TRANSFUSION MEDICINE

Original article

Perinatal outcome in pregnant women: the impact of blood transfusion

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Background - Obstetric hemorrhage is a life-threatening complication of pregnancy. Systematic collection of data on transfusion practice during pregnancy and post-partum period are scarce, as well as data on fetal or neonatal outcomes of women transfused during pregnancy.
We examined the prevalence of obstetric hemorrhage and outcome of pregnancies in hospitalized transfused women.

Materials and methods - This is a retrospective cohort study collecting clinical and laboratory data of women transfused from 2015 to 2017 in three Italian Tertiary level Obstetrical Departments. Inclusion criteria were: 1) age >18 years; 2) antepartum or peripartum hospital admission and 3) transfusion during the hospital stay of at least one unit of packed red blood cell (RBC) units. Women below 18 years and/or with transfusion outside pregnancy were excluded.
During the observation period, 18,495 women gave birth across the three Obstetrics Departments: transfusion rate was 1.7%.

Results - 315 women were included in the final analysis. Most (75.2%) needed transfusion from 35 weeks onwards. A percentage higher that that observed in general population of transfused women showed co-morbidities such as hypertensive disorders or diabetes (13.9 *vs* 5.5%). We recorded 90% of live births and 7.6% of Intra Uterine Fetal Demise or neonatal death. Perinatal outcomes were impacted by the dose of transfusion: logistic regression, correcting for age and assisted conception, showed that women transfused with 3 or more RBC units have about 3-fold higher risk of perinatal death (OR: 2.9, 95% CI: 1.0-8.4).

Discussion - In this series, several known risk factors were associated with adverse feto-neonatal outcome. In addition, the number of RBC units transfused was significantly and independently associated with the perinatal outcome. Present data can be helpful to design prospective studies taking into account timing and dose of transfusion during pregnancy with the objective to improve feto-maternal outcome.

Keywords: *hemorrhage, pregnancy, blood transfusion, maternal morbidity, perinatal outcome.*

Arrived: 3 August 2024
Revision accepted: 10 November 2024
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INTRODUCTION

Postpartum hemorrhage (PPH) significantly contributes to maternal mortality worldwide, with over 600,000 fatalities annually[1-7]. There is no universally accepted international definition of PPH. The World Health Organization (WHO) defines PPH as a blood loss of 500 mL or more within 24 hours of birth, regardless of the mode of delivery. German guidelines differentiate between blood loss of 500 mL or more following vaginal delivery and 1,000 mL or more following cesarean delivery, based on a strong consensus[8]. In 2017, the American College of Obstetricians and Gynecologists (ACOG) updated its definition, classifying PPH as blood loss of 1,000 mL or more within 24 hours of delivery, irrespective of the delivery method[8].

Numerous studies highlight the increased risk of morbidity and mortality associated with PPH[7-9], both from its direct impact on the heart, kidneys, and liver, and from the indirect effects of related interventions, such as blood transfusion[6]. Recognized risk factors for PPH include hypertensive disorders, placental abnormalities, severe antenatal anemia, advanced maternal age, cesarean delivery and known or misdiagnosed bleeding tendency[3,10-14]. Notably, PPH frequently necessitates blood transfusion[15-21], occurring in approximately 0.4-1.6% of all deliveries, often in otherwise healthy women[22,23].

Maternal transfusion may also be necessary during antenatal period, with the same risk factors mentioned for PPH playing a role[24]. The amount of RBC units transfused has been associated with worse maternal outcomes. In a nationwide retrospective study carried out in US, the odd of maternal death and hysterectomy was significantly higher when women needed 5 or more RBC units[6].

While much attention has been directed towards bleeding complications in the peri-partum period, data on the first two trimesters, are limited. This period is important for both maternal and fetal well-being, as delayed diagnosis of feto-maternal complications during this time can lead to severe outcomes.

With the objective to investigate feto-maternal morbidity and mortality in three Italian academic hospitals, we carried out an observational study describing characteristics of women transfused during pregnancy and delivery. We collected maternal and perinatal outcomes with specific attention to obstetric history, risk factors, both preexisting or acquired during pregnancy.

MATERIALS AND METHODS

Participants

In this retrospective cohort study we describe clinical and laboratory data on feto-maternal outcomes in women transfused from 2015 to 2017 in Italian Tertiary level Obstetrical Departments (Research Hospital "Casa Sollievo della Sofferenza"; Academic Hospital, University of Bari; Academic Hospital, University of Insubria).

