemoglobin measures 387 (61%) experienced an increase in haemoglobin of >10%.

After excluding women with missing data, 14257 (99.3%) women were included in the propensity score analysis. 1065 women receiving 1-2 units of RBC were matched to 1065 non-transfused women (Supp. Table 1). Within the matched sample, transfused women were more likely to experience severe morbidity (Relative risk 7.0, 95% CI(2.8,17.8)) and to experience long hospital stays (Table 2). Transfused women were less likely to be breastfeeding on hospital discharge. There were insufficient deaths (<5) available for analysis.

After probabilistic bias analysis to estimate the potential effect of anaemia on the relationship between transfusion and morbidity, the relative risk of severe morbidity was attenuated, but remained significant (RR 5.0 95% CI(1.9,13.4)). The results of the sensitivity analysis amongst those transfused having a pre-

transfusion haemoglobin ≥70 compared with non-transfused women were consistent with the primary analysis, with the transfused group experiencing higher rates of severe morbidity.

Discussion

Within this population of low-risk women, almost 1 in 10 had an obstetric haemorrhage, and of those women 1 in 10 received a transfusion, with the majority receiving 1-2 units of blood. Among those receiving no transfusion or 1-2 units, serious maternal morbidity was experienced by around 1%, with higher rates experienced by transfused women, even after accounting for differences in patient characteristics.

The transfusion rate found in this population is comparable but slightly higher than transfusion rates of 7.8-9.5% for PPH reported in other developed countries;[5, 32, 33] however differences exist in definition and ascertainment of obstetric haemorrhage between countries.[3]

Unadjusted analyses also showed that health service utilisation was higher in transfused women, with longer hospitalisations for delivery, and higher rates of readmission. Length of stay in transfused women was around 1 day longer than non-transfused women. This finding is different to that of two studies in moderately anaemic parturients where no difference in length of stay was found.[23, 34] This may reflect differences in clinical practice between countries, as in one of these studies, the median length of stay was 5 days,[34] which is longer than both transfused and non-transfused women in the current study. In the current study, around 4% of non-transfused women were readmitted within 6 weeks of giving birth, which is similar to the rate reported in a systematic review of outcomes following PPH,[35] but is approximately double readmission rates reported in the general obstetric population.[36, 37] In accordance with the principles of patient blood management[38] the ongoing risk of readmission among transfused women could be addressed by strategies to monitor and prevent anaemia during pregnancy and postnatally,[30, 39] including the use of oral iron supplementation or intravenous iron to provide women with greater haemopoietic reserve should they experience bleeding. [40, 41]

After using propensity score analysis to account for differences in patient factors which might predispose certain women to both transfusion and worse outcomes, the strength of the risk of morbidity associated with transfusion was attenuated but not removed. Transfusion was associated with increased rates of severe morbidity, ICU admission, prolonged hospital stay and readmission , as well as reduced breastfeeding rates. The residual effect of transfusion on outcomes after accounting for maternal condition suggests that transfusion of even 1-2 units of blood may convey an increased risk of morbidity, as suggested in other disciplines.[13, 42-44] The propensity score methods utilised in this study assume that data are available on all relevant confounders,[45] so that differences found between groups can be attributed to the treatment received. [27, 45] A large range of possible confounders was used in this study, however measures of anaemia were not available for all patients. Anaemia in pregnancy is known to increase risks to both the mother and the baby,[40, 41] and to increase the risk of transfusion. [39] Probabilistic bias analysis was used to estimate the possible range of effects of anaemia on morbidity, and transfusion remained an independent risk factor for severe morbidity.

Recent obstetric and other specialty guidelines suggest that in the absence of active bleeding, transfusion when the haemoglobin is >70g/L is not associated with improved patient outcomes. [9, 40, 46-48] Almost three-quarters of transfusions in this study were given to women with a pre-transfusion haemoglobin >70g/L, however it is not known whether this was in the presence of active bleeding. In an audit of obstetric transfusions at a tertiary hospital in the United Kingdom, Parker et al found that 31% of transfusions were given to women with a haemoglobin >70 g/L in the absence of symptoms or ongoing bleeding. [49] A French study however, found evidence of under-transfusion, with only half the women with clinically diagnosed PPH and having a haemoglobin <70 g/L receiving a transfusion. [32] In the current study, although more than half the women experienced a clinically significant increase in haemoglobin post transfusion, clinical outcomes following transfusion were not improved. Recent Australian guidelines for patient blood management in obstetric patients, published after the study period, specify that in the absence of active bleeding, non-transfusion therapies should be considered rather than transfusion, depending on the clinical situation. [9]

The strengths of this study include the large number of women included across a variety of hospital types which enabled the detection of rare outcomes, the use of a validated composite measure of morbidity,[26] and the restriction of the population to a homogenous group of low-risk women receiving small volumes of blood. We did not consider the age of blood as a confounder, as it has not been shown to increase adverse outcomes in obstetric[50] and other populations. [51] This is an observational study and as such transfusion was given based on clinical judgement, not randomly allocated. Although a large range of clinical and maternal characteristics were adjusted for within a restricted low-risk population, and the possible effect of anaemia on morbidity was assessed, there remains the possibility that another unmeasured confounder may be responsible for the observed association of transfusion with adverse outcomes. A limitation of the data is that information was not available on the timing of the transfusion, or estimated blood loss, however the study population was restricted to women receiving small volume transfusions, without other blood products, making it likely the transfusion was given in the absence of massive bleeding. The small number of women receiving single unit transfusions precluded a sensitivity analysis on this group. Despite limiting the study population to low-risk women having small volume transfusions and using propensity score analysis to match women, it may be that some of the identified morbidity is related to the amount of blood lost rather than the transfusion itself.

