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Factors associated with folic acid deficiency in pregnant women and its repercussions in the newborn: a cross-sectional study

Factores asociados con la deficiencia de ácido fólico en gestantes y repercusiones en el recién nacido: estudio transversal

Fatores associados à deficiência de ácido fólico em gestantes e repercussões no recém-nascido: estudo transversal

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ABSTRACT

Objective: to estimate the prevalence and identify factors associated with folic acid deficiency among pregnant women receiving care at a maternal–child referral hospital in northeastern Brazil and its repercussions on the newborn.

Method: cross-sectional study based on a secondary analysis of the cohort "Nutrition and infection: the problem revisited in light of the microcephaly outbreak," comprising 1,052 pregnant women followed between 2017 and 2019 at a maternal–child referral hospital in northeastern Brazil. Pregnant women with available serum folic acid measurements were included. An *ad hoc* database was constructed containing sociodemographic, obstetric, nutritional, lifestyle, and neonatal outcome variables. Prevalence estimates were presented with 95% confidence intervals, and associated factors were analyzed using multiple Poisson regression. The final model used the Wald test ($p<0.05$).

Results: the prevalence of folic acid deficiency (≤5.38 ng/mL) was 8.4%. Among these women, 38.6% reported using supplementation. In the multivariable analysis, marital status ($p=0.026$), second trimester of pregnancy ($p=0.020$), and absence of supplementation ($p<0.001$) remained associated with deficiency.

Conclusion: folic acid deficiency was associated with lack of supplementation, absence of a partner, and assessment during the second trimester. No neonatal repercussions were observed. The findings reinforce the importance of timely prenatal care and adequate supplementation.

Descriptors: Folic Acid Deficiency; Pregnancy; Newborn; Neural Tube Defects.

RESUMO

Objetivo: estimar a prevalência e verificar os fatores associados à deficiência de ácido fólico em gestantes atendidas em hospital de referência materno-infantil no Nordeste do Brasil e as repercussões no recém-nascido.

Método: estudo transversal baseado em análise secundária da coorte "Nutrição e infecção: o problema revisitado em função do surto de microcefalia", composta por 1.052 gestantes acompanhadas entre 2017 e 2019 em hospital de referência materno-infantil no Nordeste do Brasil. Foram incluídas gestantes com resultado disponível da dosagem sérica de ácido fólico. Foi construído um banco *ad hoc* com variáveis sociodemográficas, obstétricas, nutricionais, hábitos de vida e desfechos neonatais. As prevalências foram descritas com IC95%, e os fatores associados, analisados por regressão de Poisson múltipla. No modelo final, utilizou-se teste de Wald ($p<0,05$).

Resultados: a prevalência de deficiência de ácido fólico (≤5,38 ng/mL) foi de 8,4%. Entre essas gestantes,38,6% referiram uso de suplementação. Na análise multivariada, situação conjugal ($p=0,026$), segundo trimestre gestacional ($p=0,020$) e ausência de suplementação ($p<0,001$) mantiveram associação com deficiência.

Conclusão: a deficiência de ácido fólico esteve associada à ausência de suplementação, ausência de parceiro e exame no segundo trimestre. Não foram observadas repercussões neonatais. Os achados reforçam a importância do pré-natal oportuno e da suplementação adequada.

Descritores: Deficiência de Ácido Fólico; Gravidez; Recém-Nascido; Defeitos do Tubo Neural.

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RESUMEN

Objetivo: estimar la prevalencia y verificar los factores asociados a la deficiencia de ácido fólico en gestantes atendidas en un hospital de referencia materno-infantil del Nordeste de Brasil y sus repercusiones en el recién nacido.

Método: estudio transversal basado en un análisis secundario de la cohorte "Nutrición e infección: el problema revisitado en función del brote de microcefalia", compuesta por 1.052 gestantes seguidas entre 2017 y 2019 en un hospital de referencia materno-infantil del Nordeste de Brasil. Se incluyeron gestantes con resultado disponible de dosificación sérica de ácido fólico. Se construyó una base de datos *ad hoc* con variables sociodemográficas, obstétricas, nutricionales, hábitos de vida y desenlaces neonatales. Las prevalencias se describieron con intervalos de confianza del 95%, y los factores asociados se analizaron mediante regresión de Poisson múltiple. En el modelo final se utilizó la prueba de Wald ($p<0,05$).

