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Original Article

Therapeutic lessons from transfusion in pregnancy-effect on hematological parameters and coagulation profile

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Abstract: Introduction: Transfusion is commonly done in clinical indications and complications arising due to Anemia, shock, blood loss, thrombocytopenia due to any cause, ineffective erythropoiesis. Pregnancy is a physiological condition characterized by Anemia, fluid overload, hypercoagulable state, and antifibrinolytic condition, which can cause various reactions that could be anticipated during a blood transfusion. With an aim to understand the effects of transfusions on hematological parameters in pregnancy. The results of whole blood and component transfusion were studied to understand increments and their effects so that rationalized transfusion decisions during pregnancy can be undertaken, considering the physiological changes in pregnancy on hemodynamics are present. Methodology: A prospective study with 80 pregnant females undergoing blood transfusion was studied. Their coagulation and hematological profile were correlated to derive a conclusion for the effect of transfusion of blood and its products. Results: A mean increment of 0.55+0.07 g/dL hemoglobin (Hb) was noted along with a slight increase in RBC count (0.25+0.07 millions/mm^3), hematocrit (HCT) (1.9+0.42%), TLC (400+565 cells/mm^3). This statistically significant mean increase in hemoglobin, RBC count, and hematocrit was significantly lower than that compared to studies in the west and non-anemic patients. A mean increment of 7.79+1.51 µg/dL (statistically significant) in serum iron was seen. A significant improvement in their coagulation profile was achieved by plasma transfusion (FFP). Clotting time (CT) decreased by a mean value of 196.43+56.69 secs and prothrombin time (PT) by 2.64+0.63 secs ($P<0.05$). All transfusion reactions in our study were associated with PRBC transfusion, non-hemolytic immunological type, urticarial transfusion reactions (UTR) more common in multiparous women-0.2% in primigravida to 21.7% and 37.5% in 3rd and 4th parity similar to that observed in other studies. Conclusion: Although different researchers have done numerous studies, the physiological profile of pregnant females in India is markedly different in nutritional profile, ethnicity, environmental factors, and background. The availability of tertiary care medical facilities during ANCs is also known to affect pregnancy outcomes and the presentation of patients at term or in labor. The variety of factors affect the baseline hematological status of pregnant females and, hence, post-transfusion hematological factors. These are therefore markedly different from prior published studies. It is concluded that PRBC transfusion in pregnant women causes a lower increase in mean Hb and HCT values than in the west, and ferritin and serum iron are not reliable indicators of Anemia in transfusion. Due to lower increments in all values except platelets could be the reason for this could be contributed by confounding factors like Anemia, hyperfibrinogenemia, volume overload, and ethnicity.

Keywords: Blood transfusion, pregnancy, coagulation profile, component transfusion, transfusion reactions

Introduction

Transfusion of blood and its products is a safe and effective way of correcting hematological defects. Still, adverse effects do occur during or after transfusion, and they are commonly called transfusion reactions. They may be acute or delayed. Transfusion transmitted infections include many viral, bacterial, and protozoal infections. Transfusion therapy in pregnancy is

standard practice nowadays, particularly in India, where up to 75% of pregnant women are anemic, and obstetric hemorrhage is a common complication [1]. Many atimes the increment in the transfusion is not similar to what is expected, it could be do to a number of pre-existing conditions, co-morbidities and confounding factors. With an aim to understand the changes in the hematological profile of pregnant women post-transfusion, the study was conducted in all women presenting at term. The patients were transfused with whole blood and components depending on the data available in the west to ameliorate deficits in various components. But this data could not reliably indicate the increment will be the same in Indian women presenting with various confounding factors-namely nutritional status, ethnic differences, physical differences in BMI, and body weight. Hence a study is required to study the effects of transfusions on hematological parameters in pregnancy in the Indian population. It is essential to understand increments in hematological parameters after the unit of transfusion so that rationalized transfusion decisions during pregnancy can be undertaken, considering the physiological changes in pregnancy on hemodynamics are already present.

The present study is undertaken to analyze the effects of transfusion of blood and blood components on pregnancy, its outcome, and the adverse reactions associated with it.

Apart from complications that arise from normal physiological changes in pregnancy - like a relative expansion of plasma volume, increase in red cell mass, leukocytosis, and a hypercoagulable and antifibrinolytic state; various other indications of transfusion of blood and its products in clinical practice are antepartum hemorrhage, shock, ectopic pregnancy, severe Anemia, postpartum hemorrhage and disseminated intravascular coagulation. Mean changes in hematological parameters and coagulation profile after transfusion in pregnancy are essential to guide the requirement and predict response in pregnant women. With studies predicting the expected changes in pregnancy after transfusion, few studies in this tropical region where Anemia in pregnancy is very prevalent (52%-NFHS survey 2017). The effect of iron supplementation on serum iron and coagulation profile and the patient pre and post-transfusion is also less known in this geographic region.

Materials and methods

The present study was carried out on 80 pregnant patients attending the inpatient and outpatient services of the Department of Obstetrics and Gynaecology, J.N. Medical College, A.M.U. Aligarh. The patients selected for the study were those who required blood and component transfusion therapy during pregnancy. The study was carried out over two years, from November 2010 to November 2012. The following studies were conducted on these patients:

Hematological profile was assessed both before and after transfusion therapy in all the cases, including haemogram, red cell indices, and platelet count.

Coagulation studies such as bleeding time (BT), clotting time (CT), clot retraction time (CRT), and prothrombin time (PT) were assessed wherever necessary.