Participants were recruited from consecutive women attending hospitals between January 2015 and December 2017. Inclusion criteria were: 1) age ≥18 years; 2) antepartum or peripartum hospital admission and 3) transfusion during the hospital stay of at least one unit of packed Red Blood Cell (RBC) units. Women below 18 years and/or with transfusion outside pregnancy were excluded.

During the observation period, 18,495 women gave birth across the three Obstetrics Departments[25]. Out of these, a total of 315 women required transfusions, indicating a transfusion rate of 1.7%. Throughout the study, we documented occurrences of obstetric and perinatal complications, analyzed the various causes of hemorrhage and reasons for transfusions, and investigated potential links between perinatal outcomes and the volume of transfusions administered. Additionally, we noted the amounts of red blood cell (RBC) units transfused per hospital relative to the hemoglobin (Hb) levels of the women. Our analysis of this cohort involved reviewing medical charts containing clinical, laboratory, and treatment records, which were assessed by three authors (EG, MMas, DC).

For iron supplementation, we carefully collected information on both intravenous and oral iron supplementation.

Statistical analysis

We calculated the sample size assuming that women transfused with 3 or more RBC units were more exposed to adverse outcomes (in terms of feto-maternal outcomes) than those transfused with ≤2 RBC units. The odd of observing adverse outcomes was estimated to range between 10-15% in those transfused with 3 or more RBC and 3-5% in those who received ≤2 RBC units (statistical power: 80%, significance level: 0.05), with an estimated sample size of 250-280 women (G*Power software ver. 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

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Data are presented as counts and percentages, means with standard deviations (SDs), or medians and interquartile ranges (IQRs). We compared distribution of pretransfusion, posttransfusion Hb levels and delta (post minus pre transfusion Hb), total units transfused and transfusion-related Hb levels, using the Kruskal-Wallis test or ANOVA, as appropriate (significance for $p<0.05$).

C2-test was used to perform univariate analysis and adjusted OR with 95% confidence interval (CI) was calculated using logistic regression models that controlled for potential confounding variables. The recipient's Hb increment after transfusion was calculated as the difference in the proximate pre-transfusion Hb levels and post-transfusion Hb levels divided by the number of RBC units transfused. All analyses were carried out with SPSS 11.0.

The study was approved by local Ethics Committee and was carried out in compliance with ethical principles for medical research involving human subjects.

RESULTS

Patient characteristics

Overall, 315 women were included in the final analysis; of them, 65 (20.63%) were enrolled at hospital 1, 127 (40.31%) at hospital 2 and 123 (39.04%) at hospital 3. **Table I** shows main demographic and clinical features of the entire sample: 57% had previous cesarean section (CS) and most women (53.7%) were at their first pregnancy. Furthermore, 64.5% were admitted to hospital for delivery (both pre-term or near-term) or threatened fetal loss. Median age (interquartile range [IQR]) was 32 years (IQR: 27-35.8) at hospital 1, 35 years (IQR: 33-38) at hospital 2 and 34.7 years (IQR: 30.8-39) at hospital 3, with a significant difference among groups (p: 0.007) (*Online Supplementary*, **Table SI**).

Two out of 315 (0.6%) women had a previous documented PPH. Furthermore, two were previously diagnosed with von Willebrand disease, both showed an obstetric complication in the index pregnancy (ectopic pregnancy and premature rupture of membranes).

Hemorrhage etiology and transfusion dose

Table II illustrates blood count values at admission, before transfusion and at discharge. As expected, the number of RBC, Hb values and platelet count were significantly different at admission, after hemorrhage and at discharge.

As for the distribution of hemorrhage etiologies by gestational age and transfusion dose, women were mostly transfused between 35 gestational weeks and post-partum period (75.2%) (**Table III**). The percentage of those receiving three or more RBC units until 35 weeks was higher than that observed in transfused from 35 weeks onwards, although the difference was not significant (25.3 *vs* 19.3%, p: n.s.) (**Table III**). Overall, 11 women, all diagnosed with PPH (three at hospital 2 and eight at hospital 3), received five or more RBC units; all but 2 (81.9%) had delivered by CS.

Pretransfusion Hb levels did not differ among hospitals, as well as post-transfusion Hb (p always >0.05). Furthermore, the adjusted Hb increment per RBC unit transfused was significantly lower at the hospital 3 (median: 0.7, IQR 1.58) than at hospital 1 and 2 (hospital 1: 0.75 IQR 1.75; hospital 2: 0.85, IQR 1.2, $p<0.05$).

As for other blood components, plasma was used in 34 women (one to four units) and platelets (one to three units) in 10.

