ARCHIVOS LATINOAMERICANOS DE NUTRICION
Organo Oficial de la Sociedad Latinoamericana de Nutrición

Vol. 52 N° 1, 2002

Prevalence of anemia during pregnancy: Results of Valencia (Venezuela) anemia during pregnancy study

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SUMMARY. To determine the prevalence of anemia during pregnancy in Venezuelan pregnant women. By using a cross-sectional study, 630 Venezuelan pregnant women in their third trimester at labor from the Valencia Anemia during Pregnancy Study were studied. Anemia during pregnancy was defined according to WHO guidelines (Hb < 11g/dl), iron deficiency was considered when serum ferritin level was < 12 ng/ml, and when serum folate level was < 3ng/ml, it was considered as folate deficiency. 630 pregnant women (mean [± SD] age, 24± 6.4 years) having an average of Hb 11.38±1.47 g/dl [95%CI = 11.27 to 11.50] were studied. No patient had hemolytic anemia nor clinical infections. Almost all patients were from low or very low socioeconomic status. Prevalence of anemia was 34.44% (severe: 1.8%, moderate: 15.2%, and mild: 83%). Iron deficiency anemia (IDA) was present in 39.2% (95%CI= 32.7 to 45.7), prevalence of folate deficiency anemia (FDA) was 11.98% (95%CI = 7.6% to 16.3%). Combined anemia (IDA and FDA) occurred in 11.52% (95%CI= 7.27% to 15.7%). Multivariate analysis showed that multiparous (odds ratio -OR-: 1.95, 95%CI= 1.28 to 2.97, p =.002) and supplement use of iron (OR: .55 (95%CI= .33 to .91, p= .02) are associated with IDA. The factors associated with FDA were: supplement use of folic acid (OR: .37 (95%CI=.19 to .71, p = .003) and appropriate prenatal control (OR: .51 95%CI= .27 to .96, p = .04). Prevalence of anemia during pregnancy was found to be high. Educational efforts should be stressed in order to encourage improvements in the prenatal care visits.
Key words: Anemia, pregnancy, prevalence, Venezuela, third trimester.

RESUMEN. Prevalencia de anemia durante el embarazo: Resultados del grupo de estudio de anemia durante el embarazo en Valencia, Venezuela. El objetivo fue determinar la prevalencia de anemia durante el embarazo. Se utilizó un diseño de corte transversal. El estudio fue realizado en la Maternidad " Dr. J.L. Facchín de Boni", principal hospital obstétrico y ginecológico de Valencia, Venezuela. Se estudiaron 630 embarazadas durante el tercer trimestre gestacional, en trabajo de parto. Anemia durante el embarazo fue definida como hemoglobina menor de 11g/dl (OMS). Deficiencia de hierro fue considerada cuando el nivel de ferritina sérica era menor de 12 ng/ml y se diagnosticó deficiencia de folatos cuando el nivel era menor de 3ng/ml. La edad promedio de las pacientes fue 24± 6.4 años, siendo la media de la Hb de 11.38±1.47 g/dl [IC 95% = 11.27 a 11.50]. Ninguna paciente tenía anemia hemolítica o infección clínica. Casi todas provienen de estratos socioeconómicos bajo o muy bajo. La prevalencia de anemia fue 34.44% (severa: 1,8%, moderada: 15,2% y leve: 83%). La anemia por deficiencia de hierro (ADFe) estuvo presente en 39.2% (IC95% = 32.7 a 45.7), mientras que la prevalencia de anemia por deficiencia de folatos (ADFo) fue 11.98% (IC95% = 7.6% a 16.3%). La anemia combinada (ADFe y ADFo) se diagnóstico en 11.52% (IC95%= 7.27% a 15.7%). El análisis multivariable mostró que la multiparidad (odds ratio -OR-: 1.95, IC95%= 1.28 a 2.97, p =.002) y el aporte de hierro (OR: .55 (IC95%= .33 a .9, p= .02) están asociados con ADFe. Los factores asociados con ADFo fueron el aporte de ácido fólico (OR: .37 (IC95%=.19 a .71, p = .003) y adecuado control prenatal (OR: .51 IC95% = .27 a .96, p = .04). Se concluye que la prevalencia de anemia durante el embarazo es alta. Esfuerzos educacionales deben ser realizados para incrementar el control prenatal.
Palabras clave: Anemia, embarazo, prevalencia, Venezuela, tercer trimestre.