Serum iron studies, such as serum iron, serum ferritin, and total iron-binding capacity (TIBC), were evaluated wherever necessary.

Transfusion reactions that occurred as a result of blood/component transfusion therapy were studied.

Test for hematological profile

Two ml venous blood was sampled in Potassium Ethylene Diamine Tetra Acetic Acid (K 2 EDTA) vacutainer (Akuret Eastern Medikit Ltd, Haryana, India) both before and after transfusion of blood/products (within 24 hours of transfusion). Hematological studies were done using an automated cell counter (Lab Life H3D Premier automated hematology analyzer, RFCL). Haemogram included parameters like hemoglobin (%), total leucocyte count (TLC), differential leucocyte count (DLC), red cell count, hematocrit (%), platelet count, and red cell indices (RCI). RCI included mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) (Dacie and Lewis, 2006). The details of procedure reagents and methodology are explained in the supplementary annexure.

Coagulation studies

Bleeding time (BT): A measure of platelet number and function, capillary function, and plate-

let plug formation.Template method (Dacie and Lewis, 2006).

Normal range: 2-7 min.

Clotting time (CT): Rough indicator of the intrinsic pathway and is prolonged only when there is a severe deficiency of Factor VIII, IX, or fibrinogen. Capillary tube (Wright's) method (Pal and Pal, 2005).

Clot retraction (CRT): (Pal and Pal, 2005).

A normal serum retracts from the bottom and sides of the test tube within 1-2 hrs and expresses 45-60% of serum after 24 hrs.

Prothrombin time (PT): (Dacie and Lewis, 2006).

Quick's one stage method

PT ratio = PT coagulation time of sample plasma.

The normal PT value is 10-14 secs. Any prolongation beyond 3 secs of the control value is taken as abnormal.

INR = (PT ratio) ISI.

Serum iron profile

● SERUM IRON AND TOTAL IRON-BINDING CAPACITY (TIBC):

(Using Pointe Scientific, Inc. kit).

-Principle (Dacie and Lewis, 2006)

● TIBC (µg/dl) = Iron level + UIBC

Normal values: Total iron = 60-150 µg/dl.

TIBC = 250-400 µg/dl.

● SERUM FERRITIN

(Using Diagnostic Automation, Inc. kit)

-Principle (Dacie and Lewis, 2006)

Normal value - 15-200 µg/l in females.

Statistical analysis

The statistical analysis was done using SPSS (version 13.0) software for Windows. The data were grouped into pre-transfusion and post-transfusion variables. Considering pre-transfusion samples as control, paired t-test was calculated for post-transfusion samples. A correlation between the two groups was analyzed, and a *p*-value <0.05 was regarded as statistically significant.

Transfusion reactions

Transfusion reactions that occurred in the course of two years were studied for the following:

Proper clinical history.

Blood group.

Component transfused.

Volume transfused.

Time of reaction

Signs and symptoms that developed after the reaction.

Condition of the blood bag and its contents.

Colour of urine sample received.

Re-cross match (using gel technique) and Coomb's test (direct and indirect) were done in every case. Bacterial and fungal cultures of the contents of bags were sent.

Coomb's test

Principle (Dacie and Lewis, 2006)

Direct Coomb's Test (DCT)

Indirect Coomb's Test (ICT)

Results

The present study was carried out on 80 pregnant patients attending the inpatient and outpatient services of the Department of Obstetrics and Gynaecology, J.N. Medical College, A.M.U. Aligarh. The patients selected for the study were those who required blood and component transfusion therapy during pregnancy. Due ethical consent was taken for this study.

A total number of 80 pregnant patients were selected for the study. The mean age of the patients was 26 years ranging from 19 to 35 years. The majority (42.5%) of the cases belonged to the third trimester of their pregnan-

Table 1. Mean haematological parameters before and after transfusion of single unit of whole blood

Parameter	Pre Transfusion Mean (M_1) +SD	Post Transfusion Mean (M_2) +SD	Mean Difference (M_2-M_1) +SD	0.95 CI of difference	Paired t-test	*p*-value
Haemoglobin* (g/dL)	6.10+0.57	6.65+0.64	0.55+0.07	(-0.08)-1.86	11.00	>0.05
RBC count (millions/mm^3)	2.85+0.21	3.10+0.28	0.25+0.07	(-0.38)-0.88	5.00	>0.05
Haematocrit (%)*	20.45+1.63	22.35+2.05	1.9+0.42	(-6.06)-9.86	1.03	>0.05
Total leukocyte count (/mm^3)	13,500+707	13,900+141	400+565	(-4682)-5482	1.00	>0.05
Platelet count (lakhs/mm^3)	1.55+0.21	1.55+0.21	00.00	-	-	-
MCV (fL)	71.75+0.21	72.00+0.00	0.25+0.21	(-1.66)-2.16	1.67	>0.05
MCH (pg)	21.40+0.00	21.60+0.14	0.20+0.14	(-1.07)-1.47	2.00	>0.05
MCHC (g/dL)	29.75+0.35	29.75+0.07	0.00+0.28	(-2.54)-2.54	0.00	>0.05
RDW (%)	16.65+0.07	16.50+0.14	-0.15+0.07	(-0.79)-0.49	3.00	>0.05

*- Indicates clinically significant increment, please note all the remaining values were statistically non-significant with *P* value >0.05.

cy period, with only 6.25% cases in the first and 16.25% cases in the second trimesters. 35% of cases had ≥36 wks pregnancy. The majority of patients were from an area in and around Aligarh. The most common blood group was O (42.5%), followed by B (32.5%), the rest being A (20%) and AB (5%). The majority of cases were Rh positive (95%), and Rh-negative cases in our study were 5%.