The decision to transfuse involves a trade-off between the concern for a mother's ability to care for a new baby and concerns about adverse effects of the transfusion. [52] Treatment of anaemia in these women may improve wellbeing in the short term,[53] however must be weighed against the risks associated with transfusion. Although the risk of transfusion transmitted infections and reactions is low,[54] this study suggests that even in a low-risk population, transfusion is associated with increased morbidity and healthcare use. While our findings support restrictive use of transfusion in obstetrics, we cannot rule out that at least some of the adverse outcomes demonstrated may be driven by the indication for transfusion, rather than the transfusion itself. Increased risks of readmission, even among low-risk women experiencing haemorrhage suggest the need for ongoing monitoring in and beyond the postpartum period.

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JP was involved in study design, conducting analyses, interpreting the data and drafting the manuscript. TN, DR and JF were involved in study design, interpreting the data and revising the manuscript. DI was involved in interpreting the data and revising the manuscript. Other members of the Obstetric Transfusion Steering Group provided input on the manuscript and interpretation of the data. All authors read and approved the final manuscript.

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Table 1: Maternal and pregnancy characteristics of low-risk women with obstetric haemorrhage in NSW, 2006-2010.

	0 Units	1-2 Units
Total	13286 (100.0)	1069 (100.0)
Age		
Under 20	542 (4.1)	54 (5.1)
20-34	10311 (77.6)	843 (78.9)
35+	2432 (18.3)	172 (16.1)
Private patient	1560 (11.7)	117 (10.9)
Maternal country of birth-Australia	8198 (61.7)	678 (63.4)
Low Socioeconomic status	3052 (23.0)	274 (25.6)
Smoker	1602 (12.1)	137 (12.8)
Primiparous	6358 (47.9)	571 (53.4)**
Mode of birth		
NVD	8772 (66.0)	647 (60.5)**
Prelabour Caesarean	785 (5.9)	41 (3.8)*
Intrapartum Caesarean	1488 (11.2)	134 (12.5)
Instrumental delivery	2336 (17.6)	256 (23.9)**
Induction	4137 (31.1)	351 (32.8)
Birthweight		
SGA (<10%)	930 (7.0)	69 (6.5)
AGA	10457 (78.7)	847 (79.2)
LGA (>10%)	1899 (14.3)	153 (14.3)
PPH risk factors		
Antepartum	1633 (12.3)	139 (13.0)
Hospital Type		
Tertiary	9259 (69.7)	672 (62.9)**
Regional	1933 (14.5)	199 (18.6)
Urban/other	2094 (15.8)	198 (18.5)

* p<0.01, **p<0.001

NVD: Normal Vaginal Delivery, SGA: small for gestational age, AGA: appropriate for gestational age, LGA: large for gestational age

Table 2: Unadjusted and adjusted risk of adverse outcomes in women with obstetric haemorrhage in NSW, 2006-2010

Variable	Transfused N (%)	Non Transfused N (%)		Unadjusted Relative risk (95% CI)	Relative risk [b] (95% CI)
		All	Matched [a]		
Maternal morbidity	35 (3.3)	65 (0.5)	5 (0.5)	6.7(4.5, 10.1)	7.0 (2.8, 17.8)
Intensive care admission	36 (3.4)	288 (2.2)	17 (1.6)	1.6 (1.1, 2.2)	2.1 (1.2, 3.8)
Length of stay >5 days	205 (19.2)	1187 (8.9)	102 (9.6)	2.2 (1.9, 2.5)	2.0 (1.6, 2.5)
Length of stay (days) Median (IQR)	4 (3,5)	3 (2,4)	3 (2,4)	<0.001[c]	<0.001 [c]
Any breastmilk feeding	830 (77.9)	10716 (80.7)	858 (80.6)	0.9 (0.9, 1.0)	0.9 (0.9, 1.0)
Readmission (6 week)	63 (5.9)	512 (3.9)	34 (3.2)	1.5 (1.2, 2.0)	1.9 (1.2, 2.8)
Readmission (6 week) involving blood transfusion	5 (0.5)	36 (0.3)	<5 (0.5)	1.7 (0.7, 4.4)	2.5 (0.5, 12.9)
Readmission (6 weeks, lactation related)	7 (0.7)	112 (0.8)	7 (0.7)	0.8 (0.4, 1.7)	1.0 (0.4, 2.8)