INTRODUCTION

Anemia during pregnancy is a worldwide problem (1). The nutritional anemia is the most important cause of maternal anemia. Iron deficiency (ID) and folate deficiency (FD) are considered as the first two causes of nutritional anemia. Furthermore, iron deficiency anemia (IDA) is the most important public health problem in hematology in the developing countries (2). During pregnancy there is an increase of iron and folate requirements, therefore the likelihood of presenting ID and FD is high if there is not supplementation during the pregnancy. Diagnosing both deficiencies in pregnant women is critical because several evidences relate IDA to increased risk of maternal and fetal morbidity and mortality and premature delivery and low birth weight.

To our knowledge, there are no investigators in Latin América who have evaluated a hospital – based sample of subjects performing both serum ferritin and serum folate simultaneously with a sample calculated prior to research. The Valencia Anemia during Pregnancy Study (VAPS) was established in 1996 in order to carry out epidemiological researches in the main industrial city of Venezuela with two goals: determine the true prevalence of anemia during pregnancy and determine the association and its magnitude between prematurity and low birth weight with maternal anemia.

This cross-sectional study was performed in pregnant women during the third trimester at labor in order to evaluate the prevalence of anemia during pregnancy in Valencia, Venezuela.

METHODS

From May to December 1996, we examined 630 consecutive Venezuelan pregnant women in their third trimester at labor. No patients had clinical infections, hemoglobinopathies, or chronic inflammatory diseases. Almost all patients were from low or very low income families and live in Valencia, Estado Carabobo.

The research was conducted at the Ciudad Hospitalaria "Dr. Enrique Tejera" in Valencia, Venezuela, a tertiary hospital of 900 beds, center of reference for a population of 3.000.000 in the north central region of Venezuela. The Department of Obstetrics and Gynecology is very busied with over 18000 deliveries yearly.

An electronic counter performed complete blood count, anemia was defined according to WHO guidelines (Hb< 11 g/dl), and it was classified as severe (Hb < 7g/dl), moderate (7 g/dl to 9 g/dl), and mild (10 g/dl to < 11 g/dl). Serum ferritin was performed using Spectro Ferritin™ (Ramco Laboratories, Houston, TX, USA). ID was defined as a serum ferritin level < 12 ng/ml. Only serum folate was measured in this research, the kit to measure erythrocyte folate level was not available. We used a Folate Radioaasay Kit [^{125}I] (ICN Pharmaceuticals, Orangeburg, N.Y, USA). FD was defined when serum folate level was lower than 3 ng/mL according to Wagner (3). Microcytosis was defined as mean corpuscular volume (MCV) lesser than 76fL and macrocytosis was considered when MCV was greater than 96fL.

This research was approved by the Ethical Committee of the Ciudad Hospitalaria "Dr. Enrique Tejera", and free informed consent was obtained from all patients enrolled into the study.

Sample size: Sample size was calculated assuming an estimated prevalence of maternal anemia of 37%, a significance level of 5% and sampling error of 10%. To satisfy these conditions, the number of subjects needed for the study was 630 pregnant women.

Statistical analysis: Data is presented as mean±SD unless otherwise noted. Medians, percentiles and range are presented since most of the biological variables are not normally distributed. Categorical variables were compared by using chi-square test or Fisher's exact test when appropriate. Continuous variables were analyzed by using the Student's t-test for unpaired data. To compare means between 3 or more groups, One-way ANOVA procedure was used. To evaluate equal variances, Bartlett's test was used. To compare all pairs of means after ANOVA (multiple comparison post test), the Bonferroni test was used. All variables that showed a statistically significant association (a <.1) with anemia in univariate analysis were included in the multivariate analysis. Multivariate analysis was applied using stepwise backward logistic regression. All statistical tests were two-tailed, and p value < 0.05 was considered to indicate statistical significance. Stata software (version 6.0, Stata, College Station, Texas) was used for statistical analyses.

