Original articles

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The influence of maternal erythrocyte deformability on fetal growth, gestational age and birthweight

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1 Introduction

Numerous physiological changes occur in the pregnant woman that affect blood rheology. Significant among these are the following: a) the neo-formation of a uteroplacental vascular network with a large maternal-fetal exchange surface area, at the level of the intervillous space (this is of fundamental importance for fetal nutrition and oxygenation) [48] where blood flow depends basically on the hematocrits, cell aggregation capacity and erythocyte deformability [11, 15, 17, 24]; b) in the pregnant woman, changes occur in the protein composition of the plasma, which affects blood flow [12]. These changes are compensated by the characteristic physiological hemodilution in pregnancy which involves a fall in hematocrit levels (a circumstance that favours blood flow at the level of the intervillous space) [15, 17, 18].

The increase in blood viscosity during pregnancy produces a fall in uteroplacental blood flow [6, 43], retarded intrauterine growth with hypoxia and fetal lactic acidosis [9, 32, 42, 47], reduced normal term birthweight [21, 44, 48] and a higher incidence of fetal death and acute fetal suffering [50].

We believe the rheological properties of the gestating woman's blood may influence maternal-fetal bloodflow and fetal development. For this reason, it was decided to analyze the rheological changes that occur during the various stages of a normal term pregnancy and the factors that control such changes, together with the consequences for fetal growth and for the neonate.

2 Materials and methods

A prospective longitudinal and observational study of 36 healthy pregnant women was carried out by the Obstetrics Service of Granada University Hospital, starting in March 1992. We excluded from the study women with previous history of any chronic disease (renal, cardiac, metabolic disease etc.) and those suffering any pathology during the current pregnancy (diabetes, toxemia, retarded intrauterine growth etc.). All the pregnancies were evaluated by the same gynecologist, who followed the protocol recommended by the Consensus Group of the Spanish Perinatal Medicine Section [14]. The four evaluation dates were chosen to coincide with the check ups programmed by the Obstetrics Service that were closest to the 10th, 20th, 30th and 37th weeks of gestation. The following variables were studied at each of the evaluation dates:

Fetal and gestational variables: Gestational age, maternal weight, systolic and diastolic blood pres-

sure, fetal biparietal diameter and femur length, gestational age at birth, birthweight, Agpar score after one minute and five minutes, type of delivery (spontaneous, forceps, caesarian).

Rheological and erythrocyte variables: The risk factors in this study were taken as cut off points. For these variables, we used mean values plus 1 standard deviation (SD) (table I). Plasma viscosity was determined according to the recommendations of the International Committee for Standardization in Haematology (ICSH) [20], by means of a falling-ball Haake viscosimeter. The rigidity index was obtained according to the recommendations of the ICSH [19] using the method described by Schönbein et al [41], modified with a water pressure of −10 cm and Millipore filters with a diameter of 5 µm [4]. Intraerythrocyte viscosity was determined with the Haake viscosimeter using the procedure described by Reinhart et al [39]. The following were also obtained: levels of erythrocytes, hemaglobin (Hb), hematocrits (Hto), Mean Corpuscle Volume (MCV), Mean Hemoglobin Corpuscle Concentration (MHCC), Plasma osmolarity (calculated as Osmolarity = (Nax2) + (Glucose/18) + (Urea/2.8)).

Biochemical variables: Sodium, chlorine, potassium, calcium, urea, glucose, phosphorus, and calcium (colorimetric method).

Proteinic variables (electrophosphoresis in gel): albumin (Alb), alpha-globulins, alpha2-globulins, beta globulins, gamma globulins, total proteins, albumin/globuline index (Alb/Glo) and fibrinogen.

Lipid variables (spectrophotometer LKB-7400): total cholesterol (CT), HDL cholesterol (HDL-CT), LDL cholesterol (LDL-CT), triglycerides (TG), phospholipids (PL), free fatty acids (AACC) (enzymatic colorimetric method), A1 apoprotein (Apo-A) and apoprotein B (Apo-B) (immunodiffusion).

Statistical method: At each stage of the study we carried out a correlation study between the rheological variables (rigidity index, intraerythrocyte viscosity, plasma viscosity and osmolarity) and the other variables. We also performed logistic regression analysis for the rheological risk factors under study, erythrocyte deformability and plasma viscosity. An ANOVA study was made to identify the changes occurring in the variables during gestation and a Bonferroni test was used to determine exactly when such changes occur.