The most common indication for transfusion of PRBCs was Anemia due to obstetric hemorrhage. Active bleeding was the only indication for transfusion of whole blood. Pre-eclampsia and eclampsia together constituted the major indication for transfusion of platelets. The majority of FFPs were transfused to cases of intrauterine death (IUD), postpartum hemorrhage, and abortifacient abuse.

Blood samples were drawn both before and after transfusion of these blood/component units and analyzed. Pre transfusion samples were considered as controls for statistical analysis. **Table 1** summarizes the mean changes observed in different hematological parameters after transfusion of a single unit of whole blood. A mean increment of 0.55+0.07 g/dL haemoglobin was noted along with slight increase in RBC count (0.25+0.07 millions/mm^3), haematocrit (1.9+0.42%), TLC (400+565 cells/mm^3), MCV (0.25+0.21 fL) and MCH (0.20+0.14 pg) but no change in platelet count and MCHC was observed. RDW was reduced by 0.15+0.07% post-transfusion. Results were statistically insignificant.

Similarly, a mean increase of 0.71+0.15 g/dL in hemoglobin (statistically significant) was found after transfusion of a single unit of PRBCs. RBC count was raised significantly by 0.29+0.19 million/mm^3, hematocrit by 2.43+0.77% (all these observations were significant, P<0.05). TLC was changed by 161+500 cells/mm^3, but MCV showed a decrease by 0.47+8.81 fL and platelet count by 200+1000/mm^3, which showed a statistically insignificant result. There was a significant increase in MCH by 0.12+0.18 pg. However, MCHC decreased slightly by 0.23+0.75 g/dL (P<0.05, statistically significant) and RDW by 0.05+0.34%, which showed a statistically insignificant result (**Table 2**). Serum iron studies were done in 12 cases of severe Anemia transfused with PRBCs. A mean increment of 7.79+1.51 µg/dL (statistically significant) was noted in serum iron, and only slight insignificant changes in TIBC and serum ferritin (**Table 3**).

As shown in **Table 4**, changes were observed after transfusion of 2 units of platelet concentrate in platelet count (16,000+6,000/mm^3), bleeding time (365+275.77 secs), clotting time (10+14.14 secs), and clot retraction time (15+14.14%) only. TLC was reduced by 500+707 cells/mm^3, but no change was found in hemoglobin level, RBC count, hematocrit, red cell indices, and prothrombin time, the reason being very obvious.

FFP contains coagulation factors and plasma only. In our study, two units were transfused to each patient. As shown in **Table 5**, there is a 0.16+0.26 g/dL decrease in hemoglobin levels. Accordingly, RBC, hematocrit, MCHC, and MCV also decreased marginally. The only plausible explanation seems to be continuing hemorrhage. TLC showed a decrease by 422+948 cells/mm^3. RDW and platelet count were slight-

Table 2. Mean haematological parameters before and after transfusion of single unit of PRBC

Parameter	Pre Transfusion Mean (M_1) +SD	Post Transfusion Mean (M_2) +SD	Mean Difference (M_2-M_1) +SD	0.95 CI of difference	Paired t-test	*p*-value
Haemoglobin (g/dL)	5.71+1.26	6.42+1.22	0.70+0.15	0.66-0.74	34.01	<0.05
RBC count (millions/mm^3)	2.52+0.49	2.81+0.47	0.29+0.19	0.24-0.34	10.89	<0.05
Haematocrit (%)*	18.69+3.76	21.12+3.65	2.43+0.77	2.22-2.65	22.71	<0.05*
Total leukocyte count (cells/mm^3)	11,577+3126	11,738+3125	161+500	22-300	2.33	<0.05
Platelet count (lakhs/mm^3)	1.90+0.91	1.89+0.91	-.002+0.01	(-0.005)-0.019	1.00	>0.05
MCV (fL)	74.70+9.00	74.23+12.77	-0.47+8.81	(-2.92)-1.98	-0.38	>0.05
MCH (pg)	22.77+3.55	22.89+3.50	0.12+0.18	0.08-0.17	5.12	<0.05
MCHC (g/dL)	30.61+3.91	30.38+3.68	-0.23+0.75	(-0.02)-(-0.44)	-2.22	<0.05
RDW (%)	15.67+1.97	15.62+1.84	-0.05+0.34	(-0.15)-0.04	-1.24	>0.05

*- Indicates clinically insignificant increment.

Table 3. Mean serum iron parameters before and after transfusion of single unit of PRBC

Parameter	Pre Transfusion Mean (M_1) +SD	Post Transfusion Mean (M_2) +SD	Mean Difference (M_2-M_1) +SD	0.95 CI of difference	Paired t-test	*p*-value
Serum Iron* (µg/dL)	203.35+43.86	211.14+43.35	7.79+1.51	6.83-8.75	17.86	<0.05*
TIBC (µg/dL)	514.05+42.49	513.10+43.34	-0.95+1.97	(-2.20)-0.30	-1.67	>0.05
Serum Ferritin (µg/L)	10.03+0.85	10.08+0.82	0.05+0.11	(-0.12)-0.02	1.59	>0.05

*- Indicates clinically insignificant increment.