RESULTS

During the study period, data from 630 Venezuelan pregnant women were studied having an average age of 24±6.40 ranging from 14 to 48 years. In this group, 179 of the 630 pregnant women (28%) were teenagers. Two hundred and seventeen pregnant women (34.44%) had not appropriate prenatal control (less than 5 visit), and seventy-four subjects (11.75%) had no prenatal care visits at all. One-hundred forty eight pregnant women showed pregnancy -induced hypertension or eclampsia (23.5%). The general and obstetric characteristics of the patients are summarized in Table 1.

TABLE 1

General characteristics of pregnant women (n = 630)

Variable	Mean (±SD)	95%CI	Median	Range	n (%)
Age	24 (±6.4)	23.6 to 24.6	23	14 - 48	
Parity			1	0 - 10	
Gestation			2	1 - 15	
Interval pregnancy ϕ week	40.8(±32.8)	37.4 to 44.2	24	0 - 192	
Prenatal Care Visit	5.27 (±2.78)	5.05 to 5.49	6	0 - 17	
Multiparous					214/630 (34)
Multigesta					364/630 (58)
Uterine Bleeding					
None					514/630 (82)
I trimester					39/630 (6.1)
II trimester					25/630 (3.9)
III trimester					35/630 (5.5)
more than one					17/630 (2.7)
Total bleeding					116/630 (18)
Iron supplementation					525/630 (83)
Folate supplementation					512/630 (81)

ϕ= 364 pregnant women

The values of Hb, ferritin and serum folate levels and as well as MCV are shown in Table 2. The values of Hb ranged from 5.6 to 15.4 g/dl. The median of Hb, ferritin, serum folate and MCV was 11.5 g/dl (95%CI = 11.3 to 11.6), 16.9 ng/ml (95%CI=15.6 to18.5), 6.4 mg/ml (95%CI = 6 to 7) and 86 fL (95%CI = 86 to 87), respectively.

TABLE 2
Hematological characteristics of pregnant women (n = 630)

Variable	Mean (±SD)	95%CI	Median	Range
Hb (g/dl)	11.9 (±1.4)	11.2 to 11.5	11.5	5.6 to 15.4
Serum Ferritin (ng/ml)	30.5 (±2.1)	26.8 to 34.7	16.9	0.9 to 781
Serum Folate (mg/ml)	8.2 (±6.3)	7.7 to 8.7	6.4	0.44 to 44
MCV (fL)	86.4 (±6.2)	85.9 to 86.8	86	64 to 111

The mean concentration of serum ferritin in women with toxemia (43.5± 95.6ng/ml, 95%CI= 28 to 59.1) was significantly higher than that of healthy pregnant women (26.5 ±31.2ng/ml, 95%CI = 23.7 to 29.3) (p = 0.0008). The hematocrit values were not significantly different among the two groups. Indeed, the mean concentration of hematocrit in hypertension group was 35.8±4.1 (95%CI = 35.1 to 36.4), while in the healthy group, it was 35.5±4.2 (95%CI = 35.2 to 35.9) (p = .57).

Twenty-six patients (4%) had microcytosis, while thirty-three pregnant women (5%) presented macrocytosis.

From the 630 study participants, 217 had anemia (34.44%, 95% CI= 30.7 to 38.1). The three stages of anemia prevalence were as follow: 1.8% (4/217) severe, 15.2%(33/217) moderate and 83% (180/217) mild. The prevalence of IDA was 39.2% (95% CI = 32.7 to 45.7), FDA was present in 11.98% (95% CI= 7.6 to 16.3), combined anemia (IDA and FDA) occurred in 11.52% (95% CI =7.27 to 15.7) and other types of anemia were found in 37.33% (95% CI = 30.8 to 43.7). Twenty percent had folate deficiency (125/630). Of them, forty-one percent (51/125) had FDA. Thirty-four percent had iron deficiency (217/630), and in this cohort with ID, 51% of the subjects (110/217) had IDA.

Table 3 shows the mean of Hb by type of anemia. Analysis with one-way ANOVA indicated a non statistically significant difference among the groups ($F_{3,216}$ = 0.23; p = 0.87).

