

Association between prematurity and maternal anemia in Venezuelan pregnant women during third trimester at labor

Arturo Martí, Guiomar Peña-Martí, Sergio Muñoz, Fernando Lanas, Gabriela Comunian

Clinical Epidemiology Unit, Universidad de Carabobo and Ciudad Hospitalaria "Dr. Enrique Tejera",
Venezuela and Clinical Epidemiology Unit, Universidad de la Frontera, Chile

SUMMARY. To determine the association and its magnitude between prematurity and anemia in women in their third trimester of pregnancy and at labor. An incident case - control study was conducted using 2 controls per case. Data was obtained in a tertiary hospital in Valencia, Venezuela. A total of 543 women who delivered between May and December 1996 entered into the study. Women having a preterm delivery, less than 37 weeks of gestation at delivery, were defined as cases (n=181). Anemia was defined according to WHO as Hb less than 11g/dL. Logistic regression was used to analyze the data and likelihood ratio test was done for model comparison. Maternal anemia was found to be significantly associated with prematurity (Odds Ratio: 1.70; 95%CI = 1.18 to 2.57 $P = .001$), after adjusting for Placental Abruption, PROM, Previous Premature Labor, Prenatal Care Visits, and Uterine Bleeding during more than one trimester. Maternal anemia at the end of the third trimester of pregnancy, at labor, was associated with an increased risk of prematurity.

Key words: Prematurity, anemia, odds ratio, case control, risk, pregnancy, third trimester, Venezuela.

RESUMEN. Asociación entre prematuridad y anemia materna al final del tercer trimestre en embarazadas venezolanas. El objetivo de este estudio fue determinar la asociación y su magnitud entre prematuridad y anemia materna al final del tercer trimestre del embarazo (en el momento del trabajo de parto). Estudio de Casos y Controles (2 controles por caso). Entre mayo y diciembre de 1996 fueron estudiadas 543 embarazadas al final del tercer trimestre gestacional y en trabajo de parto. Los casos fueron 181. La anemia fue definida como la presencia de Hb < de 11g/dL (OMS). Los datos fueron analizados mediante regresión logística. Para evaluar la significancia de los modelos reducidos se utilizó la prueba de razón verosimilitud. Se determinó que la prematuridad está asociada significativamente con anemia materna (OR: 1.70 IC95% = 1.18 a 2.57, $P = .001$), después de ajustar por desprendimiento placentario, ruptura prematura de membranas - RPM - partos prematuros previos, menos de 5 visitas prenatales y sangramiento uterino en más de un trimestre. La anemia materna al final del tercer trimestre está asociada con un mayor riesgo de prematuridad. **Palabras clave:** Prematuridad, prematuro, anemia, odds ratio, casos y control, riesgo, embarazo, tercer trimestre, Venezuela.

INTRODUCTION

Anemia is the main hematological complication during pregnancy. According to the World Health Organization (WHO) (1), the diagnosis of anemia during pregnancy is established when the Hemoglobin (Hb) level is below 11 g/dL, this being the borderline between "physiologic anemia during pregnancy" and true anemia during pregnancy.

All over the world, anemia during pregnancy is a public health problem (2,3). It is considered that anemia is present in 20% to 40% of pregnant women (4). The WHO (5) points out that there is a high prevalence of anemia in the third trimester of gestation, ranging as low as 2% to as high as 82%. According to WHO (6), there are 2,150 millions anemic people the world and pregnant women represent 51% of this burden.

There is a controversy on the impact of maternal anemia on pregnancy outcome. Maternal anemia has been considered

a risk factor for prematurity (7-9). Other authors point out that there is not such effect (10-15).

Adams et al. (10) in a study about risk factors for preterm delivery in a healthy cohort, examined whether risk factors were different among subgroups of preterm deliveries, and they found that there was no association between anemia and preterm delivery. They concluded that the lack of association is consistent with the conclusion of other investigators showing that most of the causes of preterm delivery are still unknown.

Klebanoff et al. (11), in a control-cases study, reported that anemia at any time during the second trimester, was positively associated with premature delivery; however it did not account for the large ethnic difference in preterm. In other study (12), these same authors found a weak association between prematurity and maternal anemia during early third trimester, while after 30 week of gestation was found no association.

Lu et al. (13), in a uni and multivariable analysis reported that a high Hematocrit (Ht) was associated with fetal retardation and premature delivery, specially when the level of Ht was equal or superior to 43% between 31 and 34 weeks of gestation (Odds Ratio -OR- 1.5 - 2.5). In the research, that included 17.149 pregnant women, most of them took iron and folate supplements; they received prenatal control early and regularly (13).