Table 4. Mean haematological parameters before and after transfusion of 2 units of platelet concentrate

Parameter	Pre Transfusion Mean (M_1) +SD	Post Transfusion Mean (M_2) +SD	Mean Difference (M_2-M_1) +SD	0.95 CI of difference	Paired t-test	*p*-value
Haemoglobin (g/dL)	10.4±1.27	10.4±1.27	0.00	-	-	-
RBC count (millions/mm^3)	3.25±0.64	3.25±0.64	0.00	-	-	-
Haematocrit (%)	31.65±4.17	31.65±4.17	0.00	-	-	-
Total leukocyte count (/mm^3)	12,000±1410	11,500±2120	-500±707	(-8260)-7260	0.28	>0.05
Platelet count* (lakhs/mm^3)	0.40±0.14	0.56±0.08	0.16±0.06	(-0.35)-0.67	4.00	>0.05
MCV (fL)	98.05±6.15	98.05±6.15	0.00	-	-	-
MCH (pg)	32.05±2.05	32.05±2.05	0.00	-	-	-
MCHC (g/dL)	32.9±0.28	32.9±0.28	0.00	-	-	-
RDW (%)	12.7±1.27	12.7±1.27	0.00	-	-	-
Bleeding time (sec)	1120±395.98	755±120.21	-365±275.77	(-2842)-2112	-1.87	>0.05
Clotting time (sec)	470±14.14	480±28.28	10±14.14	(-117.06)-137.06	1.00	>0.05
Prothrombin time (sec)	14±1.14	14±1.14	0	-	-	-
Clot retraction (%)	20±7.07	35±7.07	15±14.14	(-112.06)-142.06	1.50	>0.05

*- Indicates clinically insignificant increment.

ly decreased after transfusion. All these changes were statistically insignificant. Coagulation parameters improved considerably after transfusion of 2 units of FFP. Clotting time (CT) decreased by a mean value of 196.43+56.69 secs and prothrombin time (PT) by 2.64+0.63 secs (P<0.05). Bleeding time (BT) also decreased slightly (11.78+16.94 secs) (**Figure 1**). Clot retraction (CRT) decreased by 2.64+7.90% (statistically insignificant).

Differential leucocyte count of the majority of pre-transfusion samples showed neutrophilia, with only 4 cases showing lymphocytosis. No significant change was noticed after transfusion.

Transfusion reactions

Ten cases of transfusion reactions that occurred during the period of study were evalu-

Table 5. Mean haematological parameters before and after transfusion of 2 units of FFP

Parameters	Pre Transfusion Mean (M_1)	Post Transfusion Mean (M_2)	Mean Difference (M_2-M_1)	0.95 CI of difference	Paired t-test	*p*-value
Haemoglobin (g/dL)	6.72+1.59	6.56+1.60	-0.16+0.26	(-0.01)-(-0.31)	2.27	<0.05
RBC count (millions/mm^3)	2.85+0.57	2.79+0.57	-0.06+0.11	(-0.12)-0.01	1.96	>0.05
Haematocrit (%)	21.36+4.61	20.92+4.68	-0.44+0.81	(-0.91)-0.03	2.05	>0.05
Total leukocyte count (/mm^3)	14,279+3250	13,857+3041	-422+948	(-968)-126	1.66	>0.05
Platelet count (lakhs/mm^3)	1.46+0.49	1.44+0.47	-0.02+0.04	(-0.05)-0.003	1.88	>0.05
MCV (fL)	75.04+6.15	75.03+6.13	-0.01+0.03	(-0.02)-0.01	1.000	>0.05
MCH (pg)	23.28+2.64	23.28+2.64	0.00	-	-	-
MCHC (g/dL)	31.41+3.40	31.32+3.33	-0.09+0.24	(-0.23)-0.05	-1.33	>0.05
RDW (%)	15.33+1.47	15.29+1.53	-0.04+0.23	(-0.18)-0.09	0.68	>0.05
Bleeding time* (sec)	234.64+65.27	222.86+56.18	-11.78+16.94	(-2.01)-(-21.57)	-2.60	<0.05*
Clotting time* (sec)	592.14+84.21	395.71+93.70	-196.4+56.69	(-127.08)-(-265.77)	-5.83	<0.05*
Prothrombin time (sec)*	19.29+1.33	16.64+0.93	-2.64+0.63	(-2.28)-(-3.01)	-15.61	<0.05*
Clot retraction (%)*	53.50+7.52	50.86+3.37	-2.64+7.90	(-7.20)-1.92	-1.25	>0.05

*- Indicates clinically insignificant increment.

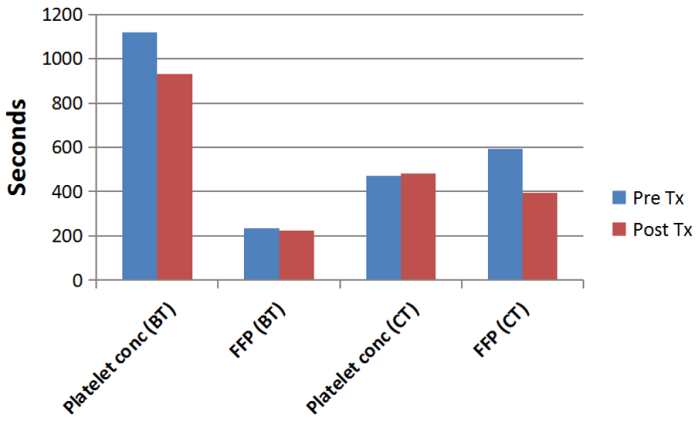

Figure 1. Pre and post transfusion bleeding time (BT) and clotting time (CT).

