

# **The association between ABO blood group and obstetric hemorrhage**

Lior Drukker MD<sup>1\*</sup>, Naama Srebnik MD<sup>1\*</sup>, Deborah Elstein PhD<sup>1</sup>, Lorinne Levitt MD<sup>2</sup>, Arnon Samueloff MD<sup>1</sup>, Rivka Farkash MPH<sup>1</sup>, Sorina Grisaru-Granovsky MD PhD<sup>1</sup>, and Hen Y Sela MD<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, affiliated with the Hebrew University Medical School, Jerusalem, Israel <sup>2</sup>Department of Obstetrics and Gynecology, Hadassah Medical Center, affiliated with the Hebrew University Medical School, Jerusalem, Israel

\* L.D. and N.S. contributed equally to this work.

## **Funding**

No financial support was provided for its performance.

## **Conflict of interest**

The authors declare that they have no conflicts of interest.

## **Corresponding author**

Naama Srebnik, MD  
Department of Obstetrics and Gynecology,  
Shaare Zedek Medical Center  
Hebrew University Medical School  
12 Bayit Street  
Jerusalem 91031, Israel  
e-mail srebnik@gmail.com  
Tel +972-2-655-5562  
Fax +972-2-666-6053

**Key words:** anemia; blood group; blood transfusion; delivery; maternal outcome; postpartum hemorrhage;

## Abstract

Whether intra- and early post-partum hemorrhage is influenced by ABO blood groups remains unknown. Therefore, we compared women with O to non-O blood groups with regard to maternal post-partum hemorrhage and transfusion need. This retrospective study was conducted in a single tertiary center between 2005 and 2014. For the purpose of the study, parturients were categorized as O and non-O blood groups. Data included all deliveries but excluded patients with missing blood grouping or hemoglobin values, and/or stillbirth. Drop in hemoglobin was defined as hemoglobin concentration at admission for delivery minus lowest hemoglobin concentration post-delivery. Study outcomes were postpartum hemorrhage, hemoglobin drop  $> 2$ -7gr/dL inclusive, and packed red blood cells transfusion. Statistics: descriptive,  $\chi^2$  ( $p < 0.05$  significant) and multivariable regression models (odds ratio [OR], 95% confidence interval [CI], p value). 125,768 deliveries were included. After multivariable analysis, women with O blood type relative to women with non-O blood type had significantly higher odds of postpartum hemorrhage (OR=1.14; 95%CI 1.05-1.23,  $p < 0.001$ ), higher odds of statistically significant hemoglobin decreases of  $>2$ , 3, or 4gr/dL (OR=1.07; 95%CI 1.04-1.11,  $p < 0.001$ , OR=1.08; 95%CI 1.03-1.14,  $p = 0.002$  OR=1.14; 95%CI 1.05-1.23,  $p = 0.001$ ; respectively), and higher odds, albeit not statistically significant of 5, 6, or 7gr/dL decreases in hemoglobin (OR=1.13; 95%CI 1.00-1.29,  $p = 0.055$ , OR=1.05; 95%CI 0.84-1.32,  $p = 0.66$ , OR=1.15; 95%CI 0.79-1.68,  $p = 0.46$ ; respectively), but no difference in blood products transfusion (OR=1.03; 95%CI 0.92 – 1.16,  $p = 0.58$ ). In conclusion, women with blood type O may be at greater risk of obstetrical hemorrhage.

## **Introduction**

Maternal post-partum hemorrhage is a major cause of maternal morbidity, and is among the three most important causes of maternal mortality in both high and low per capita income countries [1]. Identifying the women at risk for hemorrhage has continued to be a priority in the hope that early identification may lead to appropriate prevention strategies and elicit prompt response upon post-partum hemorrhage.