Knottnerus et al. (14) shown that low birthweight and prematurity were associated with Ht over 38% reporting OR varying between 2.4 and 4.2. They argued that high blood viscosity is a risk factor for a good placental perfusion (14).

Murphy et al. (15) determined, in 54.832 singleton pregnancies, that perinatal death frequency, low weight and prematurity were more frequent in pregnant women with high Ht.

All studies about this issue, with or without association between prematurity and maternal anemia, have been performed in developed countries. The importance of this study is due to the fact of having been carried out in a developing country, in particular in a city (Valencia) where there is a prevalence of 34.44% of anemia during pregnancy.

The main objective of the present research was to determine the association between prematurity and maternal anemia, at the end of third trimester of pregnancy. A case-control study with incident cases was performed.

METHODS

Subjects and data acquisition

The data of this research was obtained from "Valencia Anemia during Pregnancy Study -VAPS-", a large research about prevalence of maternal anemia during third trimester, carried out between May and December 1996. It was done in Maternidad "Dr. J.L. Facchín de Boni" of Ciudad Hospitalaria "Dr. Enrique Tejera," in Valencia, Venezuela. Valencia is the first Industrial City of Venezuela.

Both cases and controls came from the VAPS above mentioned. Since pregnant women entered at labor, as much the cases as the controls delivered the same day from the admission to hospital. The process to gathering data is shown in the Appendix No.1.

The inclusion criteria for this study was stated as all pregnant women in their third trimester of gestation at labor. All these patients are based in Valencia (450 meters above sea level). Women with multifetal pregnancies and pregnant women who did not remember their last menstrual period (LMP) were excluded.

A medical history and physical examination were performed for all patients. A questionnaire was used to obtain information about sociodemographic, obstetric, medical non-obstetric, drug, and exposure to toxic substance data. Gestation age at delivery was determined by LMP and was

confirmed by clinical examination in each patient. In each newborn, Capurro's test was done.

By using WHO criteria (1), maternal anemia was defined as Hb less than 11 g/dL in any stage of gestation, and prematurity (16) was defined as any delivery of a live single infant between 24 and 36 weeks of gestation.

Any pregnant woman having systolic blood pressure greater than or equal to 135 mm Hg and/or diastolic blood pressure greater than or equal to 85 mm Hg or receiving antihypertensive therapy, at admission was considered as hypertensive patient.

Smoking and alcohol during pregnancy were also recorded.

Uterine bleeding was categorized as without, bleeding in any one trimester and bleeding in more than two trimesters.

No attempt was made to match the controls for age, parity, or any other variable. Ethnic group classification was not attempted due to the strong race mixture in our population.

At labor, 12 ml of venous blood were obtained in a EDTA containing tube to perform a complete blood count (CBC) using an electronic counter Cobas Helios 3ä (Roche Diagnostic Systems). Blood sample was analyzed at main hospital laboratory within a 2-hour period after drawn.

Every patient agreed to participate in the study and this protocol was conducted with permission from Institutional Review Board.

Data analysis

Sample size was determined assuming 37% prevalence of anemia in the controls, with an expected minimum prevalence of 50% in cases. In addition, it is assumed a 95% confidence level, 80% power, and a ratio of 2 controls per case. The final sample size was 543 pregnant women (181 cases and 362 controls). Epi Info software (version 5.0, CDC, Atlanta, Ga) was used to perform sample size calculation.

A two-sided chi square or Fisher's exact test (where appropriate) was used to compare differences between cases and controls for dichotomous variables and Student's t-test was used to analyze continuous variables. A two-tailed *P* value of less than 0.05 was considered to indicate statistical significance. Stratified analysis was done using the Mantel-Haenszel procedure.

To adjust for potential confounding factors, multiple logistic regression was used in order to determine the association between prematurity and maternal anemia and its magnitude. Model evaluation was done by using likelihood ratio test (17-19). Only biologic variables and other variables clearly associated with prematurity were included in the initial model to avoid a final model that could lack logical explanation (20).

Initial model was composed by prematurity as the dependent variable, maternal anemia as the exposure variable, and age, obstetric variables [placenta previa, placental abruption,

premature rupture of membranes (PROM), previous preterm birth, number of prenatal care visits (PCV) and uterine bleeding], hypertension and smoking, as potential confounders.