Further assessment of blood and urine samples was done. RBC color was found to be red in all the blood bags, and the color of plasma was clear. Urine was also clear in all the cases, with only 2 showing intact RBCs as sediment. The condition of blood bags was acceptable, and there was no clot/mass seen. Direct and Indirect Coomb's tests were negative in all the samples. Hence, all these reactions were classified as immediate, non-hemolytic immunological types. Bacterial and fungal cultures were sent and were later found to be negative (**Table 6**).

ated. All these reactions occurred during PRBC transfusions, and the cases belonged either to A Rh+ve or B Rh+ve blood groups. None of the cases was Rh-ve.

8 out of these 10 cases were multiparous women, out of which 3 were third para. The rest of the two women was primiparous. As seen above, most of these units were transfused to combat Anemia. Most of the reactions occurred within 30 min of starting a transfusion, i.e., they were of immediate type, and the mean volume transfused was 116 ml. Fever, chills, and rigors were the most common symptoms experienced by these patients. Other signs and symptoms were respiratory distress, hypotension, palpitations and tingling, and numbness.

The present 2-year prospective study on 80 pregnant female patients was undertaken to evaluate changes in hematological profile after transfusion of blood and its products. Many parameters were assessed, including hemoglobin levels (Hb), RBC count, hematocrit (Hct), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, and red cell indices (RCI). Special studies (iron and coagulation studies) were done wherever necessary. Associated transfusion reactions were also studied in detail. The following points were concluded from this study:

1. Majority of transfusions are required in the third trimester of pregnancy, and most of them were RBC transfusions.

Table 6. Summary of transfusion reactions

Feature	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (yrs)	25	20	22	22	32	28	34	31	23	25
Gestational age (wks)	30	35	37	35	20	28	32	34	38	25
Parity	2	1	3	0	4	4	2	4	0	1
Indication	Anaemia	Anaemia	Anaemia	Anaemia	H'age	H'age	Anaemia	Anaemia	Anaemia	H'age
Blood/component	PRBC	PRBC	PRBC	PRBC	PRBC	PRBC	PRBC	PRBC	PRBC	PRBC
Blood group	B+	A+	A+	B+	A+	A+	B+	B+	B+	A+
Vol. transfused (ml)	150	10	150	150	150	100	50	200	100	100
Time of reaction (min)	90	10	30	120	50	15	10	60	20	25
Symptoms/Signs	Chills, rigors	Rigors, hypotension	Chills	Fever, chills	Palpitations	Chills, rigors	Tingling, numbness	Dyspnoea	Palpitations	Hypotension
Colour of RBC	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red
Color of plasma	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
Colour of urine	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
Any abnormal mass/clot	No	No	No	No	No	No	No	No	No	No
Any peculiar odor	No	No	No	No	No	No	No	No	No	No
Leakage/breakage	No	No	No	No	No	No	No	No	No	No
Ports	1 broken	1 broken	1 broken	1 broken	1 broken	1 broken	1 broken	1 broken	1 broken	1 broken
Transfusion set filter	Present	Present	Present	Present	Present	Present	Present	Present	Present	Present
Bacterial and fungal culture	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
DCT	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
ICT	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Repeat crossmatch	Compatible	Compatible	Compatible	Compatible	Compatible	Compatible	Compatible	Compatible	Compatible	Compatible
Type of reaction	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic	Immediate/ Non-haemolytic

Abbreviations: WHO- world Health Organisation, BMI- Body Mass Index, FFP- Fresh frozen plasma, ANC- Antenatal care, Hb- Haemoglobin, HCT- Haematocrit, TLC- Total Leucocyte count - Red blood cell, MCH- Mean corpuscular Haemoglobin, MCV- Mean Corpuscular Volume, MCHC- Mean Corpuscular Hemoglobin Concentration, RDW- Red cell distribution width, TIBC- Total Iron Binding Capacity, UIBC- unsaturated iron-binding capacity, INR- International normalized ratio, DCT- Direct Coombs Test, ICT- Indirect Coombs Test, PRBC- Packed Red Blood Cell, CI- confidence interval.

Table 7. Mean haematological parameters before and after transfusion of 2 units of platelet concentrate

Parameter	Pre Transfusion Mean (M_1) ±SD	Post Transfusion Mean (M_2) ±SD	Mean Difference (M_2-M_1) ±SD	0.95 Confidence Interval of difference	Paired t test	*p* value
Haemoglobin (g/dL)	10.4±1.27	10.4±1.27	0.00	-	-	-
RBC count (millions/mm^3)	3.25±0.64	3.25±0.64	0.00	-	-	-
Haematocrit (%)	31.65±4.17	31.65±4.17	0.00	-	-	-
Total leukocyte count (/mm^3)	12,000±1410	11,500±2120	-500±707	(-8260)-7260	0.28	>0.05
Platelet count (lakhs/mm^3)	0.40±0.14	0.56±0.08	0.16±0.06	(-0.35)-0.67	4.00	>0.05
MCV (fL)	98.05±6.15	98.05±6.15	0.00	-	-	-
MCH (pg)	32.05±2.05	32.05±2.05	0.00	-	-	-
MCHC (g/dL)	32.9±0.28	32.9±0.28	0.00	-	-	-
RDW (%)	12.7±1.27	12.7±1.27	0.00	-	-	-
Bleeding time (sec)	1120±395.98	755±120.21	-365±275.77	(-2842)-2112	-1.87	>0.05
Clotting time (sec)	470±14.14	480±28.28	10±14.14	(-117.06)-137.06	1.00	>0.05
Prothrombin time (sec)	14±1.14	14±1.14	0	-	-	-
Clot retraction (%)	20±7.07	35±7.07	15±14.14	(-112.06)-142.06	1.50	>0.05

2. Obstetric hemorrhage is the most common indication for transfusions in pregnancy.

3. Generalized leukocytosis is seen in pregnancy, with a predominance of polymorphs.

4. Transfusion of both whole blood (WB) and packed red blood cells (PRBCs) causes significant elevation of Hb, Hct, and RBC count. Still, no or insignificant changes in TLC, platelet count, and RCI are seen. Hence, transfusion of WB to increase platelet count is not recommended.