Resultados: la prevalencia de deficiencia de ácido fólico (≤5,38 ng/mL) fue del 8,4%. Entre estas gestantes, el 38,6% refirió uso de suplementación. En el análisis multivariado, la situación conyugal ($p=0,026$), el segundo trimestre gestacional ($p=0,020$) y la ausencia de suplementación ($p<0,001$) se mantuvieron asociados con la deficiencia.

Conclusión: la deficiencia de ácido fólico se asoció con la falta de suplementación, la ausencia de pareja y la realización del examen en el segundo trimestre. No se observaron repercusiones neonatales. Los hallazgos refuerzan la importancia del prenatal oportuno y de la suplementación adecuada.

Descriptores: Deficiencia de Ácido Fólico; Embarazo; Recién Nacido; Defectos del Tubo Neural.

INTRODUCTION

Pregnancy is a period that requires special attention to maternal health due to the physiological changes that occur in a woman's body, including immunological, cardiovascular, pulmonary, and hemodynamic modifications, which are essential for maintaining a healthy pregnancy. In this context, the demand for essential nutrients, such as folic acid, also increases significantly compared to non- pregnant periods[1,2].

Folic acid plays a crucial role in cell division, tissue growth, and various metabolic reactions. Its deficiency can result in significant consequences for both mother and fetus, including neural tube defects (NTDs) such as anencephaly and spina bifida. Folic acid supplementation before and during pregnancy helps reduce these outcomes, as well as reducing the risk of premature birth and pre-eclampsia[3]. Studies also suggest that continuous folic acid intervention during pregnancy, beyond the initial period necessary to prevent NTDs, is beneficial for the child's neurocognitive development[4].

The World Health Organization (WHO) recommends daily supplementation of 30–60 mg of elemental iron combined with 400 µg (0.4 mg) of acid before conception and throughout pregnancy as an effective strategy to prevent maternal anemia, NTDs, premature birth and low birth weight[5].

However, the effectiveness of these recommendations depends not only on the prescription of the supplement, but also on adequate guidance, adherence and follow-up during prenatal care. Health education and regular access to the micronutrient are therefore fundamental components to reduce maternal and fetal complications[6,7]. In situations where pregnancy is unplanned and supplementation is not initiated early, embryonic development may occur without adequate protection[6,8].

Although there are national and international recommendations on the role of folic acid supplementation in pregnancy[5,9], we are unaware of studies that have simultaneously assessed the prevalence and factors associated with laboratory folic acid deficiency, based on serum levels, in pregnant women treated at a public referral hospital. This gap makes it difficult to identify more vulnerable groups and to target care strategies.

Therefore, the present study aimed to estimate the prevalence and verify the factors associated with folic acid deficiency in pregnant women treated at a maternal and child reference hospital in Northeast Brazil and the repercussions on the newborn. It was hypothesized that the deficiency would be related to specific maternal characteristics, particularly the absence of supplementation, and could negatively impact neonatal outcomes.

METHOD

This is a cross-sectional, analytical study developed from a secondary analysis of the cohort "Nutrition and infection: the problem revisited in light of the microcephaly outbreak". composed of 1,469 pregnant women followed at the Women's Care Center of the Instituto de

Medicina Integral Professor Fernando Figueira (IMIP), a public hospital of reference in maternal and child health located in Recife, Pernambuco. Cohort recruitment occurred between April 2017 and July 2018, with follow-up of pregnant women until March 2019. Data extraction and analysis for this study were performed between May and October 2023.