Stata version 6.0 (Stata Corp, College Station, Houston, Tx) was used for statistical analyses.

RESULTS

Demographic, obstetric characteristics and relevant clinical information for cases and controls are shown on Tables 1 and 2.

Mean of Hb (\pm SD) in the preterm group ($n=181$) was 10.71(\pm 1.7) g/dL (95%CI = 10.46 to 10.96) while in the control group ($n=362$) it was 11.54(\pm 1.4) g/dL (95%CI = 11.39 to 11.69 $P = .001$). While in the term group anemia was present in 31.22%, in the preterm group it was 48.62% ($P = .001$). Differences between both groups were not significant, for hypertension and alcohol ($P = 0.48$, $P = 0.52$).

The mean of gestational week in the preterm group was 33.73 (95%CI = 33.39 to 34.07) while in the term group it was 39 (95%CI = 38.96 to 39.26) ($P = .001$).

On the other hand, it is very important to point out that the term group did not have an appropriate PCV number. They should have arrived to full term with a PCV number in the range between 10 and 12. In accordance with the gestational age that had for the moment of the childbirth, the case group had an appropriate PCV.

TABLE 1
Background continuous variables of pregnant women according to occurrence of premature birth

Variables	Cases (n=181) Mean (\pm SD) (95% CI)	Controls (n=362) Mean (\pm SD) (95% CI)	P
Age (years)	24.8 \pm 7.2 (23.77 to 25.90)	23.8 \pm 6.3 (23.18 to 24)	0.101
Hb (g%)	10.7 \pm 1.7 (10.46 to 10.96)	11.5 \pm 1.4 (11.39 to 11.69)	.001
Ht (%)	33.5 \pm 4.8 (32.81 to 34.22)	36.1 \pm 4.0 (35.73 to 36.57)	.001
Prenatal Care Visits	4.5 \pm 2.9 (4.10 to 4.98)	5.2 \pm 2.6 (5.00 to 5.56)	.0036 0.34
Parity [‡]	2.7 \pm 2.0 (2.36 to 3.12)	2.5 \pm 1.8 (2.25 to 2.78)	
PI*	40.6 \pm 34.4 (34.45 to 46.92)	42.0 \pm 33.6 (37.40 to 46.73)	0.72

‡ Cases: 112 controls: 192

PI: pregnancy interval

* Cases = 120 controls = 203

TABLE 2
Background dichotomic variables of pregnant women according to occurrence of premature birth

Variables	Cases (n=181)	Controls (n=362)	P
Anemia	48.62%	31.22%	.001
Prior fetal death	4.97%	1.38%	.001
Prior preterm birth	13.81%	4.70%	.001
Prior abortion	20.44%	13.54%	.03
Uterine bleeding in any trimester	26.52%	16.02%	.003
Placental abruption	3.21%	0.28%	.001
PROM	31.49%	20.17%	.03
Hypertension	27.07%	24.31%	.48
Smoking	10.50%	5.80%	.001
Alcohol	3.31%	3.04%	.52

PROM: premature rupture of membranes

Table 3 shows the risk of prematurity according to the hemoglobin's level of the pregnant women. Crude evaluation of association between prematurity and anemia showed an OR of 2.08 (95%CI = 1.44 to 3.0 $P = .001$).

After adjustment for potential confounders, OR and their 95%CIs show that anemia during pregnancy in third trimester is an important predictor of prematurity. Table 4 shows the final model.

TABLE 3
Risk of prematurity according to hemoglobin's levels.

Hb's Levels (g/dl)	Prematurity	Odds Ratio (95% CI)	P
5 to 8 (n = 20)	13 (65%)	3.92 (1.58 to 9.72)	.001
9 to 9.99 (n=26)	16 (61.54%)	3.41 (1.54 to 7.54)	.001
10 to 10.99 (n= 59)	25 (42.37%)	1.54 (0.89 to 2.66)	.11
11 to 11.99 (n= 119)	42 (35.29%)	1.11 (0.73 to 1.71)	.6
12 to 12.99 (n=144)	48 (33.33%)	1 (0.66 to 1.49)	1.0
13 to 13.99 (n= 112)	25 (22.32%)	0.50 (0.31 to 0.821)	.001
\geq 14 (n= 63)	12 (19.05%)	0.43 (0.22 to 0.821)	.01

TABLE 4
Final model of Association Between Prematurity and Maternal Anemia

Variable	Odds Ratio	95% CI	P
Anemia	1.74	1.18 to 2.57	.005
Placental abruption	9.15	1.01 to 82.40	.048
PROM	2.02	1.32 to 3.09	.001
Previous preterm delivery	2.95	1.50 to 5.79	.002
Prenatal care visits (< five)	1.78	1.06 to 2.97	.027
Uterine bleeding (During more than one trimester)	2.50	1.33 to 4.69	.004

PROM: premature rupture of membranes

DISCUSSION

Prematurity is major cause of perinatal mortality (21). The findings support our hypothesis that anemia during pregnancy, evaluated during third trimester, at labor, is a risk factor for prematurity.