3 Results

The neonates in the study had a birthweight of 3,190 (SD 520) g and a gestational age of 38.6 (SD 1.9) weeks. There were 3 preterm deliveries, with no apparent cause (at a gestation age of 32, 34 and 36 weeks). Twelve women were excluded from the study due to gestational diabetes, high blood pressure, pre-existing renal disease or because their consent could not be obtained. During the gestation monitoring process, 6 women did not keep their third appointment (n = 30) and 13 missed the fourth one (n = 23). All the women had normal pregnancies and were analyzed when they attended the follow up session.

During normal term pregnancy, we observed a progressive increase in plasma viscosity, with no statistically significant differences between the trimesters. Osmolarity remained constant during the whole gestational period (table I).

Erythrocyte rigidity increased between weeks 20 and 30 of gestation ($p < 0.05$), coinciding with a decrease in intracellular viscosity ($p < 0.01$) (table I). The fetuses of the women with high levels of erythrocyte rigidity (mean ± 1 DS) between weeks 24 and 36 of their pregnancy presented a smaller biparietal diameter and shorter femurs; moreover, birth occurred earlier and neonates had a significantly lower birthweight. Erythrocyte rigidity was also related to increases in serum levels of alpha2-globulins and decreases in the albumin/globuline index (table II). Simple logistic regression analysis also identifies the increase in erythrocyte rigidity as the sole maternal rheological factor associated with a smaller fetal biparietal diameter (Relative Risk (RR) = 3.98), lower birthweight (RR = 3.67) and lower gestational age at birth (RR = 3.42). In relation to hematocrits and plasma viscosity, multiple logistic regression analysis reveals that the increase in erythrocyte rigidity is the most influential factor in fetal growth and development (table IV). To a certain extent, the lower birthweight of these neonates depends more on the increase in erythrocyte rigidity (RR = 2.44) than on their lower gestational age ($p = 0.64$).

The fall in intraerythrocyte viscosity occurring between weeks 25 and 36 of gestation (30.9 weeks (SD 2.5)) (table I) is related to an increase in MHCC ($r = -0.62$, $p < 0.01$), in LDL-cholesterol ($r = -0.67$, $p < 0.01$) and in serum phospholipids ($r = -0.82$, $p < 0.001$).

The small increase in plasma viscosity during the course of normal pregnancy (table I) is not a factor associated with fetal development or birthweight (table 4).

4 Discussion

There is a great variability in the parameters of normality during pregnancy: in fetal growth variability [2], in the normal gestational age at birth (37–42 weeks' gestation), in full-term birthweight (3,500 g (SD 800)), in the Apgar score of the neonate (normal score 7–10), etc. Thus, numerous factors contribute to fetal and perinatal normality.

Insufficient uteroplacental blood circulation is the main cause of reduced fetal growth and retarded intrauterine growth. Studies of gestating infants presenting retarded intrauterine growth (IUGR) have shown that when the Doppler velocimetry of uteroplacental flow is abnormal, most fetuses present hypoxia, acidosis and hyperlactacidemia [35, 37, 47]. This has not been observed, however, in the IUGR fetuses with normal maternal-fetal blood flow [36].

During gestation, the uterine arteries ramify into radial arteries and into an important vascular network that forms the intervillous space (the location of maternal-fetal blood exchange, which is fundamental in fetal nutrition and oxygenation) where the blood flows through a pressure gradient at low flow. In this vascular network, the uteroplacental blood flow depends fundamentally on hematocrit levels, erythrocyte deformability and on erythrocyte aggregation [7, 13, 27, 29, 38].

On studying the factors contributing to blood flow in the intervillous space, we found that during the gestation period of greatest fetal growth (from weeks 20 to 30) there is an increase in the rigidity of the maternal erythrocytes [10, 21, 26, 28] (table I), a risk factor contributing to reduced fetal growth, lower birthweight [21] and lower gestational age at birth, probably due to a diminution in maternal-fetal perfusion arising from an increase in blood viscosity in the intervillous space (tables II–IV).

The deformability of the red blood cell depends on cellular morphology, the surface/volume ratio of its membrane, the viscoelastic properties of the membrane and on its intracellular viscosity [24]. Taking all this into account, during a normal term pregnancy the increase in erythrocyte rigidity cannot be attributed to increases in the size of the erythrocyte (MCV is invariable during gestation), to increases in MHCC (which after a decrease at the start of the gestation remained constant from week 20 until delivery) or to increases in intraerythrocyte viscosity (which fell, counterbalancing the increase in erythrocyte rigidity) (table I). This led us to speculate that the increased rigidity of the erythrocytes in the pregnant woman may be due to alterations in the fluidity or elasticity of the red blood cell membrane, induced by the pregnancy [1, 10, 28], which coincide with alterations in intracellular viscosity, in turn related to increases in LDL-cholesterol, phospholipids and blood atherogenic indices [31], influencing the fluidity and permeability of the erythrocyte membrane and fetal and placental size [30, 45].

