

Evaluation of Gasometric Behavior of Transfused Fetuses in Alloimmunized Pregnant Women According to the Concentration of Circulating Adult Hemoglobin



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Abstract

Introduction: Perinatal hemolytic disease occurs due to the passage of antibodies from maternal to fetal circulation through the placenta; this leads to fetal erythrocytes hemolysis and death (in extreme cases). Regarding the treatment by intrauterine transfusion, little is known about the effect of the concentration of transfused adult red blood cells on the hemodynamics and gas exchanges in the fetal blood.

Objective: to compare the gasometric values between fetuses with gradual elevation of adult hemoglobin (HbA) concentration after intrauterine transfusion and anemic fetuses with only fetal hemoglobin (HbF).

Methods: a longitudinal observational study was carried out from 1998 to 2015 with 365 transfusions performed on 143 fetuses. The HbF concentration was determined by the Kleihauer-Betke test and pH, pCO₂, pO₂, SatO₂, HCO₃ and BE values were obtained from umbilical cord venous blood. The cases were ordered according to the deficit of Hb concentration in comparison with normality curve given for each gestational age.

Results: the gradual substitution of fetal by adult red blood cells did not significantly influenced the gasometric parameters for both Hb deficit lower than 5 g/dL [pH (p=0.958), pCO₂ (p=0.400), pO₂ (p=0.493), SatO₂ (p=0.698), HCO₃ (p=0.495) and BE (p=0.522)] and higher than 5 g/dL [pH (p=0.601), pCO₂ (p=0.065), pO₂ (p=0.770), SatO₂ (p=0.096), HCO₃ (p=0.096) and BE (p=0.525)].

Conclusions: Due to the existence of a hematological system with great capacity of metabolic balance, no associations between gasometric parameters and the percentage of HbF replacement were observed; this, regardless the degree of anemia resulted from Hb deficit

Keywords: Perinatal Hemolytic Disease; Maternal alloimmunization; Intrauterine transfusion; Fetal gasometry; Kleihauer; Fetal hemoglobin

Introduction

The incidence of Rhesus (Rh) alloimmunization has decreased following the implementation of prophylaxis programmes with anti-D immunoglobulin (Ig); however, it continues to be a cause of perinatal morbidity and mortality due to lack and/or failure of prophylaxis. In addition, some fetuses are affected by this hemolytic disease due to maternal

sensitization by other atypical antigens [1]. A fetus with anemia becomes able to withstand extremely low levels of hemoglobin (Hb) due to the maintenance of blood circulation through the placenta; however, the severity of this condition results in depletion of the depurative capacity of the placenta [2].

Among invasive procedures for treatment of anemia, intrauterine transfusion by cordocentesis allows the replacement of large quantities of adult red blood cells (RBC) [3]. The volume of transfused blood leads to an expansion of fetoplacental circulation, increases the concentration of adult RBC; thus, there is a consequential reduction of venous return and changes in the physical characteristics of fetal blood that is replaced by adult RBC. In comparison with fetal erythrocytes, adult RBC present lower volume, higher rigidity, decreased oxygenation capacity and increased propensity to aggregate when present in the fetal circulation [4].

A 15% decrease in fetal RBC is expected after each transfusion and severe alterations of biochemical fetal blood indexes are present at the first transfusion, but most variables tend to normalize [5]. The analysis of adult RBC concentration and the knowledge of metabolic gasometric changes due to intrauterine transfusion will contribute to the procedure planning and to the evaluation of fetal heart rate response. Nevertheless, the question arises whether only the replacement of adult RBC without antibodies or also the RBC's behavior would influence the fetal response to anemia caused by perinatal hemolytic disease after intrauterine transfusion.

The intrauterine transfusion in an anemic fetus results in replacement of fetal hemoglobin (HbF) with adult hemoglobin (HbA). Therefore, in addition to reestablishing hematimetric levels, qualitative changes in the fetal blood profile are also observed. Thus, the aim of this study was to compare the gasometric values between fetuses with gradual elevation of HbA concentration after intrauterine transfusion and anemic fetuses with only HbF.

Methods

This longitudinal observational study included 143 alloimmunized pregnant women whose fetuses with risk of anemia presented the criteria for intrauterine transfusion. From April 1998 to January 2015, a total of 365 transfusions were conducted and each cordocentesis was considered one case. Subjects included in the study were pregnant women alloimmunized by erythrocyte antigens whose fetuses were indicated for intrauterine transfusion. They were followed up since prenatal until child's birth at the Fetal Medicine Center in the Hospital of Clinics of the Federal University of Minas Gerais (CEMEFE HC-UFGM). In addition, subjects must have absence of fetal malformations, no risk of premature birth and intrauterine infection.