5. However, increment caused by PRBC transfusion appears to be more than whole blood and associated with lesser complications. Hence use of PRBCs for the correction of anemia is encouraged.

6. Serum iron and ferritin are not a good measure of anemia in pregnant patients on long-term iron therapy.

7. Only serum iron increases after transfusion of PRBCs.

8. Platelet concentrates (PC) are effective in the case of thrombocytopenia in pregnancy.

9. Fresh frozen plasma (FFP) improves coagulation profile in pregnancy by reducing clotting time (CT) and prothrombin time (PT).

10. Transfusion reactions are more commonly seen in red cell transfusions as compared to other blood products.

11. Transfusion reactions occur more commonly in multiparous women.

12. Immediate non-hemolytic type of transfusion reactions are the commonest in pregnancy.

The values post-transfusion increments were significantly lower than those published by other studies [2-4] on transfusion in pregnancy are limited to few studies and are essential to the underlying problem of iron deficiency anemia in this age group [5]. The transfusion reaction in this age group can be threatening both maternal and fetal outcomes and is complicated by the pathophysiological changes in pregnancy. TIBC and serum ferritin are strongly regulated by dietary iron supplementation and showed no change in these pregnant women [5, 6]. Two units of FFP were transfused to 14 patients each in our study, and a significant improvement in their coagulation profile was achieved. Clotting time (CT) decreased by a mean value of 196.43±56.69 secs and prothrombin time (PT) by 2.64±0.63 secs ($P<0.05$). Bleeding time (BT) also decreased slightly (11.78±16.94 secs). Clot retraction (CRT) decreased by 2.64±7.90% (statistically insignificant), contrary to that quoted by Abdel-Wahab and Healy [7], who observed only a partial correction in PT, probably because of subjects being patients of coagulation disorders in their study.

A mean increase in platelet count of 16,000±6,000/mm^3 (8,000/mm^3 per unit) was noted (**Table 7**), which is in concordance with

the fact that a single unit of platelet concentrate elevates the count by 5000-10,000/mm^3 [8]. BT also decreased by 365±275.77 secs, indicating that platelet transfusion increases the numbers and improves platelets' function.

All transfusion reactions in our study were associated with PRBC transfusion, non-hemolytic immunological type, urticarial transfusion reactions (UTR) more common in multiparous women-0.2% in primigravida to 21.7% and 37.5% in 3rd and 4th parity similar to that observed in other studies [9, 10].

An average increment of 0.55±0.07 hemoglobin g/dL per unit, platelet count of 8,000/mm^3 per unit, slightly improved coagulation profile can be expected in Indian pregnant females on oral iron supplementation. It is concluded that PRBC transfusion in pregnant women causes a lower increase in mean Hb and HCT values than in the west, and ferritin and serum iron are not reliable indicators of Anemia in transfusion.

Discussion

Maternal physiological changes in pregnancy are the normal adaptational mechanisms that a female undergoes during pregnancy to accommodate the embryo or fetus better. These physiological changes are considered normal, including cardiovascular, haematologic, metabolic, renal and respiratory changes, and assume great importance in the event of complications. The body must change its physiological and homeostatic mechanisms in pregnancy to ensure that the fetus should get the necessary nutrients from the maternal blood circulation. Paidas and Hossain (2010) reported profound changes in hematological profiles during pregnancy [10].

Physiological changes

Plasma volume increases progressively in pregnancy and results in 1100-1600 mL (30-50%) increase above found in the non-pregnant state [10]. Red cell mass rises by 250-450 mL (20-30%) compared to non-pregnant women in those receiving iron supplements and 15%-20% in women not on iron supplementation. Erythropoietin levels increase by 50%, but MCV decreases to 80-84 fl in the third trimester. Thus, a more significant expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume is responsible for the modest fall in hemoglobin levels (physiological or dilutional anemia of pregnancy) [11]. Shehata et al. demonstrated that red cell distribution width (RDW) increased significantly between 34 weeks of gestation and the onset of labor [12]. Pregnancy is associated with leukocytosis (TLC range 9000-26,000 cells/cu mm), mainly neutrophilia, and the number of white blood cells, especially polymorphs, increases considerably during pregnancy (between 8,000 to 16,000 cells/mm^3), especially in the second and third trimesters [10, 12]. Although platelet counts remain in the normal non-pregnant range in most cases, they are slightly lower than in their healthy counterparts [10].

Serum iron profile

Normal iron indices during pregnancy as reported are: Plasma iron- 40-175 µg/dL, Plasma total iron-binding capacity (TIBC)- 216-400 µg/dL, Transferrin saturation- 16-60% and Serum ferritin- 10 µg/L [10]. In a study of 13 cases, Rath et al. found the serum iron values for the three trimesters as 111, 123, and 112 µg/100 ml, respectively. Values for TIBC of the serum in the three trimesters in µg/100 ml. were, respectively, 290±32, 313±40, and 336±45 [13]. Romslo et al. determined serum iron, TIBC, serum ferritin, and erythrocyte protoporphyrin during uncomplicated pregnancy in 45 healthy women; 22 were given oral iron while the others were given a placebo. When iron was not given, 15 out of 23 women had exhausted iron stores and iron deficiency at term, as judged from low serum ferritin, low serum transferrin saturation, and high erythrocyte protoporphyrin values [14].