[a] *propensity score matched women*

[b] *in the propensity score matched cohort*

[c] *Wilcoxon test*

Table 3- Reasons for readmission within 6 weeks for low-risk women with obstetric haemorrhage, NSW, 2006-2010

	0 Units (N %)	1-2 Units (N %)
Total readmitted	512 (100.0)	63 (100.0)
Bleeding	122 (23.8)	26 (41.3)
Infection	92 (18.0)	10 (15.9)
Wound disruption	15 (2.9)	<5 [a]
Lactation	62 (12.1)	<5[a]
Other obstetric	114 (22.3)	12 (19.0)
Other	107 (20.9)	9 (14.3)

[a]Fewer than 5

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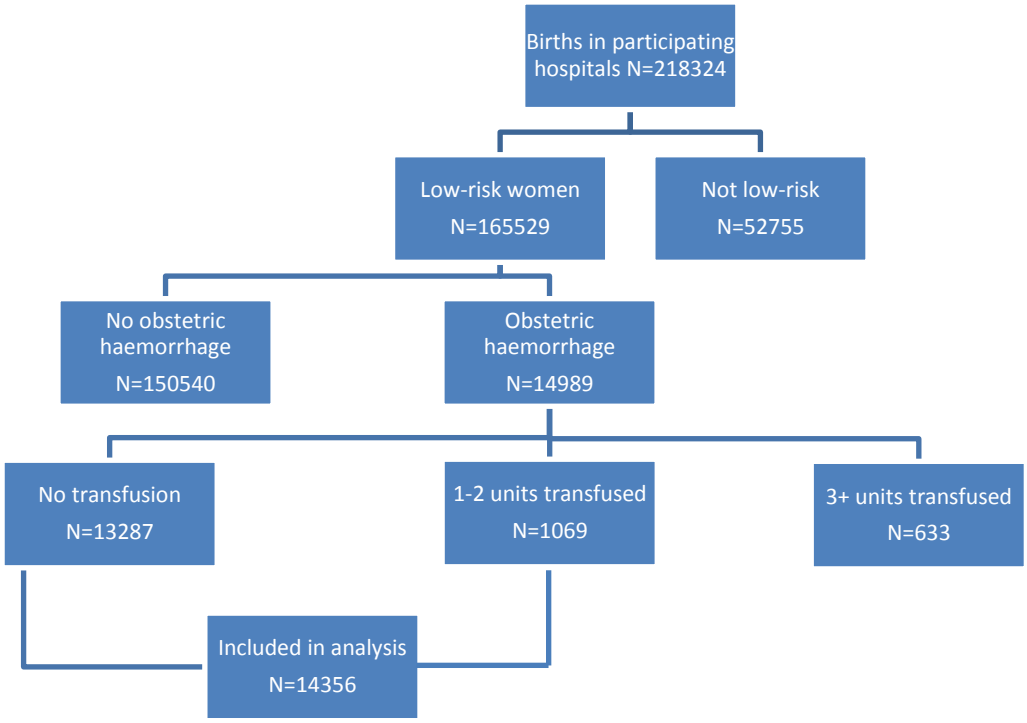
Supplementary figure 1: Study flowchart of low-risk women with obstetric haemorrhage in NSW, 2006-1010



Supplementary Table 1: Balance in covariate parameters between transfused and non-transfused women after propensity score matching.

Variable	Code	Total	Case	Control
Total		2130 (100.0)	1065 (100.0)	1065 (100.0)
Maternal Age	Under 20	113 (5.3)	54 (5.1)	59 (5.4)
	20-34	1687 (79.2)	839 (78.8)	848 (79.6)
	35+	330 (15.5)	172 (16.2)	158 (14.8)
Private patient	Yes	244 (11.5)	116 (10.9)	128 (12.0)
Smoker	Yes	280 (13.1)	136 (12.8)	144 (13.5)
Low SES	Yes	551 (25.9)	274 (25.7)	277 (26.0)
Australian Born	Yes	1356 (63.7)	676 (63.5)	680 (63.8)
Primiparous	Yes	1148 (53.9)	570 (53.5)	578 (54.3)
Previous CS	Yes	191 (9.0)	95 (8.9)	96 (9.0)
NVD	Yes	1296 (60.8)	644 (60.5)	652 (61.2)
Prelabour CS	Yes	80 (3.8)	41 (3.8)	39 (3.7)
Intrapartum CS	Yes	278 (13.1)	134 (12.6)	144 (13.5)
Instrumental Delivery	Yes	498 (23.4)	255 (23.9)	243 (22.8)
Induction	Yes	689 (32.3)	350 (32.9)	339 (31.8)
Birthweight	SGA	128 (6.0)	69 (6.5)	59 (5.5)
	AGA	1696 (79.6)	844 (79.2)	852 (80.0)
	LGA	306 (14.4)	152 (14.3)	154 (14.5)
PPH Risk factors	Antepartum	277 (13.0)	137 (12.9)	140 (13.1)
Hospital	Tertiary	1340 (62.9)	670 (62.9)	670 (62.9)
	Regional	396 (18.6)	198 (18.6)	198 (18.6)
	Urban/Other	394 (18.5)	197 (18.5)	197 (18.5)