Cordocenteses were indicated in the following situations: ultrasonographic signs suggestive of fetal compromise due to anemia, severe fetal anemia diagnosed by ultrasound scans, peak systolic velocity in the cerebral artery above 1.5 MoM (multiple of the median), cardiofemoral index above 0.61 [6,7]. Regarding the metabolic evaluation, the following gasometric parameters were evaluated: pH (potential of hydrogen), partial pressure of carbon dioxide (pCO₂), partial pressure of oxygen (pO₂), oxygen saturation (SatO₂), bicarbonate concentration (HCO₃) and base

excess (BE). The curves of normal distribution of umbilical cord blood gasometry were based on a study with the highest number of fetuses conducted by Riley & Johnson [8].

The concentrations of fetal and adult RBC present in fetal samples were measure by using the Kleihauer-Betke test, which is a quantitative method based on the principle that HbF present in fetal RBC is relatively resistant to acid elution when compared to HbA present in adult RBC [9]. The cases were ordered according to the deficit of Hb concentration in comparison with normality curve; this, based on the gestational age proposed by Nicolaides et al. [10]. Next, the Hb deficits were calculated from the difference between the expected Hb for a given gestational age and the Hb found at the time of cordocentesis. The degree of anemia was based on the Hb deficit and classified as proposed by Bahado-Singh et al. [11]: Hb deficit lower than 5g/dL represents nonanemic fetuses or mild anemia, while severe anemia is predicted for values higher or equal to 5g/dL.

The data description of the variables were analyzed using frequency tables. Quantitative variables were described by mean, median and standard deviation (SD) in order to verify their distribution. Dependency ratios between continuous variables, fetal RBC concentration, gasometric parameters and deficit of Hb concentration were evaluated by using an univariate linear regression. Results were considered significant for an error probability lower than 5% (p<0.05).

Results

A total of 143 alloimmunized pregnant women submitted to 365 cordocenteses at the CEMEFE HC-UFGM between April 1998 and January 2015 were followed to determine HbF values and gasometric parameters. Subjects had a mean maternal age of 29.5 years and 27.8 weeks was the mean gestational age at the first transfusion. Recorded data also revealed an average of 3.6 gestations and 2.3 deliveries per patient (Table 1).

Table 1: Subjects means regarding maternal age, gestational age, number of pregnancies, number of deliveries and number of abortions at the time of the first transfusion.

Characteristics	Mean
Maternal age (years)	29.5
Gestational age (weeks)	27.8
Gestations	3.6
Deliveries	2.3
Abortions	0.4

Table 2 shows that the major cause of maternal sensitization was the non-administration of Ig after delivery, followed by non-

administration of post-abortion Ig. The highest incidence of the immunized antigen is related to the presence of both anti-D and anti-C antibodies, while the anti-Kell antibody was the most related to irregular antigens (Table 3).

Table 2: Distribution of subjects regarding the causes of maternal alloimmunization.

Cause of sensitization	n
No post-abortion Ig	9
No post-partum Ig	122
Incompatible transfusion	7
Ig failure	3
During pregnancy	2
n: number; Ig: immunoglobulin.	

Table 3: Data distribution according to the incidence of maternal antibodies that caused sensitization.

Antibody	Incidence	Percentage (%)
D	76	53.1
D + C	48	33.6
D + C + E	7	4.9
D + Kell	2	1.4
D + Kell + Lea	2	1.4
D + C + Fya	2	1.4
D + C + E + K + Lea	2	1.4
D + Jka	1	0.7
Kell + Jka	1	0.7
C + Fya + M + S + K	1	0.7
D + C + K + Fyb + Jkb	1	0.7
Kell: anti-Kell; Lea: Lewis-a; Fya: Duffy-a; Jka: Kidd-a; Fyb: Duffy-b; Jkb: Kidd-b.		

Table 4: Data distribution according to the gasometric parameters, HbF concentration and Hb deficit lower than 5g/dL.