Coagulation profile

There is a state of hypercoagulability due to increased coagulation factors and a decrease in fibrinolytic activity. Fibrinogen rises to 4-6 g/L, and Factors VII, VIII, and X increase by 20-100% [11]. The bleeding time is unchanged during normal pregnancy. Blood coagulation inhibitors are mainly unchanged, but the level of free protein S decreases markedly, and the level of tissue factor pathway inhibitor increases. Thrombomodulin levels increase during pregnancy. Fibrinolytic capacity is diminished during pregnancy. Thrombin-activated fibrinoly-

sis inhibitor is reported to be unaffected. The total hemostatic balance has been studied by analyses of prothrombin fragment 1+2, thrombin-antithrombin complex, fibrinopeptide A, soluble fibrin, D-dimer, and plasmin-antiplasmin complex.

Uchikova and Ledjev found significantly higher values for prothrombin time (PT), thrombin time (TT), fibrinogen, the activity of factor VII, factor X, and alpha2-antiplasmin, the plasma concentration of d-dimer (plsDD), and activity of heparin cofactor II (HCII) in pregnant females [15].

Anemia in pregnancy

Anemia is defined as a reduction in circulating hemoglobin mass below the critical level. The normal hemoglobin (Hb) concentration in the body is between 12-14 gm/dL. WHO (1968) has accepted up to 11 gm percent as the average hemoglobin level in pregnancy. Therefore, any hemoglobin level below 11 gm in pregnancy should be considered as anemia. However, in India and most other developing countries, the lower limit is often accepted as 10 gm/dL [16].

The estimated prevalence of Anemia among pregnant women in India is higher than the global prevalence at 49.7% [17]. According to survey data, 84.9% of pregnant women are anemic, with 60.1% having moderate Anemia and 13.1% having severe Anemia [18]. The prevalence of anemia in South Asian countries is among the highest in the world. In India, the prevalence of anemia is high because of (i) low dietary intake, insufficient iron (less than 20 mg/day) and folic acid intake (less than 70 mg/day); (ii) poor bioavailability of iron (3-4% only) in phytate and fiber-rich Indian diet; and (iii) chronic blood loss due to infection such as malaria and hookworm infestations [19]. It also increases maternal morbidity, fetal and neonatal mortality, and morbidity significantly.

Maternal risk during the Antenatal period: Poor weight gain, preterm labor, pregnancy-induced hypertension, placenta praevia, accidental hemorrhage, eclampsia, premature rupture of membrane (PROM), etc. Maternal risk during intranatal period: Dysfunctional labor, intranatal hemorrhage, shock, anesthesia risk, cardiac failure. Maternal risk during the postnatal period: Postnatal sepsis, sub involution, embolism [20].

Indications of transfusion in pregnancy

There are no published guidelines for the use of red cell transfusion in obstetrics and gynecology. The United States Report of Health and Human Services laid down guidelines for generally using blood products. It stated that adequate oxygen-carrying capacity to maintain cardiopulmonary function could be met by a hemoglobin level of 7 gm/dL (equivalent to a haematocrit of approximately 21%) intravascular volume is adequate for perfusion. A study where two transfusion strategies were used in patients undergoing myocardial revascularization found no difference in postoperative recovery between patients with hematocrits of 21.00% and 30.29%. United States guidelines developed a care provider strategy for the use of red cells [21]. Those of relevance to obstetrics are:

• A Hb of <7 gm/dL (hematocrit of 21%) if not due to a treatable cause.

• Symptomatic anemia regardless of Hb level.

• Patients receiving general anesthesia if their preoperative Hb is <7 gm/dL.

• A major bloodletting operation and a Hb of <10 gm/dL (haematocrit of <30%) [22].

Recent trends in obstetric transfusion

Despite published guidelines, a proportion of red blood cell (RBC) transfusions seem unnecessary. To evaluate the indications for appropriate RBC transfusions in the postpartum patient, a retrospective observational study of transfused obstetric patients over one year in two Dutch hospitals, admitted in 2006 to the Departments of Obstetrics of a university and a general hospital showed that of 311 RBC units transfused, 143 units (46%) were possibly inappropriate, partly due to over-transfusion. They concluded that a significant proportion of postpartum RBC transfusions are possibly inappropriate, partly due to over-transfusion [23]. If current guidelines would be more specific, particularly with respect to the target Hb levels, the total amount of RBC transfusions may be considerably decreased.

Several studies have documented this decline in transfusion rates with an increase in c-section rates [22, 24, 25]. During Caesarean sec-

tion in a developing country, blood transfusion practices showed a total of 117 out of 463 (25.2%) cesarean section cases were transfused [26]. A total of 78 (67.2%) of Caesarean section cases were emergency which is considered high.

Alexander et al. have suggested that the use of whole blood may have advantages over PRBCs in the treatment of obstetric hemorrhage. A more frequent complication of whole blood transfusion in obstetric patients is pulmonary edema compared to PRBC transfusion, where acute tubular necrosis occurs as a complication [27].