We do not believe that alterations in fetal growth or the perinatal variations observed in normal gestations are exclusively the result of the 20% increase in the rigidity of maternal erythrocytes. As demonstrated in table 2, increases in the globulins (mainly alpha2-globulins) and the decrease in the albumin/globuline ratio (Alb/globulins) as well as being associated with lower erythrocyte deformability, reinforces the attraction between cells and erythrocyte aggregation capability [8, 40], especially in areas of low velocity blood flow, such as the intervillous space [16, 17].

For these reasons, between weeks 25 and 36 the blood viscosity in the intervillous space is affected by an increase in the rigidity of the erythrocytes and in their aggregation capacity. These rheological alterations might explain a reduced blood flow in the pregnant woman at the period of greatest fetal growth (between weeks 20 and 30 of gestation) (table I) [15, 17, 23]. The fall in hematocrit levels (the physiological hemodilution of pregnancy) as well as reducing the viscosity of the woman's blood also lowers the aggregation capability of the red blood cells and im-

Table I. Rheological, erythrocyte and fetal growth alterations during normal pregnancy

	< 12 SG (n = 36)	12 – 24 SG (n = 36)	25–36 SG (n = 30)	> 36 SG (n = 23)
Gestational age (weeks)	8.7	19.2 (3.1)	30.9 (2.5)	37.4 (1.0)
Biparietal diameter (mm)	19.3 (8.3)	44.4 (9.3)	80.0 (7.4)	92.9 (3.3)
Length of femur (mm)	–	28.3 (8.4)	58.3 (6.2)	71.4 (2.7)
Rigidity Index	23.2 (8.6)	22.4 (7.4)	28.5 (13.8)	29.7 (13.3)
Erythrocyte internal viscosity (mPa.s) (mPa.s)	7.4 (3.2)	6.5 (4.1)	4.2 (1.8)	5.9 (4.6)
Plasma viscosity (mPa.s)	1.33 (0.11)	1.31 (0.09)	1.34 (0.08)	1.38 (0.12)
Hemoglobin (g/dL)	13.1 (1.0)	12.3 (0.9)	12.1 (0.8)	12.4 (1.0)
Hematocrit (%)	37.2 (3.1)	35.7 (2.8)	35.2 (2.3)	35.8 (2.6)
MCV mm^3	87.3 (3.8)	89.4 (4.1)	88.7 (4.2)	88.6 (4.3)
MHCC (mmol/L)	35.1 (1.0)	34.3 (0.7)	34.5 (0.7)	34.7 (0.8)

Table II. Correlation of erythrocyte rigidity (ER) with fetal growth, perinatal results and proteinic variables

	< 12 SG (n = 36)		12–24 SG (n = 36)		25–36 SG (n = 30)		> 36 SG (n = 23)	
	r	p	r	p	r	p	r	p
Biparietal diameter (mm)			0.25	NS	−0.50	**	0.04	NS
Length of femur (mm)			−0.20	NS	−0.48	*	−0.01	NS
Delivery gestational age (weeks)	−0.01	NS	0.11	NS	−0.73	***	0.13	NS
Weight of newborn (g.)	0.13	NS	−0.08	NS	−0.63	***	0.29	NS
Apgar 1'	0.06	NS	0.05	NS	−0.36	NS	−0.08	NS
Apgar 5'	0.21	NS	0.15	NS	0.67	***	−0.01	NS
a2-globulins (g/dl)	0.02	NS	−0.19	NS	0.87	***	−0.31	NS
Albumin./Globulins (g/dl)	0.03	NS	−0.07	NS	−0.76	***	0.29	NS

NS = No significance, * = $p < 0.05$, ** p 0.01, *** $p < 0.001$

Table III. Differences between pregnancies featuring increased erythrocyte rigidity (mean ± SD) and normal pregnancies from weeks 25 to 36 of gestation