There are contradicting studies in the literature regarding the correlation between ABO blood groups and bleeding tendency in the non-pregnant state, with the O blood group being a risk factor for bleeding. In cardiac surgery, the AB blood group is associated with significantly fewer transfusions and improved late survival [2]. In patients with bleeding peptic ulcers, the prevalence of O blood group was significantly increased over controls [3]. However, other studies have shown that blood groupings are not associated with either major cerebral or non-cerebral bleeding or peptic hemorrhage [4,5]. The hypothesized mechanism for the link between blood group and hemorrhage is alleged to be related to the von Willebrand factor (VWF) [6]. Individuals with O blood type compared with other blood groups have 25%-35% lower plasma levels of VWF.

In pregnant women the question of whether intra- and early post-partum hemorrhage is influenced by ABO blood groups has only been evaluated in a single small study among unselected patients [7]. In this study, there was no statistically significant trend for reduced obstetrical hemorrhage among women with a non-O blood type. The purpose of the current study is to explore whether blood type O is associated with an increased risk for obstetrical hemorrhage and packed red blood cells transfusion in a large cohort from a single center.

## **Materials and Methods**

This was a retrospective cohort study of all births  $\geq 24$  weeks' gestation in a single large tertiary center between August 2005 and December 2014. The only exclusions were women with missing blood grouping and/or hemoglobin values and those with intra-uterine fetal death or stillborn. De-identified data including patients' demographic characteristics, procedures, diagnoses, and other pertinent coding, were extracted from the departmental electronic medical record database which is continuously updated during hospital admission.

The study protocol was approved by the institutional Helsinki (Ethics) Committee. For this type of study formal consent is not required.

The Shaare Zedek Medical Center is a university affiliated medical center with a large obstetric service. Approximately 15,000 deliveries are attended annually. National Health and Drug Insurance plans cover all antenatal and peripartum care. All women upon admission routinely undergo ABO phenotyping by standard serology as well as a complete blood count (CBC). Furthermore, on the first post-partum day, all women routinely undergo a second CBC. All samples are drawn in a uniform manner using the same protocol and transported immediately for analysis; results are computerized. Early postpartum hemorrhage is defined by departmental policy as an estimated blood loss of  $>500\text{ml}$  or  $>1000\text{ml}$  following vaginal or cesarean delivery, respectively [8,9]. A decrease in hemoglobin concentration was calculated by subtracting the lowest hemoglobin after delivery from the hemoglobin concentration noted at admission for delivery. Departmental policy specifies transfusion on an emergency basis of

hemodynamic instability, or if hemoglobin concentration is  $\leq 7$ gr/dL or if symptomatic anemia with hemoglobin concentration  $\leq 8$ gr/dL is noted.

For the purpose of this study outcomes were defined as postpartum hemorrhage, hemoglobin drop  $> 2$ -7gr/dL inclusive, and transfusion of packed red blood cells.

The primary exposure variable was blood type O relative to non-O blood groups. Univariate analysis for categorical variables was performed using  $\chi^2$  or the Fisher's exact test. Continuous variables were compared using the Student's t-test or Mann-Whitney U-test. Furthermore, in order to evaluate independent relationships between blood type and each outcome, multivariate logistic regression models were devised including adjusting for patients' demographics and the following co-morbidities: maternal age, parity, assisted reproductive techniques, hypertensive disorder, diabetes mellitus, multi-fetal gestation, anemia, gestational age, trial of labor after cesarean, mode of delivery, and birth weight. Multiple linear regression models were used to investigate the blood type and outcomes controlling for aforementioned potential confounders. Odds ratio (OR) and 95% confidence intervals (CI) are reported. All tests are two-tailed; P value  $< 0.05$  was considered statistically significant. Analyses were carried out using SPSS software package version 20.0 (IBM, Armonk, NY).

## Results

During the study period, there was a total of 126,693 deliveries. Based on pre-determined exclusion criteria, the following were excluded: 9 women because of missing blood type information; 404 (0.3%) women because of a missing hemoglobin value; and 512 (0.4%) women because of stillbirth delivery. Thus, the study cohort comprised 125,768 births (99.2% of total deliveries) for analysis (Figure 1).