After adjustment for potential confounding factors, we have shown that the effect associated with anemia remains recognizable. Therefore, our results suggest that there is an increased risk of a poor obstetric outcome when the level of Hb is less than 10g/dL. We did an analysis to find out what would happen with cut-off points of maternal Hb higher than 11 g/dL, and we founded that hemoglobin's level above 12 g/dL is associated with a reduced risk.

Our study found mild, but positive, relationship between both variables. According to Scholl and Hediger (22), the relationship between anemia during pregnancy, evaluated in third trimester and poor obstetric outcome is not strong.

Defining maternal anemia as maternal Hb lower than 10g/dL in a study done in Hong Kong (at sea level), Lao and Pun (23) concluded that pre-natal anemia is not associated with a poor obstetric outcome for both nulliparous and multiparous pregnant women. However, these authors did not use logistic regression analysis in order to adjust for potential confounders.

Several socioeconomic and demographic risk factors for prematurity, such as: never (24) or single (25) married marital status, being nonwhite (24) or belonging to the black race (25), low socioeconomic status (25), poor education (24) have been identified. Nonetheless, we preferred to include only biological and other potential confounding factors which could be modified and/or truly associated with prematurity in order to get a model with a good possible explanation. Lumley (26) suggests that marital status may be a weak measure for some complex social factors. It is important to point out that nearly all of our pregnant women have a low-income status, have never been married or were abandoned by their spouses or partners. These socioeconomic and demographic factors could be the hidden biological reasons causing nutritional maternal anemia, i.e., multiparity, starvation, hookworm and other intestinal parasites, low PCV number, etc.

According to our results, it would seem reasonable to assume that preterm group had fewer visits, nevertheless that group with a better prenatal care attendance had a lower Hb. No reasons to explain this fact were found.

Although in the multivariable analysis, smoking was not significant in the final model, in the univariable analysis this variable was found statistically associated with premature delivery. In this regard, de Hass et al. (24) and Kramer (27) have shown the same results. However, smoking is a modifiable risk factor through prenatal care program.

We have mentioned that the operating criterion for anemia

during pregnancy is defined as Hb less than 11 g/dL, regardless of the stage of gestation and the physiological and/or pathologic factors that take part in the reduction of Hb level. Therefore, it is difficult to interpret and to compare the studies.

The usual cut-off point for Hb (< 11 g/dL, WHO) which define maternal anemia has been questioned, (28) being however the most accepted at present.

Indeed, this criterion has been considered inappropriate because it does not take into account several important factors, such as stage of gestation and altitude. Indeed, Klebanoff (11) has pointed out that the precise definition of pregnant women with anemia is confounded by many factors such as altitude, ethnicity, and use of iron supplements and obstetric changes in plasma volume. Thus, there will be controversy, until a new definition of maternal anemia is established. Lao and Pun (23) proposed to re-evaluate the "normal" Hb level.

What would be the "optimal" maternal Hb level to protect against a poor pregnancy outcome? The problem is that currently the exact mechanisms by which maternal anemia could cause prematurity are unknown (29). It would be better to talk of an association between prematurity and maternal anemia and not to conclude that maternal anemia causes prematurity.

It is necessary to improve the health of women with maternal anemia of the third trimester. The iron and folate supplements could be beneficial in countries with a high prevalence of iron deficiency anemia (30-33).

We believe this study may have one limitation, and therefore its results must be interpreted taking it into account. There is a chance of recall bias in the process of gathering data. Given low income and low socioeconomic status of the pregnant women of this study, it was not feasible to carry out longitudinal studies. These studies tend to be more costly and need many logistic problems in their execution. However, in our country this is the first time that research like this has been carried out.

The need to design an educational program about appropriate use of prenatal care may be one of the implications of this study.

In summary, educational efforts addressing appropriate use of prenatal care should be initiated in our city. All efforts to change patterns of use of the prenatal care program must be encouraged.

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