In the original cohort, pregnant women with prenatal care up to the beginning of the third trimester and with gestational age defined by the date of their last menstrual period or by ultrasound were eligible. For the present study, only pregnant women with available serum folic acid level results were considered eligible. Participants without this laboratory record were not eligible for the present analysis. Because this study was based on a previously established database, there were no additional exclusions or sample losses. After applying the eligibility criteria, the final sample consisted of 1,052 pregnant women.

In the original study, pregnant women were approached during prenatal appointments, at which time they received explanations about the research objectives and signed the Informed Consent Form (ICF). Participants were followed up in subsequent appointments, with active searches conducted in medical records and the laboratory database to obtain the results of previously performed tests. In the absence of these records, the necessary test was requested. Other maternal variables were obtained through interviews conducted during routine appointments. Information regarding neonatal outcomes was collected after birth, through consultation of medical records or contact with postpartum women.

The variables analyzed included maternal age, origin, marital status, education level, per capita family income, gestational age at the time of data collection, and maternal nutritional status, classified according to the Body Mass Index limits per gestational week of the Atalah curve (underweight, adequate weight, overweight, and obesity). As a lifestyle variable, the history of tobacco use and tobacco use during the current pregnancy were assessed.

Folic acid deficiency was defined as values ≤ 5.38 ng/mL, according to the institution's laboratory reference. Anemia was classified according to WHO cut-off points: hemoglobin <11.0 g/ dL in the first and third trimesters; and <10.5 g/ dL in the second trimester. Maternal age was categorized as ≤19 years and >19 years.

Regarding neonatal outcomes, birth weight, occurrence of live birth, presence of malformations, and prematurity were evaluated, defined as births with a gestational age < 37 weeks. Birth weight was classified as: low birth weight, when < 2,500 g; insufficient weight, between 2,500 and 2,999 g; adequate weight, between 3,000 and 3,999 g; and macrosomia, when ≥ 4,000 g. Malformations included microcephaly, alterations in the nervous system and in the circulatory, respiratory, and digestive systems, as well as cleft lip and/or palate, musculoskeletal deformities, and unclassified chromosomal anomalies.

Per capita family income was calculated by dividing the total household income by the number of residents, and was categorized as < ½ minimum wage, ½ to 1 minimum wage, and > 1 minimum wage.

The data were extracted from the original database and organized into a previously defined *ad hoc* database containing the variables available for this analysis. Since this is a secondary analysis, no specific sample size calculation was performed; the sample size was determined by the availability of records. For variables with missing data, the analyses were conducted considering only the valid cases, duly indicated in the tables, and the percentages were calculated based on this denominator. Information bias was minimized through the use of standardized forms, a trained team, and official laboratory records.

Statistical analyses were performed using Stata® 12.1 software. The prevalence of adequate and inadequate folic acid levels, as well as hemoglobin, was presented using simple and relative frequencies with 95% Confidence Intervals (95% CI). To investigate associated factors, simple and multiple Poisson regression models were fitted, estimating crude and adjusted Prevalence Ratios (PR) and their respective 95% CIs. Variables with a p-value < 0.20 in the univariate analysis were enabled for multivariate analysis, while those with a p-value < 0.05 remained in the final model. The Wald test was used to assess the statistical significance of each variable.

The original study followed the ethical guidelines established by Resolution No. 510/2016 of the National Health Council. It was approved by the Research Ethics

Committee Involving Human Beings of IMIP, under the Certificate of Presentation for Ethical Appraisal (CAAE) No. 54690316.0.0000.5201 and Substantiated Opinion No. 2.020.481, issued on April 18, 2017, with funding from the Foundation for Support of Science and Technology of the State of Pernambuco and the National Council for Scientific and Technological Development. The current study, derived from this database, was also approved by the same Research Ethics Committee, under CAAE No. 68787523.0.0000.5201 and Substantiated Opinion No. 6.050.725, issued on May 10, 2023. This study constitutes a novel and independent analysis of the original cohort, with a distinct specific objective and its own analytical approach, not configuring undue overlap or fragmentation of results. There was no additional external funding. All participants signed the Informed Consent Form. The authors declare no conflicts of interest.