Plasma for transfusion is most often used where there are abnormal coagulation screening tests, either therapeutically or prophylactically, in non-bleeding subjects before invasive procedures or surgery. Little evidence exists to inform the best therapeutic plasma transfusion practice [28].

Acute transfusion reactions present as adverse signs or symptoms during or within 24 hours of a transfusion. The most frequent reactions are fever, chills, pruritus, or urticarial rashes, which typically resolve promptly without specific treatment or complications. Other signs are occurring in a temporal relationship, such as severe shortness of breath, red urine, high fever, or loss of consciousness, maybe the first indication of a more severe reaction. Transfusion reactions are broadly divided into two types.

Immunologic reactions: A. Alloimmunization to transfused antigen may not be present on red cells, leukocytes, platelets, or the recipient's plasma. Serological evidence of a delayed transfusion reaction is common; however, these reactions rarely cause clinical symptoms [29]. The probability of these events occurring together was 1 in 500,000 deliveries.

B. Haemolytic transfusion reactions occur most commonly in women due to prior sensitization of RBCs during pregnancy.

They are of three types:

a) Immediate intravascular hemolytic transfusion reactions - Mostly due to ABO incompatibility.

b) Delayed hemolytic transfusion reactions-Predominantly extravascular, antibody to Jk and Rh are the usual causes.

c) Pseudohaemolytic transfusion reactions-Similar to hemolytic reaction but no incompatibility detected. Drugs, bacterial contamination are the usual causes.

The risk of hemolytic transfusion reactions (HTRs) is approximately 1:70,000 per unit. Acute HTRs occurring during or within 24 h after administration of a blood product are usually caused by transfusion of incompatible red blood cells (RBCs) and, more rarely, of a large volume of incompatible plasma. Delayed HTRs are caused by a secondary immune response to an antigen on the donor's RBCs. In some patients with delayed HTRs, additional bystander hemolysis of the patient's RBCs can be assumed [30].

C. Febrile transfusion reactions due to alloimmunization to the antigen on leukocytes, platelets, and cytokines develop in-vitro. Most febrile non-hemolytic transfusion reactions (FNHTR) to platelets are caused by cytokines that accumulate in the product during storage, probably the result of an incompatibility between leukocytes erythrocyte product and antibodies in the recipient's plasma.

D. Transfusion-related acute lung injury (TRALI) caused by transfusion of antibodies in donor plasma that reacts with recipient granulocytes. Transfusion-related acute lung injury (TRALI) is a syndrome that includes dyspnoea, hypotension, bilateral pulmonary edema, and fever. Two different aetiologies have been proposed. The first is a single antibody-mediated event involving the transfusion of anti-HLA class I and class II or antigranulocyte antibodies into patients whose leukocytes express the cognate antigens. The second is a 2-event model: the first event is the clinical condition of the patient resulting in pulmonary endothelial activation and neutrophil sequestration, and the second event is the transfusion of a biologic response modifier (including lipids or antibodies) that activates these adherent polymorphonuclear leukocytes (PMNs), resulting in endothelial damage, capillary leak, and TRALI [31].

E. Post transfusion purpura (PTP): It is a rare bleeding disorder caused by alloantibodies specific to platelet antigens. The antibody against the human platelet alloantigen HPA-1a is responsible for most of the cases. The majority of affected patients are multiparous women who presumably have been previously sensitized during pregnancy. Blood transfusions

rarely have been implicated as the primary cause for alloimmunization in PTP [32].

Non-immunologic reactions: A. Circulatory volume overload may result in pulmonary edema.

Transfusion-associated circulatory overload (TACO) and TRALI have emerged as significant causes of post-transfusion morbidity and mortality. There is no sentinel feature that distinguishes TRALI from TACO.

B. Bacterial contamination of blood and blood products - Various sources of contamination have been suggested, including infection in the donor and invasion of the blood product during the process of collection, preparation, and storage. Frequent clinical manifestations are fever (80%), chills (53%), hypotension (37%), and nausea or vomiting (26%) [33].

C. Transfusion-associated viral infection - such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV). However, the risk of transmitting HIV, HTLV, HCV, or HBV infection by the transfusion of screened blood is tiny. New screening tests will reduce the risk even further [34].

Many studies have found that transfusion reactions were much more frequently associated with platelet transfusion (30.8%) than with red cell transfusion and were dependent on the length of storage partly [35-37].

Conclusion

Again, it is reiterated that there are no current obstetric guidelines for managing Indian pregnant women who have/have not received ANC care during pregnancy and present with complications at term/in labor. If the increment is noted that is associated with whole blood/plasma transfusion is so small, the outcome suggested by prior studies will not depend on transfusion and hence are un-warranted in most cases.

An average increment of 0.55±0.07 hemoglobin g/dL per unit, platelet count of 8,000/mm^3 per unit, slightly improved coagulation profile can be expected in Indian pregnant females on oral iron supplementation. It is concluded that PRBC transfusion in pregnant women causes a lower increase in mean Hb and HCT values than in the west, and ferritin and serum iron are not reliable indicators of Anemia in transfusion.

To summarize, although numerous studies have been done to investigate the effects of transfusion-whole blood and its components and associated infection. The real-time data on pregnant women in the Indian subcontinent is limited, which is perhaps one of the largest studies. The increment in hematological parameters post-transfusion is marginal and highlights the rationalized use of transfusion in these high-risk groups. Also, there is a need to establish a standard guidance document that clearly demarcates the essentiality of transfusion benefits in pregnancy outcomes and hence needs more studies.

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Disclosure of conflict of interest

None.

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