Parturients with blood group O compared with non-O were comparable for Rhesus positive status, maternal age, education, prior miscarriages, prior cesarean deliveries, and parity. The incidence of assisted reproductive techniques, multi-fetal gestation, placenta previa, diabetes mellitus, **placenta accrete**, and hypertensive disorders did not differ between groups although anemia was significantly more common in women with the O blood group (11.8% *versus* 10.6%,  $P < 0.001$ ). The labor characteristics were also generally comparable between the two groups, **importantly rates of trial of labor after cesarean, operative vaginal deliveries, cesarean deliveries and uterine rupture did not differ between groups. The only labor characteristic that was somewhat different was the slightly higher rate of preterm deliveries among women with non-O blood type** (Table 1).

On univariate analysis, women with the O blood type had a significantly increased risk for early postpartum hemorrhage (2.3% *versus* 2.0%,  $P = 0.001$ ) and for a hemoglobin drop  $> 2$  or 3 or 4 or 5 gr/dL, but not with hemoglobin drop  $> 6$  or 7gr/dL. The incidence of packed red blood cells transfusion did not differ between groups (Table 2).

The association between hemorrhage and blood group O remained statistically significant after multivariable regression models: early post-partum hemorrhage (OR = 1.14; 95% CI 1.05-1.23,  $P = 0.001$ ) and hemoglobin drop of 2 or 3 or 4 gr/dL (OR = 1.07; 95%CI 1.04-1.11,  $p < 0.001$ ), (OR=1.08 ;95%CI

1.03-1.14,  $p=0.002$ ), and (OR = 1.14; 95%CI 1.05-1.23,  $p=0.001$ ), respectively. O blood group was marginally associated with hemoglobin drop  $>5\text{gr/dL}$  (OR = 1.13; 95%CI 1.00-1.29,  $p=0.055$ ), but not with a hemoglobin drop 6 or 7 gr/dL (Table 3).

To further assess whether blood group impacts risk of obstetrical hemorrhage, a post hoc analysis was performed comparing the incidence of hemorrhage in blood group AB versus non-AB. Compared with non-AB blood group, women with the AB blood type had a comparable risk for decreased hemoglobin concentration post-partum at all levels: a hemoglobin drop of 2gr/dL (16.6% *versus* 16.5%,  $P=0.92$ ),  $>3\text{gr/dL}$  (5.8% *versus* 5.6%,  $P=0.65$ ),  $>4\text{gr/dL}$  (2.2% *versus* 2.2%,  $P=0.91$ ),  $>5\text{gr/dL}$  (0.8% *versus* 0.8%,  $P=0.88$ ); and comparable need for packed red blood cells transfusions (1.1% *versus* 1.0%,  $P=0.21$ ).

## Discussion

This study highlights a significant association between blood type O and the risk for parturient hemorrhage. Post-partum, blood group O was associated with 1.14-fold increased risk of early postpartum hemorrhage, and a 1.07-1.14-fold increased risk of hemoglobin drop of 2-5gr/dL. There was no difference in the risk for hemoglobin drop  $>6$  or 7gr/dL and in the need for packed red blood cells transfusion between blood groups.

The incidence of postpartum hemorrhage and the need for transfusions in the current study are consistent with large, population-based data [10]. There is no consensus regarding the definition of postpartum hemorrhage [11]; and generally postpartum hemorrhage is based on the attending medical professional's visual approximation [12]. Moreover, postpartum hemorrhage may be underreported thus limiting the use of this diagnosis in retrospective studies [13]. Hence, we chose to evaluate the incidence of hemorrhage indirectly as well, using the difference in the hemoglobin concentration from before delivery relative to after delivery, and thereby avoiding estimation of blood loss. Although postpartum hemorrhage and a drop in hemoglobin concentration of 2 or 3 or 4 or 5 gr/dL was significantly associated with blood group O, there was no difference in the OR for transfusion. This may be due to the relatively low overall incidence of giving packed red cells transfusion (which has specific indications as per departmental routine practice).