TABLE 3
Mean of hemoglobin according to type of anemia

TYPE (n = 217)	%	Mean (±SD)	95%CI	Range
IDA (85)	39.2	9.7 (±1)	9.5 to 9.9	5.6 to 10.9
FDA (26)	11.98	9.7 (±.98)	9.3 to 10.1	7.5 to 10.9
MDA (25)	11.52	9.7 (±.79)	9.4 to 10.1	7.9 to 10.9
Others Anemia (81)	37.33	9.8 (± .1)	9.6 to 10.1	5.9 to 10.9

IDA = Iron Deficiency Anemia
FDA = Folate Deficiency Anemia
MDA = Mixed Deficiency Anemia

One-way Analysis of variance analysis showed a non statistically significant difference among the groups of anemic patients according their ages. Indeed, the mean of ages is as follow: IDA (24.9±6.1), FDA (24.8±7.6), Mixed Anemia (23.4±6), and Other types of Anemia (24.1±6.3) ($F_{3,216}$ = 0.47; p = 0.70).

The mean of MCV was different according to the type of anemia ($F_{3,216}$ = 5.55; p = 0.001) (Table 4). For each of the six possible pairwise tests, Bonferroni's correction is as follow: IDA vs FDA (p = 0.003), IDA vs mixed anemia (p = 1), IDA vs others anemia (p = 0.04), FDA vs mixed anemia (p = 0.047), FDA vs others anemia (p = 0,59), and mixed anemia vs others anemia (p = 0.59).

TABLE 4
MCV among fourth type groups of anemic pregnant women(n =217)

Anemia TYPE	MCV (fL) Mean (±SD) 95%CI	n(%)
Iron Deficiency Anemia	83.3(±7) 69 to 102	85(39.2)
Folate Deficiency Anemia	88.5(±6.4) 76 to 101	26(11.9)
Mixed Anemia	83.6(±6) 70 to 99	25(11.5)
Others Anemia	86.1(±6.3) 72 to 101	81(37.3)

In the teenagers group (179 patients), 59 of them (33%) had anemia. However, teenager pregnant women did not have an increased risk of anemia (Table 5).

TABLE 5
Anemia in pregnant women teenagers

Variable	n	%	OR	95%CI	P
Anemia	59	32.9	.91	.63 to 1.3	.62
Iron Deficiency	53	29.6	.73	.50 to1.06	.10
Folate Deficiency	35	19.5	.97	.63 to 1.5	.90
Iron Deficiency Anemia	18	30.5	.64	.37 to 1.1	.11
Folate Deficiency Anemia	10	16.9	1.6	.72 to 3.5	.24
Mixed Anemia	7	11.8	.97	.41 to 2.3	.96
Other Anemia	24	40.6	1.07	.64 to 1.7	.79

The odds ratio and 95% confidence intervals of the variables that were found to have a statistically significant association with FDA and IDA in the univariate analysis are as follow: For FDA, multiparous (OR: 1.9, 95%CI = 1.3 to 2.8, $p= 0.001$), inappropriate prenatal control (OR: 1.8, 95%CI = 1.2 to 3.0 , $p = 0.001$), supplement use (OR: 0.33, 95%CI = 0.21 to 0.51, $p= 0.001$), and for IDA, multiparous (OR: 1.8, 95%CI = 1.3 to 2.6, $p= 0.001$), inappropriate prenatal control (OR: 1.59, 95%CI = 1.1 to 2.4, $p = 0.007$), supplement use (OR: 0.53, 95%CI = 0.35 to 0.82, $p= 0.001$)

Primigravid women had protection against ID (OR = 0.52, 95%CI = 0.37 to 0.73 $p = 0.0002$) and FD (OR = 0.48, 95%CI = 0.32 to 0.73 $p = 0.0006$)

Associated factors with IDA and FDA in the multivariate analysis are shown in Table 6.

TABLE 6
Multivariate analysis of risk factors for maternal nutritional anemia

Anemia Type	Odds Ratio	95%CI	P
Folate Deficiency Anemia			
Supplement Use	.37	.19 to .71	.003
Appropriate Prenatal Control	.51	.27 to .96	.04
Iron Deficiency Anemia			
Multiparous	1.95	1.28 to 2.97	.002
Supplement Use	.55	.33 to 91	.02
Mixed Anemia			
Multiparous	2.6	1.12 to 5.8	.024
Bleeding	.33	.07 to 1.8	.15
Inappropriate Prenatal Control	1.9	.82 to 4.2	.13

Supplement use of folic acid and appropriate prenatal control (>5 visits) were independently associated with FDA, both factors had protector effect against FDA. While multiparity and supplement use of iron were associated with IDA. Multiparity had deleterious effects on pregnant women.