The manuscript was written following the recommendations of the checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for cross-sectional observational studies.

RESULTS

Among the pregnant women evaluated, 91.6% had adequate folic acid levels (>5.38 ng /mL), while 8.4% (n=88) had a deficiency of these levels (≤5.38 ng / mL).

Teenage pregnancy occurred in 11% of cases. The declared races, considering the categories Black and Brown, occurred in 71.1% of cases. The mothers were from urban areas (96.7%), were in a stable union or were married (79.4%), had 12 or more years of schooling (75.1%), were employed without pay (51.1%), and had a family income of less than half the minimum wage (41.4%). In addition, 39% of them were primiparous. A history of abortion occurred in 42.5%; cigarette use during pregnancy was reported by 9.9%; and initiation of prenatal care in the first trimester of pregnancy was reported in 70.1%. Folic acid supplementation was found in 66.3%, and Atalah classification considering overweight and obesity together occurred in 53.6% (Table 1). Some variables had missing data; therefore, the percentages were calculated based on valid cases.

Table 1 – Estimates of Prevalence Ratios for folic acid deficiency in pregnant women treated at the Instituto de Medicina Integral Professor Fernando Figueira. Recife, Pernambuco, Brazil, April 2017 to July 2018

Variables	Total n* (%)	Folic acid deficiency n* (%)	PR (95% CI)	p-value
Race				0.328
White	211 (20.2)	13 (6.2)	1.0	
Black/brown	743 (71.1)	65 (8.7)	1.42 (0.80 - 2.53)	
Indigenous/yellow	91 (8.7)	10 (11.0)	1.78 (0.81 - 3.92)	
Maternal age				0.057
<=19 years old	116 (11.0)	15 (12.9)	1.66 (0.98 - 2.79)	
>19 years old	936 (89.0)	73 (7.8)	1.0	
Origin				0.573
Urban	1017 (96.7)	86 (8.5)	1.48 (0.38 - 5.77)	
Rural	35 (3.3)	2 (5.7)	1.0	

Table 1 – Cont.

Variables	Total n* (%)	Folic acid deficiency n* (%)	PR (95% CI)	p-value
Marital status				0.015
Single/Separated/Widowed	217 (20.6)	27 (12.4)	1.70 (1.11 - 2.61)	
Married/common-law marriage	835 (79.4)	61 (7.3)	1.0	
Years of education				0.116
Up to 8	132 (12.6)	15 (11.4)	1.55 (0.90 - 2.65)	
9 to 11	130 (12.4)	15 (11.5)	1.57 (0.92 - 2.68)	
12 or more	789 (75.1)	58 (7.4)	1.0	
Paid occupation				0.028
Yes	513 (48.9)	33 (6.4)	1.0	
No	537 (51.1)	55 (10.2)	1.59 (1.05 - 2.41)	
***Per capita* income (MW)**				0.197
<1/2 MW	397 (41.4)	41 (10.3)	1.28 (0.80 - 2.04)	
1/2 to 1 MW	322 (33.6)	26 (8.1)	1.0	
>1 MW	240 (25.0)	15 (6.3)	0.77 (0.42 - 1.43)	
Pregnancy				0.394
Primigravida	410 (39.0)	31 (7.6)	1.0	
Secundigravida	304 (28.9)	23 (7.6)	1.00 (0.60 - 1.68)	
Multigravida	338 (32.1)	34 (10.1)	1.33 (0.84 - 2.12)	
Abortion story				0.536
Yes	274 (42.5)	22 (8.0)	1.0	
No	371 (57.5)	35 (9.4)	1.17 (0.71 - 1.96)	
Has smoked				0.018
Yes	141 (13.4)	19 (13.5)	1.78 (1.11 - 2.86)	
No	911 (86.6)	69 (7.6)	1.0	

Table 1 – Cont.