	R. I. Normal	R. I. Elevado	t Student	p
Rigidity index	22.4 SD5.1	46.7 SD15.6	3.82	0.008
Erythrocyte internal viscosity (mPa.s)	4.6 SD1.9	3.5 SD0.9	1.08	NS
Plasma viscosity (mPa.s)	1.33 SD0.1	1.35 SD0.1	0.36	NS
Biparietal diameter (mm)	81.1 SD7.4	76.6 SD7.3	1.37	NS
Length of femur (mm)	59.4 SD6.4	55.5 SD5.5	1.30	NS
Delivery, gestational age (weeks)	39.0 SD1.2	37.5 SD3.4	1.24	NS
Weight of newborn (Kg)	3.26 SD0.4	2.83 SD0.6	1.96	0.06
Hematocrit (%)	34.7 SD2.3	36.6 SD1.8	1.94	0.06
MCV	89.4 SD4.1	87.6 SD3.2	1.04	NS
MHCC	34.4 SD0.7	34.8 SD1.0	1.27	NS
Cholesterol (mg/dl)	249 SD47	273 SD26	1.23	NS
Phospholipids (mg/dl)	244 SD37	276 SD39	1.42	NS
alpha2-globulins	0.71 SD0.1	1.04 SD0.4	1.64	NS
Albumin/Globulins	1.37 SD0.3	1.09 SD0.2	1.97	0.06

Table IV. Influence of erythrocyte rigidity from 25 to 36 weeks of gestation on BPD, birthweight and gestational age at birth

Multiple Regression Analysis	Biparietal diameter ($\bar{x}$ − SD) SRR	Birthweight ($\bar{x}$ − SD) SRR	Gestational age at birth ($\bar{x}$ − SD) SRR
Erythrocyte rigidity	9.27	3.94	5.06
Plasma viscosity	0.86	0.85	1.01
Hematocrit	0.38	0.88	1.70

SRR: Standardized relative risk (relative risk divided by the typical deviation of the relative risk. This allows us to compare different relative risks).

proves the blood flow in areas of low flow, such as the intervillous space [8, 16, 40].

In processes that involve alterations in placental microcirculation (IUGR, gestational diabetes, gestational toxemia) the increase in maternal hematocrits could raise blood viscosity and lower uteroplacental blood flow, factors which have been related to low birthweight neonates [22, 25].

We agree with Norcliffe et al. [33], who analyzed hemorheological variations in 150 normal gestations and concluded that there is a critical period in maternal hemorheology between weeks 22 and 30 of gestation (table II). We believe that in normal pregnancies, fetal growth and development is fundamentally influenced by uteroplacental blood flow, and that rheological alterations (decreases in erythrocyte deformability, increases in cellular aggregation, etc.) may produce real erythrocyte blockages in the vessels of the intervillous space and lead to vascular lesions, though not as severe as those observed in pregnant fetuses with IUGR [5, 34], which affect fetal growth and development. Uzan et al. [46] showed that in pregnant women with a high risk of IUGR, platelet antiaggregants raised birthweight and reduced the number of perinatal complications.

On the basis of our results, we conclude that the reduction in erythrocyte deformability is the most important factor involved in the hemorheological equilibrium during a normal gestation. As this is a maternal characteristic that informs us of the efficiency of placental perfusion and fetal development, it could be a useful parameter in the evaluation of the perinatal prognosis.

Abstract

The increase in blood viscosity during pregnancy reduces maternal-fetal blood flow, which can lead to fetal hypoxia and acidosis. These factors have been related to a reduction in fetal growth and to premature births. We carried out a longitudinal study of 36 normal-term gestations at different stages of the pregnancy. We analyzed the erythocyte deformability, the intraerythocyte viscosity and the plasma viscosity in the mother, as well as the relation of these parameters to fetal growth (biparietral diameter (BPD) and length of the femur), birthweight, gestational age at birth and the Agpar score. The results obtained were as follows: from weeks 25 to 36 of pregnancy (30.9 (SD 2 weeks)) there occurs a significant increase in maternal erythocyte rigidity ($p < 0.05$) (despite the compensatory decrease in intracellular viscosity). This increase is very significantly related to the fetal biparietral diameter ($r = -0.50$, $p < 0.01$), the length of the fetal femur ($r = -0.48$, $p < 0.02$), gestational age at birth ($r = -0.73$, $p < 0.0001$, birthweight ($r = -0.63$, $p < 0.001$) and the Agpar score 5 minutes after birth ($r = 0.67$, $p < 0.001$).

Our conclusions are that the reduction in erythocyte deformability (which we attribute to alterations in the fluidity or elasticity of its membrane) and the factors that increase the aggregation capacity of the red cells (modulators of blood viscosity and of blood flow in the placental intervillous space) are risk factors for reduced fetal growth, lower birthweight and lower gestational age at birth. By avoiding maternal hematocrit levels higher than 36% we could improve uteroplacental perfusion, fetal growth and perinatal results.

Keywords: Deformability, fetal growth, hemorheology, newborn, viscosity.

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