DISCUSSION

In this study population, the prevalence of maternal anemia was 34.44%. This level is as high as others seen in developing countries (1,4-7). Although the burden of this problem is higher in some other countries, such as West Africa (66%) (4), Singapore (81%) (8), or Perú (70%) (9).

Anemia during gestation is an indicator of the precarious nutritional status of any country and it remains as a world wide public health problem. WHO defends that ID is the most common deficiency disease of the world (10). The main cause of anemia in pregnancy is nutritional, being ID and FD its most important responsible factors (11,12).

According to what is mentioned above, we will introduce the discussion in two sections: first, iron deficiency anemia, and second, folate deficiency anemia.

As a result of ID, it is considered that more than half a billion people of the world have deleterious effects (13). So, Ogbeide et al (14) recommend a regular review of factors which may contribute to prevent the maternal anemia. However, there is still controversy surrounding the impact of the anemia on outcome of pregnancy, at least in developed countries (15,16). Nevertheless, Scholl et al point out that the relationship between inadequate iron intake and increased likelihood of preterm delivery is kept during the third trimester (17,18).

Independently of its impact on fetal health, maternal anemia increases the risk of maternal morbidity (19). Therefore, it is very important to prevent and to treat maternal anemia.

Looker et al (20) report 2% to 5% of American teenagers with iron deficiency. In a recent study in Brasil (21), in São Paulo, the prevalence of anemia in pregnant adolescents was 14.2%, nevertheless the frequency of ID was high (48.4%). Regarding Looker´s results (20), our study showed a prevalence four times higher and in comparison with Brasil (21) it was twice as high.

Although the pregnant adolescent was not our central objective, we should mention that the adolescent didn't have a statistically significant association with anemia in general or anyone of its types. Similar results are shown in a review and Meta-analysis by Scholl et al (22). Contrary to Beard (23) that points out that adolescence is a risk factor for maternal anemia. We considered that the rational approach to IDA in this group is not different to the other pregnant woman. The evaluation of anemia during pregnancy is not very different than that of any anemic adult.

Serum ferritin concentration is currently the gold standard to detect iron deficiency, however it is also known that ferritin is an acute-phase reactant associated with acute and chronic disorders. We found high levels of serum ferritin in patients with toxemia; this has also been reported by Tamura (24), Entman (25) and Maymon (26). The exact mechanisms that induce an increases of ferritin levels in toxemic pregnant women are not known. This fact is very important because our prevalence of ID and IDA could be higher. Therefore, it is necessary to use a more sensitive and specific indicator of body iron stores such as serum transferrin receptors (27-29).

Many and Duffy (11) point out that an increase of ferritin in the third trimester may rarely be found associated with inflammatory or autoimmune disorders and toxemia of gestation. It has pointed out that high serum ferritin concentration in the third trimester, resulting from a failure of ferritin to decline, is associated with very preterm delivery and markers of maternal infection (30).

Two aspects deserve a comment: First, comparing the healthy group with the toxemia group using the results of hematocrit, we found that those results permitted to discard the possibility of insufficient blood volume expansion among both groups. Second, in connection with the MCV, it must be kept in mind that its value is limited because there exists a physiologic increase of the red cell size during pregnancy. We find that the mean MCV for the patients with IDA is somewhat lower than the mean for the patients with FDA.

¿What would be the reasons to explain the high prevalence of maternal anemia in our region? The main factors are ID and FD which are associated with multiparity, low socioeconomic status, low rate of prenatal control and iron and folic acid supplementation. The same factors are reported by others researchers (4,14,31,32). Of course, worldwide, the main cause of ID in adults is gastrointestinal blood loss, however, in premenopausal women with IDA the most important cause is excessive menstrual blood loss or pregnancy (20). In the tropical area, hookworm is also a very common cause. We think that in our region another associated factor for IDA could be the increase of vegetable consumption. The low bioavailability of iron in vegetables is well known. Calcium intake during pregnancy could impair iron absorption (33), even though we can only suggest it since our study does not include this issue.

Meda et al (4) report hemolysis due to hemoglobinopathies and malaria as factor responsible for high prevalence of maternal anemia, none of our pregnant women showed hemolytic disorders.