Variables	Total n* (%)	Folic acid deficiency n* (%)	PR (95% CI)	p-value
Is smoking during the current pregnancy?				0.066
Yes	14 (9.9)	3 (21.4)	2.62 (0.94 - 7.29)	
No	1038 (90.1)	85 (8.2)	1.0	
Trimester of beginning of prenatal care				0.073
1st quarter	693 (70.1)	49 (7.1)	1.0	
2nd quarter	296 (29.9)	31 (10.5)	1.48 (0.96 - 2.27)	
GA in folic acid collection				0.013
1st quarter	343 (32.6)	16 (4,7)	1.0	
2nd quarter	703 (66.8)	71 (10.1)	2.17 (1.28 - 3.67)	
3rd quarter	6 (0.6)	1 (16.7)	3.57 (0.56 - 22.79)	
Folic acid supplementation				< 0.001
Yes	698 (66.3)	34 (4.9)	1.0	
No	346 (32.9)	52 (15.0)	3.09 (2.04 - 4.66)	
Doesn't know	8 (0.8)	2 (25.0)	5.13 (1.48 - 17.82)	
Atalah Classification				0.174
Low weight	140 (13.4)	18 (12.9)	1.82 (1.00 - 3.31)	
Adequate	343 (32.9)	25 (7.3)	1.03 (0.59 - 1.81)	
Overweight	298 (28.6)	21 (7.0)	1.0	
Obesity	261 (25.0)	22 (8.4)	1.20 (0.67 - 2.12)	

Legend: PR – Prevalence Ratio; 95% CI – 95% Confidence Interval; MW – minimum wage; GA – gestational age.
Note: *n corresponds to the number of valid observations in each category. Percentages were calculated based on these values. Total N = 1,052 pregnant women. **p-value obtained by the Wald test.

After univariate Poisson analysis among sociodemographic, lifestyle, gestational, nutritional, anthropometric, and biological variables, it was observed that marital status (single/divorced/widowed, p=0.015), unpaid occupation (p=0.028), smoking habit (p=0.018), gestational trimester at the time of the examination (second and third trimesters, p=0.013), and the absence of folic acid supplementation (p<0.001) were associated with a higher prevalence of folic acid deficiency.

After multivariate Poisson analysis with initial and final adjusted PR, marital status, whether single/divorced/widowed (p=0.026), when compared to married/stable union, marital status (p=0.026) of single/divorced/widowed, when compared to married/stable union, gestational age at examination (p=0.020) in the second trimester, when compared to the first, and non-supplementation of folic acid during pregnancy (p<0.001), when compared to supplementation, showed a higher PR in presenting folic acid deficiency (Table 2).

The biological and clinical characteristics of the newborns are described in Table 3. The live birth rate was 94.8%; 88.9% of the babies were born at term; and 59.8% of the babies had adequate birth weight.

When performing the association test between folic acid deficiency in these pregnant women and the subsequent birth of their children in the categories of low birth weight (p=0.621), prematurity (p=0.652), malformation (p=0.286) and stillbirth (p=0.631), there was no statistical significance in any of these variables.

Table 2 – Multivariate Poisson model for factors associated with folic acid deficiency in pregnant women. Recife, Pernambuco, Brazil, April 2017 to July 2018

Variables	$_{\text{Initial adjusted}}$PR	p-value	$_{\text{final adjusted}}$PR	p-value
Maternal age		0.433		0.282
≤ 19 years old	1.32 (0.66 - 2.62)		1.37 (0.77 - 2.45)	
>19 years old	1.0		1.0	
Marital status		0.073		**0.026**
Single/Separated/ Widowed	1.56 (0.80 - 2.18)		1.60 (1.06 - 2.42)	
Married/stable union	1.0		1.0	
Education (years)		0.483		0.258
Up to 8	1.16 (0.66 - 2.05)		1.23 (0.71 - 2.14)	
9 to 11	1.41 (0.79 - 2.52)		1.53 (0.91 - 2.58)	
12 or more	1.0		1.0	
Paid occupation		0.269		0.537
Yes	1.0		1.0	
No	1.32 (1.02 - 1.87)		1.15 (0.74 - 1.77)	
***Per capita* family income**		0.895		0.895
<1/2 MW	0.95 (0.56 - 1.60)		0.95 (0.56 - 1.60)	
1/2 to 1 MW	1.0		1.0	
>1 MW	1.10 (0.55 - 2.20)		1.10 (0.55 - 2.20)	

Table 2 – Cont.