Hb deficit < 5g/dL							
		pH	pC	pO ₂	Sat	HCO ₃	BE
HbF < 30%	SD	0.040	12.390	9.070	22.933	4.130	3.539
	Median	7.400	38.000	40.900	65.200	21.800	-3.600
	Mean	7.396	40.108	39.969	57.862	21.454	-3.385
HbF 30-50%	SD	0.041	10.115	15.182	19.598	2.698	15.225
	Median	7.395	34.850	34.000	43.950	20.800	-4.000
	Mean	7.393	37.322	35.239	52.189	20.083	-10.117
HbF 50-70%	SD	0.074	17.753	11.865	22.363	3.106	3.343
	Median	7.400	37.600	37.800	60.000	21.100	-2.400
	Mean	7.377	42.852	37.281	57.742	20.774	-3.352
HbF 70-90%	SD	0.131	18.884	10.866	23.294	4.057	5.154
	Median	7.400	37.100	41.000	42.950	21.200	-2.700
	Mean	7.371	44.848	37.383	52.886	21.010	-4.069
HbF > 90%	SD	0.081	14.024	12.721	21.445	3.664	8.161
	Median	7.400	34.300	35.800	65.700	21.200	-3.000
	Mean	7.380	39.600	36.839	59.413	20.585	-4.992
Kruskal Wallis test	p<0.05	0.958	0.400	0.493	0.698	0.495	0.522
		Equal	Equal	Equal	Equal	Equal	Equal

Hb: hemoglobin; HbF: fetal hemoglobin; SD: standard deviation; pH: potential of hydrogen; pCO₂: partial pressure of carbon dioxide; pO₂: partial pressure of oxygen; SatO₂: oxygen saturation; HCO₃: bicarbonate concentration; BE: base excess.

The 7 followed up fetuses were ordered in accordance with gasometric parameters (pH, pO₂, pCO₂, BE and HCO₃) and HbF concentration, and separately analyzed according to the Hb concentration deficit. Regarding the Hb deficit lower than 5g/dL, there was no difference between HbF concentrations and the gasometric parameters: pH (p=0.958), pCO₂ (p=0.400), pO₂

(p=0.493), SatO₂ (p=0.698), HCO₃ (p=0.495) and BE (p=0.522). Similarly, no difference was observed between HbF concentrations and the gasometric parameters if Hb deficit was higher than 5g/dl: pH (p=0.601), pCO₂ (p=0.065), pO₂ (p=0.770), SatO₂ (p=0.096), HCO₃ (p=0.096) and BE (p=0.525). The results are presented in Table 4 and 5.

Table 5: Data distribution according to the gasometric parameters, HbF concentration and Hb deficit higher than 5g/dL.

Hb deficit > 5g/dL							
		pH	pCO ₂	pO ₂	SatO ₂	HCO ₃	BE
HbF < 30%	SD	0.136	18.049	11.824	20.858	9.827	4.791
	Median	7.400	38.000	37.700	63.600	21.300	-4.000
	Mean	7.329	44.920	38.352	54.764	22.848	-5.416
HbF 30-50%	SD	0.133	16.512	12.030	18.908	3.033	5.319
	Median	7.320	44.200	34.000	39.000	21.300	-3.900
	Mean	7.298	47.427	35.938	45.048	21.552	-5.748
HbF 50-70%	SD	0.122	19.957	20.345	22.048	9.991	6.994
	Median	7.370	35.700	33.000	59.000	19.350	-4.400
	Mean	7.322	40.341	37.113	55.916	19.006	-7.578
HbF 70-90%	SD	0.138	22.071	14.194	19.024	18.527	8.681
	Median	7.350	36.600	32.800	48.400	20.000	-5.700
	Mean	7.288	45.208	36.400	46.963	27.937	-7.837
HbF > 90%	SD	0.129	14.891	18.419	22.021	12.383	9.655
	Median	7.350	35.500	34.000	62.000	21.000	-4.550
	Mean	7.306	37.482	36.092	57.268	22.142	-7.566
Kruskal Wallis test	p<0.05	0.601	0.065	0.770	0.096	0.096	0.525
		Equal	Different	Equal	Different	Different	Equal

Hb: hemoglobin; HbF: fetal hemoglobin; SD: standard deviation; pH: potential of hydrogen; pCO₂: partial pressure of carbon dioxide; pO₂: partial pressure of oxygen; SatO₂: oxygen saturation; HCO₃: bicarbonate concentration; BE: base excess.