Folate deficiency is considered as the second cause of nutritional anemia (34). In our city, 20% was the prevalence of FD but in the pregnant women with FD the magnitude of the FDA was 51%.

Folate deficiency (FD) is the main cause of megaloblastic anemia (MA) during pregnancy. But, the majority of MA in pregnant women are seen during the third trimester and postpartum period (35). This could be explained by the existence of an appropriate folate´s storage for up to 20 weeks. The associated factors with FD and FDA in our pregnant women were multiparity and inappropriate prenatal control, which could hide an inadequate diet. It is well established the effectiveness of periconceptional folate supplementation to prevent neural tube defects, nevertheless, controversy exists surrounding the effectiveness of folic acid to prevent low birth weight (LBW), duration of gestation (36), and other obstetric complications. None of our pregnant women had newborn with malformations. It has been described that lower concentrations of serum folate at week 28 are associated with a greater risk of preterm delivery and low birth weight (37). To the moment, this paper was written, we are analyzing the association between maternal anemia, FDA, IDA, LBW and prematurity.

Despite the significant body of evidence about the various aspects of ID and FD, why do ID and FD remain as a major public health problem throughout the world, specially in developing countries? Are the health policy makers doing all efforts to reduce the magnitude of the problem? Do health programs have enough effectiveness to reduce it? All data indicate lack of effectiveness and poor efficiency. Without any doubts, the programs remain poorly implemented. What is the main etiologic fraction of the cause that does not allow reducing the problem? Why do not we globalize the health all over the world?

In order to reduce the burden of the problem, we propose some strategies for preventing IDA and FDA during pregnancy: 1.- Use of quality assurance methods (QA) such as those proposed by Abubaker et al (38). They authors demonstrated that QA has been effective in reducing iron deficiency anemia in a rural population from Egypt, 2.- We consider that, at least in those developing countries with high or very high rate of maternal anemia, it must be mandatory guarantee free iron and folic acid supplementation to pregnant woman, even six month postpartum. This must be all associated with food fortification. This last issue has been proved useful by Layrisse et al (39). 3.- Practitioners should take decisions related to the strategies "daily versus intermittent" iron supplementation based on economic, cultural, personal aspects of the pregnant woman, and side effects of drug.

In an elegant review, Walker (40) asks himself "what priority should it have? in relation to the remedying of iron deficiency". He recommends iron supplementation associated with food fortification. Suggestions about how to do prophylactic iron administration in pregnancy and management of IDA and FDA appears in many reviews (11,13,31,41). 4.- Medical Societies of Hematologists and Obstetricians must use their position in society to influence public opinion and government health planners.

To have carried out this study might have contributed to give an idea of the magnitude of the problem in this city and in Venezuela. These results can be the tip of the iceberg that is the national situation.

One limitation of this study was that red blood cell folate levels, which reflect tissue levels, could not be measured. Despite that limitation, however, this factor does not obscure the basic message that pregnant women in this city have a significant FD, and it is very important to supply this micronutrient to this population. Also, these results have contributed, in Venezuela, to improve the knowledge of the epidemiology of this very important public health problem in hematology.

In summary, in the conditions studied, there is a high prevalence of nutritional anemia in pregnancy in Valencia, main industrial city, in Venezuela. Strategies must be carried out to reduce the burden of the problem.

ACKNOWLEDGMENTS

The authors thank to Professor Miguel Layrisse for critical reading of the manuscript and helpful suggestions.

We want to express our deep gratefulness to the Dra. Liseti Solano, Director of the Centro de Investigaciones en Nutrición (CEINUT), Universidad de Carabobo and IVSS. Likewise to the Lic. Gloria El Khoury to carry out the determinations of serum ferritin. Finally, to the Lic. Mariana Lucco and to the technical personnel of the Laboratory of Hormones of the "Centro Policlínico Valencia" for the technical attendance in the determination of the folic acid. But overalls, for the human support that they gave us. Thank you.

This research was supported by a grant # CDCHT-UC-742-97 from Consejo de Desarrollo Científico y Humanístico of Universidad de Carabobo, Venezuela.

Conflicts of interest: None.

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Recibido: 14-08-2000
Aceptado: 19-11-2001