A MEDLINE search (English literature; 1954-2015; search terms: "blood group" or "blood type" and "hemorrhage") revealed that prior to this study, only one study had examined the potential association between blood type and hemorrhage during and after labor [7]. In this study, there was a non-significant statistical trend for reduced obstetrical hemorrhage among women with non-O blood types (OR 0.81 [CI 0.6-1.08]). Although that study included only a small, unselected sample (304 cases of hemorrhage) wherein hemorrhage was defined either by visual assessment or because of requirement for clinical intervention, the trend was similar. In terms of numbers of patients included, the current study is one of the largest published cohort studies to assess the relationship between hemorrhage and blood type [14].

A recent meta-analysis evaluated the relationship between ABO blood group and hemorrhage in patients with all medical conditions, including upper gastrointestinal bleeding, cerebral hemorrhage, mucocutaneous hemorrhage, one study on patients with menorrhagia and one of post-partum hemorrhage. Reviewing 22 studies they found the pooled OR to be 1.33 (95%CI 1.25-1.42,  $P<0.001$ ) for hemorrhage in patients with blood group O, though heterogeneity among the studies not negligible ( $I^2 =$

39%). The bleeding risk did not vary according to the site of bleeding. Funnel plot of OR versus standard pointed to the absence of a publication bias. Furthermore, they estimated that in patients with bleeding event, the attributable risk conferred by O blood group to be 12.7% [14]. In the current study, the OR for hemorrhage was 1.10. The lower OR for hemorrhage might reflect normal, physiologic changes of pregnancy, since lower VWF levels in individuals with O blood group are thought to be the pathophysiology for the association between hemorrhage and blood group. During the third trimester of pregnancy the levels of VWF are higher than in non-pregnant women, and VWF levels continue to increase postpartum: increases of 121-258% in VFW levels may be seen in the third trimester [15]. Thus, these physiologically elevated VWF levels as a response to gestation may reduce the increased risk for hemorrhage that is seen in non-pregnant patients with blood type O.

Although anemia on admission was significantly lower among women with blood type O, it has been previously shown not to be associated with hemorrhage [16]. Adding anemia at admission as a variable to the multivariable regression models in the current study did not alter outcomes, and the use of packed cells transfusion did not differ between the groups.

The mechanism by which O blood type decreases risk of anemia during pregnancy risk is virtually unknown, specifically one would assume that due to the lower levels of von Willebrand factor, there might be an increased tendency for bleeding in pregnancy and hence higher anemia rate. Yet we found that blood type O is associated with lower rate of anemia. Apparently, blood type O carries a significant survival advantage in pediatric malaria, in this study, the survival advantage was associated with lower rates of anemia as well, and whether the lower rates of anemia in pregnant women with blood type O share, the same mechanism of lower rate of anemia in pediatric malaria is yet to be determined. [17]

We query the clinical importance of blood group O as a risk factor for bleeding tendency. Although there was a statistically significant risk for hemorrhage in patients with blood group O, there was no difference in the risk for transfusion. Hence, it is undetermined whether the calculated higher risk for hemorrhage is clinically significant.

The limitations of this study are: {1} pre-gestational body mass index and adverse maternal and neonatal outcomes [18] were not available; {2} adjusted OR are <2; {3} ramification to other populations may be limited; and {4} there was no measure of socioeconomic status and therefore the proxy of maternal education was used with the caveat that there is only a weak correlation between education and income in multi-ethnic populations [19].

The strengths of the present study are: {1} large sample size; {2} real-time recording in the electronic medical records; {3} the relative long period of the study as opposed to time limited observation; and {4} blood typing and samples were processed rapidly and in a uniform manner.

In conclusion, the results of this study indicate a significant association between blood type O and the risk of bleeding in the context of delivery. Consequently, women with blood type O may be regarded as at greater risk for obstetrical hemorrhage and may benefit from targeted hemodynamic observation and care during labor and in the postpartum period.