Discussion

The fetal response to hypoxia has been extensively studied in Obstetrics. The deficient gas exchange between fetus and maternal organisms promotes imbalance in the fetal acid-base system, in which its biochemical expression is fetal acidosis [12]. Gasometry has been used as the main method to measure fetal acidosis; this, using pH value as a fundamental parameter for this diagnosis [13]. Intrauterine transfusion is a treatment for the most severe form of perinatal haemolytic disease and its main objective is the correction of fetal anemia and normalization of hemodynamic conditions, which allows adequate transport of oxygen through the fetal organism. In cases of alloimmunization, invasive procedures for intrauterine transfusion also allow the assessment of fetal acid-base balance by the analysis of blood obtained during cordocentesis [14].

The relationship between Hb deficiency and acid-base balance parameters makes it possible to recognize anemic fetuses that develop anaerobic metabolism due to the low oxygen levels and consequently become acidemic. In this study, the fetal behavior was assessed by the gasometric point of view that is related to the capacity to maintain fetal well-being and to contribute to the evaluation of fetal cardiac response. The analysis of most important

gasometric parameters of umbilical cord venous blood samples allowed to emphasize how these fetuses behave towards the compensation of circulating blood volume with adult RBC. A relation between adult RBC concentration and gasometric parameters was not observed, independent of the anemia classification (mild or severe).

Even in Hb deficits higher than 5g/dL, values of pH (p=0.601), pCO₂ (p=0.065) and pO₂ (p=0.770), which are parameters with high diffusion capacity through the placental barrier, were not related to adult RBC concentrations. Within normal limits, pO₂ values after intrauterine transfusion probably denote gas exchanges in the placental territory. No accumulation of CO₂ in the fetal circulation was observed since no drop of pH values was recorded; thus, our findings suggest adequate gaseous transfer provided by the volume and the replacement of fetal RBC by adult RBC.

The parameters SatO₂ (p=0.096), HCO₃ (p=0.096) and BE (p=0.525) and their association with adult RBC concentrations were not correlated to the increase of fetal anemic process due to alloimmunization. These results show that the anemic fetus uses several compensatory mechanisms in order to maintain acid-base balance. It is possible that the gasometric parameters represent only a state of fetal metabolism compensation in the face of anemia.

In comparison to other studies, Osanan et al. [15] described factors related to perinatal mortality and intrauterine transfusion; however, none of the gasometric parameters was significant. Goldaber & Gilstrap [12] demonstrated that both pH value and gases concentration in the umbilical vein blood were not altered in fetuses with moderate anemia. Soothill et al. [16] demonstrated that pH changes in the umbilical cord blood occurred only at very advanced stages of fetal anemia, in which Hb from umbilical cord blood was lower than 4g/dL. In fetuses with mild or moderate anemia, Leite [17] did not observe alterations in the blood gas balance and pH values remained above 7.35 in the umbilical vein. Even in cases of severe anemia, Nicolaides et al. [18] found that the blood gasometric parameters remained unchanged; however, pH values dropped below 7.25 in case of Hb deficit above 8g/dL.

A correlation between Hb deficit and fetal pH was not found in our research; however, this was observed in the abovementioned studies mainly in cases considered as severe anemia. This divergence is due to the classification method used for the disease severity. The majority of these studies assume the classification proposed by Nicolaides et al. [10], in which severe anemia is defined by a Hb deficit above 7g/dL; thus, samples present a more evident hematological and metabolic compromise.

The classification proposal of Bahado-Singh et al. [11] was used in our study, in which severe anemia was assumed in case of Hb deficit higher than 5g/dL. This classification was adopted following the precepts of the CEMEFE HC-UFMG follow-up protocol of pregnant women that is in agreement with the studies of Ghi et al. [19], Van Kamp et al. [20] and Simonazzi et al. [21], which described a higher incidence of neurological lesions in fetuses with severe hematological alterations. In order to avoid these lesions and to preserve the neurological potential, fetal metabolic conditions must be observed for timely indication of intrauterine transfusion before gasometric changes.

These results corroborate with the importance of diagnosis and early treatment of fetuses affected by perinatal haemolytic disease. Nomura et al. [22] demonstrated that the treatment itself may result in transient increase of acidemia level and the risk of long-term neurological damage. Therefore, in order to avoid metabolic worsening and consequent neurological damage, transfusion must be indicated at the moment that fetuses do not present alterations in acid-base balance.

Conclusion

Due to the existence of a hematological system with great capacity of metabolic balance, no associations between gasometric parameters and the percentage of HbF replacement were observed; this, regardless the degree of anemia resulted from Hb deficit.

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