Lastly, we calculated the length of stay (LOS, in days) for our cohort of 315 transfused women. The overall median

Table I - *Demographic and clinical features of transfused women*

Features	Data
Age years, median (IQR)	34 (29.5-38)
Previous fetal loss No. (%)	73/296 (24.7)
BMI quartile (IQR)	23.1 (20.6-27.6)
Smokers No. (%)	22 (7.2)
Gravidity	**(No.=313)**
First pregnancy	168/313 (53.7)
Second pregnancy	89 (28.4)
Third pregnancy	33 (10.5)
Fourth or more	23 (7.3)
Previous CS No. (%)	154/270 (57.0)
Gestational age, median (range)	38 (6-42)
ART use (%)	33 (10.9)
Admission reasons No. (%)	**(No.=296)**
Near term delivery	117 (39.5)
Pre-term delivery/Threatened FL	74 (25)
Bleeding for abnormal placentation	29 (9.8)
Hypertensive disorders of pregnancy IUGR or diabetes	41(13.9)
Pregnancy loss	11 (3.7)
Ectopic pregnancy	12 (4.1)
Anemia	9 (3.0)
Other	3 (1.0)
RBC units transfused (IQR)	2 (2-2)

Data not available for all women. IQR: interquartile range; CS: cesarean section; ART: assisted reproductive techniques; FL: fetal loss; IUGR: intra uterine growth restriction.

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Table II - *Blood count at admission, before transfusion and at discharge*

	Admission value Median (range)	Pre-transfusion value Median (range)	Discharge value Median (range)	p
RBC 10^{12}/L	3.9 (2.1-5.2)	2.7 (1.2-4.6)	3.3 (2.1-9.8)	<0.001
Hb g/L	10.600 (5.1-15.3)	7.2 (3.4-13.5)	9.2 (6.2-13.4)	<0.001
Hct %	31.700 (18.3-44.2)	22.0 (10.7-39.0)	27.8 (17.2-42.0)	<0.001
Plt 10^9/L	360.0 (15.0-606.0)	78.0 (7.0-499.0)	519.0 (45.0-723.0)	<0.001
MCV fl	84.3 (58.0-116.7)	84.5 (51.0-146.0)	85.9 (58.2-222.0)	<0.001

RBC: red blood cells; Hb: hemoglobin; Hct: hematocrit; Plt: platelets; MCV: mean cell volume

Table III - *Obstetric hemorrhage and distribution of hemorrhage etiologies by gestational age and transfusion dose*

	Transfusion-associated morbidities No.=303	No. of RBC units transfused: 1-2	No. of RBC units transfused: ≥3
Gestational age <22 weeks No. (%)	18 (5.9)	16	2
Fetal loss (%)	7 (43.8)	7	/
Ectopic pregnancy (%)	5 (31.3)	5	/
Cooley disease (%)	2 (12.5)	1	1
Abnormal bleeding after therapeutic termination (%)	4 (22.2)	3	1
Gestational age ≥22-34 weeks No. (%)	57 (18.8)	40	17
Threatened preterm delivery (%)	15 (26.3)	9	6
Preterm delivery* (%)	9 (15.8)	7	2
Abnormal placentation (%)	10 (17.5)	5	5
Abnormal bleeding after therapeutic termination (%)	4 (7.0)	3	1
Uterine atony	5 (8.8)	3	2
Anemia (%)	3 (5.3)	2	1
Hysterectomy[§] (%)	11(19.3)	4	7
Gestational age 35 weeks - 72 h post-delivery No. (%)	228 (75.2)	184	44[@]
Uterine atony (%)	93 (40.1)	75	18
Preterm delivery	46 (20.2)	40	6
Surgical (including iatrogenic lesions) (%)	31 (13.6)	24	7
Hypertensive disorders	21 (10.5)	15	6
Abnormal placentation (%)	17 (7.5)	9	8
Placental abruption	8 (3.5)	6	2
IUGR/Gestational diabetes (%)	12 (5.3)	10	2

*: 6 twin/triplet pregnancies (in 3 cases intrauterine fetal death of one fetus); [§]: 4 with abnormal placentation; [@]: missing information in 13 cases.

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LOS was 5.0 days (IQR: 3-9), with a median of 3 days (IQR: 1-5) after transfusion. There were no significant differences in LOS among the different centers.