Variables	Initial adjusted PR	p-value	final adjusted PR	p-value
He smoked		0.181		0.095
Yes	1.48 (0.83 - 2.64)		1.53 (0.93 - 2.53)	
No	1.0		1.0	
Smokes during the current pregnancy?		0.067		0.365
Yes	2.63 (0.93 - 7.40)		1.70 (0.54 - 5.32)	
No	1.0		1.0	
Quarter in which PN begins		0.655		0.282
1st quarter	1.0		1.0	
2nd quarter	0.89 (0.55 - 1.46)		0.77 (0.48 - 1.24)	
Gestational age at examination		<0.001		**0.020**
1st quarter	1.0		1.0	
2nd quarter	2.14 (1.13 - 4.03)		2.05 (1.22 - 3.46)	
3rd quarter	3.62 (0.39 - 28.33)		3.71 (0.48 - 28.42)	
Folic acid supplementation		<0.001		**<0.001**
Yes	1.0		1.0	
No	3.10 (1.95 - 4.93)		2.99 (1.98 - 4.52)	
Does not know	3.94 (1.27 - 12.30)		4.11 (1.21 - 14.02)	
Atalah Classification		0.685		0.670
Low weight	1.38 (0.69 - 2.75)		1.36 (0.70 - 2.66)	
Adequate	0.96 (0.51 - 1.81)		0.94 (0.51 - 1.75)	
Overweight	1.0		1.0	
Obesity	1.21 (0.64 - 2.29)		1.16 (0.64 - 2.10)	

Legend: PR – Prevalence Ratio; *Wald Test; MW – minimum wage; PN – prenatal care.

Table 3 – Distribution of biological and clinical characteristics of newborns. Recife, Pernambuco, Brazil, April 2017 to July 2018

Variables	n* (%)
Born alive (N=1,003)	
Yes	951 (94.8)
No	16 (1.6)
Abortion	36 (3.6)
Sex of the NB (N=961)	
Masculine	486 (50.6)
Feminine	475 (49.4)
Birth weight (N=950)	
Low weight < 2,500 g	102 (10.7)
Insufficient weight 2,500 to 2,999 g	209 (22.0)
Suitable weight 3,000 to 3,999 g	568 (59.8)
Macrosomal ≥ 4,000 g	71 (7.5)
Prematurity (N=964)	
Yes	107 (11.1)
No	857 (88.9)
Malformation (N=961)	
Yes	44 (4.6)
No	917 (95.4)

Caption: NB – newborn.
Note: *n corresponds to the number of valid observations for each variable; percentages were calculated based on these values.

DISCUSSION

Given the importance of adequate folic acid for maternal and child health, the present study identified a deficiency prevalence of 8.4% in pregnant women treated at a referral hospital. Although relatively low, this prevalence is clinically relevant, as it indicates that a significant group remains exposed to an avoidable risk.

The deficiency was more frequent among women without a partner, in the second trimester of pregnancy, and among those who did not use supplementation. These findings are directly related to the objective of the study, by highlighting that social, reproductive, and caregiving factors influence the nutritional status related to folic acid.

In the Brazilian context, where prenatal care is widely provided by the Unified Health System (SUS) and there is a policy of flour fortification, the results indicate that supplementation alone is not sufficient to guarantee adequate levels of folic acid. The fact that women without

partners are more likely to have a deficiency suggests a relationship with less social support, greater vulnerability, and possible difficulty in adhering to prenatal guidelines. The higher frequency of deficiency in the second trimester may reflect late initiation of monitoring or interruption of supplementation during pregnancy. On the other hand, the lack of a consistent association with maternal age and education level may be related to the care profile of the service investigated, with a structured offer of supplementation and guidance.