## Reference

1. World Health Organization (2012). Recommendations for the prevention and treatment of postpartum haemorrhage.  
[http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf). Accessed 17 November 2015.
2. Welsby IJ, Phillips-Bute B, Mathew JP, Newman MF, Becker R, Rao S, et al (2014) ABO blood group influences transfusion and survival after cardiac surgery. *J Thromb Thrombolysis* 38:402-8.
3. Horwich L, Evans DA, McConnell RB, Donohoe WT (1996) ABO blood groups in gastric bleeding. *Gut* 7:680-5.
4. Franchini M, Crestani S, Rossi C, Frattini F, Mengoli C, Giacomini I, et al (2013) O blood group and the risk of major bleeding: a single-center survey. *J Thromb Thrombolysis* 35:65-6.
5. Kuyvenhoven JP, Veenendaal RA, Vandenbroucke JP (1999) Peptic ulcer bleeding: interaction between non-steroidal anti-inflammatory drugs, *Helicobacter pylori* infection, and the ABO blood group system. *Scand J Gastroenterol* 34:1082-6.
6. Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr, Montgomery RR (1987) The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood* 69:1691-5.
7. Clark P, Walker ID, Govan L, Wu O, Greer IA (2008) The GOAL study: a prospective examination of the impact of factor V Leiden and ABO(H) blood groups on haemorrhagic and thrombotic pregnancy outcomes. *Br J Haematol* 140:236-40.
8. Stafford I, Dildy GA, Clark SL, Belford MA (2008) Visually and calculated blood loss in vaginal and cesarean delivery. *Am J Obstet Gynecol* 199:519.e1-7.
9. James AH, Paglia MJ, Gernsheimer T, et al (2009) Blood component therapy in postpartum hemorrhage. *Transfusion* 49:2430-2433.
10. Callaghan WM, Kuklina EV, Berg CJ (2010) Trends in postpartum hemorrhage: United States, 1994-2006. *Am J Obstet Gynecol* 202:353.e1-6.
11. Helman S, Drukker L, Fruchtman H, Ioscovich A, Farkash R et al (2015) Revisit of risk factors for major obstetric hemorrhage: insights from a large medical center. *Arch Gynecol Obstet* 292:819-28.
12. Hancock A, Weeks AD, Lavender DT (2015) Is accurate and reliable blood loss estimation the 'crucial step' in early detection of postpartum haemorrhage: an integrative review of the literature. *BMC Pregnancy Childbirth* 15:230.
13. Lain SJ, Roberts CL, Hadfield RM, Bell JC, Morris JM (2008) How accurate is the reporting of obstetric haemorrhage in hospital discharge data? A validation study. *Aust N Z J Obstet Gynaecol* 48:481-4.
14. Dentali F, Sironi AP, Ageno W, Bonfanti C, Crestani S et al (2013) Relationship between ABO blood group and hemorrhage: a systematic literature review and meta-analysis. *Semin Thromb Hemost* 39:72-82.
15. Wickström K, Edellstam G, Löwbeer CH, Hansson LO, Siegbahn A (2004) Reference intervals for plasma levels of fibronectin, von Willebrand factor, free protein S and antithrombin during third-trimester pregnancy. *Scand J Clin Lab Invest* 64:31-40.

16. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S (2015) Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. *Transfusion* 55:2799-2806.
17. Cserti-Gazdewich CM, Dhabangi A, Musoke C, Ssewanyana I, Ddungu H, Nakiboneka-Ssenabulya D et al (2012) Cytoadherence in paediatric malaria: ABO blood group, CD36, and ICAM1 expression and severe *Plasmodium falciparum* infection. *Br J Haematol* 159:223-36.
18. Blomberg M (2013) Maternal obesity, mode of delivery, and neonatal outcome. *Obstet Gynecol* 122:50-5.
19. Horowitz KM, Ingardia CJ, Borgida AF (2013) Anemia in pregnancy. *Clin Lab Med* 33:281-91.