Outcome of the index pregnancy

Obstetric outcomes were available for 296 women. Overall, 10.9% of pregnancies resulted from assisted reproductive techniques (ART) (**Table I**), with 2% (comprising five triplets and one twin pregnancy) being multiple pregnancies. Maternal outcomes of the index pregnancy were generally good in terms of mortality, with one death occurring in a patient diagnosed with leukemia, a condition unknown at the onset of pregnancy. Additionally, 11 out of 303 women (3.6%) underwent hysterectomy, with one case following IUFD at 22 weeks.

As for fetal outcomes, we recorded a pregnancy loss rate of 5.9% (No.=17) (both early and late) and a neonatal death rate of 5.5% (No.=16) and (**Table IV**). Among the 271 women with liveborn children, 100 (36.9%) delivered via CS (**Table IV**).

Sixty-three women were transfused with more than three units: five of them had an outcome of fetal or neonatal death. Among 242 women who received 1 or 2 units, there were four cases of fetal or neonatal death. Univariate analysis revealed that the odds of perinatal death (IUFD or neonatal death) were significantly higher in women transfused with three or more RBC units (p value: 0.02, OR: 5.1, 95% CI: 1.3-19.7). Logistic regression, adjusting for age and conception by ART, confirmed the association between IUFD or neonatal death and transfusion doses.

Table IV - *Obstetric outcome of the index pregnancy**

Obstetric outcome	No. (%)
Live-born children	**271 (90.0)**
Vaginal delivery	110 (40.6)
Elective cesarean section	100 (36.9)
Urgent cesarean section	58 (21.4)
Operative delivery	3 (1.1)
Neonatal death	**16/288 (5.5)^**
Fetal loss	11/290 (3.8)
Intra uterine fetal death	6/289 (2.1)
Voluntary termination	8/289 (2.18)

*: Data available in 301 women; ^: 5 triplet and 1 twin pregnancy; in 6 cases Small for Gestational Age newborns; 5 missing information.

Specifically, women transfused with three or more RBC units exhibited a nearly three-fold higher risk of perinatal death (OR: 2.9, 95% CI: 1.0-8.4).

Medical therapies

Throughout their hospital stay, 215 out of 301 women (71.4%) underwent antithrombotic prophylaxis (LMWH) even in the presence of active bleeding. Only 20 (6.6%) were administered tranexamic acid (TXA), while 152 (50.5%) received iron supplementation, the majority of them (110 out of 152, 72.4%) intravenous therapy.

DISCUSSION

Principal findings

The main findings of the present study can be summarized as follows: first, the majority of transfusions occurred from 35 weeks onwards, with the likelihood of receiving a transfusion increasing throughout pregnancy. From the 22nd week onwards, the proportion of women receiving more than two units also increased; about 11% (34/315) received plasma in combination with RBC Among those who required five or more units (No.=11), 81.8% delivered via CS.

Secondly, a significant number (13.9%, **Table I**) of transfused women had co-morbidities such as hypertensive disorders or diabetes. The most common causes of hemorrhage were uterine atony and preterm delivery (40.1 and 20.2%, respectively).

Thirdly, overall delivery outcomes were good in terms of live births, but IUFD and neonatal death were observed in a high number of cases (7.6%). Regarding maternal outcomes, we recorded one maternal death not directly related to pregnancy; 11 out of 303 (3.6%) transfused women underwent hysterectomy.

Fourthly, perinatal outcomes were impacted by the dose of transfusion. Specifically, women transfused with three or more RBC units had a approximately three-fold higher risk of perinatal death, independent of age and conception by ART.

With respect to this, it is worth noting that the application of Patient Blood Management (PBM) in obstetrics, also focusing on antepartum iron supplementation, especially intravenous iron, aims to reduce the need for RBC transfusion in obstetrics. Furthermore, cell salvage, although currently underutilized in obstetrics, with a reported usage of only 0.07% in women with PPH[26], is an important blood conservation strategy. Increasing the use of cell salvage in cases of PPH could significantly reduce the risk of RBC transfusion, further supporting blood conservation efforts in obstetric care.

Results in the context of the available literature

The peripartum period is associated with a higher risk of bleeding, that can lead to transfusion. Consistent with other data[27], our findings suggest that blood transfusions were primarily needed (75.2%) from 35 weeks of gestational age to 72 hours post-delivery. Maternal history of hypertension or acquired conditions like HELLP syndrome or preeclampsia is associated with critical hemorrhage and massive transfusion, as recently demonstrated in a nationwide administrative cohort of obstetric patients[28]. In Europe, diabetes and hypertensive disorders complicate approximately 0.5% and 5% of pregnancies, respectively[29]. In our study, women with such comorbidities are more represented (13.9%) than in other cohorts of pregnant women, suggesting that among transfused women, the impact of comorbidities is significant. Women with hypertensive disorders or diabetes are generally at higher risk of preterm delivery. Therefore, it is unsurprising that in the present study, the percentage of women admitted for preterm deliveries is higher (25%) than that observed in other cohorts of pregnant women in Europe (5-10%)[30].