Compared to the literature, a study on periconceptional folic acid supplement intake and serum folic acid levels conducted with 120 mothers registered at the prenatal clinic of a tertiary referral center, with serum folic acid dosage of samples collected during the first trimester, found that 21/120 (17.5%) of pregnant women who were in their first pregnancy had serum folic acid values that indicated deficiency and possible deficiency[10].

A study conducted in rural areas of China showed that, despite free access to supplements, many pregnant women did not use folic acid adequately during the periconceptional period, mainly due to a lack of knowledge about supplementation[11]. In another study, which included 250 pregnant women, folic acid deficiency was found in 56 (22.4%) pregnant women. Of these, 21 (4.4%) used folic acid supplements[12], while in the present study, 66.3% of pregnant women reported using folic acid supplements, which may justify, at least in part, the low deficiency of this micronutrient in the pregnant women in this study, when compared to those in other studies. It should be noted that these studies took place in countries that do not adopt food fortification with folic acid and, even with supplementation available, presented a higher prevalence of deficiency than that observed here.

Studies have shown that folic acid supplementation is an important factor associated with folic acid deficiency or insufficiency[13], further emphasizing the importance of supplementation during the periconceptional period in raising folic acid concentrations for the prevention of NTDs. In this scenario, due to the low adherence to folic acid supplements, food fortification with folic acid seems to be a truly important complementary micronutrient intervention for the prevention of NTDs[14].

Regarding supplementation in Brazil, although the WHO and the Ministry of Health recommend universal folic acid supplementation for women of childbearing age who wish to become pregnant and for all pregnant women until the end of pregnancy, there are still significant challenges regarding adherence[5,9]. A recent national review found that factors such as low education, insufficient income, late initiation of prenatal care, and lack of adequate guidance from health professionals are associated with lower adherence to iron and folic acid supplementation during pregnancy[15]. These aspects may also have contributed to the deficiency levels identified in the present study.

These findings highlight significant challenges for Primary Health Care. Although supplementation is recommended in the guidelines, many women begin prenatal care late, do not receive adequate guidance, or do not have prior reproductive planning, which compromises periconceptional use, the period of greatest impact on the prevention of NTDs. Structural aspects, such as difficulty accessing services, discontinuity of care, and limitations in the training of teams regarding nutritional surveillance, contribute to these gaps. Thus, strengthening health education, reproductive planning, and active monitoring of pregnant women can more consistently reduce folic acid deficiency.

It should noted that in the present study the use of folic acid supplements was evaluated at any point during pregnancy. This analysis is relevant because, considering the pre-conception period, recommended for the prevention of NTDs, the prevalence tends to be lower. It is also worth noting that the study was conducted in a referral hospital and that most (70.1%) pregnant women began prenatal care in the first trimester, which may have contributed to the low prevalence of deficiency and the high frequency of supplementation.

A cohort study conducted in São Luís, Maranhão found that 77.3% (n=3,118) of postpartum women used folic acid during pregnancy, but only 0.37% (n=15) started supplementation before conception[16]. More recent national data revealed that less than 20% received folic acid supplementation through Primary Health Care between 2019 and 2021[17]. These findings demonstrate a significant gap between national and international recommendations, which advocate universal folic acid supplementation for pregnant women and women of

childbearing age, and the observed practice[5,9]. Even so, despite low coverage in the periconceptional period, folic acid deficiency has become less prevalent, partly due to the mandatory fortification of flours with this vitamin in Brazil[18–20].

Regarding tobacco use, national studies indicate increased consumption among women and variable prevalence during pregnancy, ranging from 4.1% to 16.5% in different regions of the country[21,22]. These results are similar to the findings of the present study, in which 13.4% of pregnant women reported having smoked at some point and 9.9% reported use during their current pregnancy. Pregnancy appears to be an opportune period for smoking cessation interventions.

A French cohort of 16,809 pregnant women evaluated factors associated with folic acid supplementation and observed lower use in the periconceptional period among younger, multiparous, single women with low education, lower income, unemployed, and smokers. Furthermore, compared to women who had never smoked, those who quit smoking before pregnancy were more likely to use the supplement, while the opposite was observed among those who smoked throughout their pregnancy[23]. These findings converge with those of the present study, in which single, widowed, and divorced pregnant women presented greater deficiency.