A National Health Screening Program for Infants and Children found that among 36,868 women transfused a week before birth until one month after birth, those undergoing cesarean deliveries had an OR of 1.64 (95% CI 1.60-1.68) for transfusion[4]. Thus, efforts to reduce unnecessary CS might be a strategy to decrease morbidity associated with pregnancy, as suggested by numerous

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authors[31]. Our data also highlight the relevance of uterine atony, the leading cause of PPH, which was observed in 40.1% of those transfused after 35 weeks and in 8.8% of those transfused between 22 and 34 weeks.

Regarding feto-maternal outcomes, IUFD and neonatal death were observed in 5.5% and 2.1% of the pregnancies, respectively. These figures are higher than those recently observed in the general population (IUFD rate 3-4 per 1,000, neonatal death rate 2-3 per 1,000)[32] and support the concept that transfusion is an index of severity for morbidity outcomes.

It has previously been suggested that assisted conception is associated with severe PPH (crude OR=2.92; 95% CI 2.18-3.92, p<0.001)[33]. Therefore, we adjusted the association between perinatal death and transfusion dose for maternal age and ART conception. Present data suggest that, independently of maternal age and ART conception, transfusion dose significantly affects perinatal outcomes. This is a novel finding that adds knowledge on risk factors affecting perinatal mortality.

In our cohort, more than 70% of women received antithrombotic prophylaxis (LMWH) despite active bleeding. This likely inconsistency can be explained by professionals' concerns about the risk of venous thromboembolism during pregnancy and postpartum[34,35], coupled with fears of exacerbating this risk with blood transfusions[36,37]. Indeed, RBC transfusion is an independent risk factor for postpartum venous thromboembolism and has been included in thromboprophylaxis algorithms for pregnancy[38]. Conversely, only 6.6% of our patients were administered TXA, a safe and effective therapeutic option for reducing the risk of PPH and blood transfusion[39]. This finding underscores the need for implementation research to guide practitioners and decision-makers in adopting TXA as part of PPH treatment.

Lastly, we observed a significant difference in the increase of Hb per unit; hospital 3 showed a significantly smaller increment than the other two. Several factors could account for these differences, including donor age, RBC storage duration, donor gender, irradiation, and Rh-D positivity of recipients[40].

Strengths and limitations

The retrospective design is a limitation of this study, making it susceptible to recall bias or stemming bias from missing or inaccurate data. However, being a multicenter study with a sizable sample size, it provides more precise estimates than smaller, single-center studies. It is possible that, as documented in other series, diagnoses recorded in medical records may not fully capture the reasons for maternal transfusion, either due to incomplete coding practices or the prevalence of other risk factors. Furthermore, the observational nature of the study prevents *a priori* control of all possible confounders. However, the study's objective was to report on maternal and perinatal outcomes in women requiring transfusion during pregnancy, while considering obstetric history and risk factors.

CONCLUSIONS

In this series of transfused women, most women needed transfusion from 35 weeks onwards, with the likelihood of receiving a transfusion increasing throughout pregnancy. Perinatal mortality was significantly and independently affected by the number of RBC units transfused. These findings can guide the design of prospective studies aimed at improving fetal-maternal outcomes by considering the timing and dosage of transfusions required during pregnancy.

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ACKNOWLEDGMENTS

We acknowledge all women who participated in this study.

FUNDING

This research was in part funded by Italian Ministry of Health, RC2021. It is also partially funded by the European Union under the Horizon Europe Innovation Action ThrombUS+ (Grant Agreement No.101137227). The views and opinions expressed are solely those of the Authors and do not necessarily represent those of the European Union or HADEA, the granting authority. Neither the European Union nor HADEA can be held responsible for these views.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of "Casa Sollievo della Sofferenza" (protocol code 184/CE 21/12/2021).

AUTHORS' CONTRIBUTION

EG, AC, MMas, MMar: designed the study; MMas, EG, AO, AM, JK,VB, GLT: analyzed data and critically revised the final draft; MV, AdL, DC, NS, GL, EC: collected data and revised final draft; EG, MMas, MMar, LN: wrote the manuscript.

The Authors declare no conflicts of interest.

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