The low prevalence of folic acid deficiency observed in this study may be related to the sample profile, composed mainly of women over 19 years of age, married or in a stable relationship, and with higher levels of education. These characteristics suggest a possible association between higher educational attainment, marital stability, and a greater likelihood of adherence to recommended prenatal practices.

Regarding neonatal repercussions, no association was found between maternal deficiency and low birth weight, prematurity, malformations, or fetal death. A possible explanation is the low overall prevalence of deficiency observed, associated with the national policy of flour fortification and the early initiation of prenatal care, which likely reduced the power to detect differences between groups without implying a lack of clinical relevance of folic acid.

However, the literature remains divided regarding folic acid supplementation and its effects on newborns, with studies describing both associations and a lack of effect for prematurity, low birth weight, and malformations.

A recent multicenter study, which compared 1,471 women with live preterm births and 1,471 with term births, observed that approximately 40% of pregnant women with preterm births did not use folic acid at the beginning of pregnancy. The study also demonstrated a positive additive interaction between the absence of folic acid supplementation at the beginning of pregnancy and pre-eclampsia, increasing the risk of prematurity[24].

On the other hand, in a cohort published in 2023 involving 16,332 women, of whom 37.8% used folic acid in the periconceptional period, 52.9% used multivitamins containing folic acid and 9.3% did not use supplements, no association was identified between supplementation and risk of premature birth[25].

In another cohort, which included 9,231 participants and found 650 cases of low birth weight, folic acid supplementation was associated with a reduction in this outcome, and the risk decreased progressively as the duration of use increased[26].

Regarding congenital malformations, a prospective multicenter study with 17,713 women identified 273 confirmed cases (16.3 per 1,000 live births) and found a lower incidence among pregnant women who supplemented with folic acid, especially among those who started using it one to two months before conception[27]. In addition, a systematic review based on almost 1 million participants demonstrated that periconceptional and gestational folic acid supplementation is associated with a 38% to 51% reduction in the risk of NTDs (aRR between 0.49 and 0.62)[28].

In the present study, no association was found between folic acid deficiency and maternal age. Although advanced maternal age is described in the literature as a factor related to a higher risk of NTDs, the mechanisms involved are not yet fully understood[29]. In a retrospective cohort study of 48,750 births, which identified 522 cases of NTDs, a higher proportion of defects was observed among women aged 25 to 34 years, mainly anencephaly and spina bifida[30], highlighting that the relationship between maternal age and NTDs may vary according to the population context and exposure factors.

This study has some limitations. The most significant was the fact that the sample consisted of women who gave birth in a maternal and child referral hospital, most of whom began prenatal care in the first trimester. This context may have contributed to the lower frequency of folic acid deficiency observed when compared to other settings. Thus, the results should be interpreted with caution, especially for populations served in less complex services or outside the hospital environment.

Furthermore, since this is a secondary database analysis, it was not possible to include potentially relevant variables such as dietary habits, reproductive planning, initiation and regularity of supplementation use in the pre-conception period, and dosage used, which could be related to the deficiency. Therefore, the possibility of selection bias is acknowledged, as this is a referral hospital, as well as the limitation arising from the availability of variables in the database.

The study's strengths include the sample size and the use of a clinical database built by a trained team, with standardized procedures and methodological rigor.

CONCLUSION

The present study identified a low prevalence of folic acid deficiency among the pregnant women evaluated and a high frequency of supplementation, which may explain the absence of observed neonatal repercussions. Even so, the deficiency was associated with the absence of a partner, the second trimester of pregnancy, and the possible interruption of supplementation.

The results contribute to strengthening prenatal care practices, especially in nursing and public health, by reinforcing the need for routine monitoring of nutritional status and the appropriate use of folic acid. Early identification of pregnant women at higher risk allows for better targeting of care actions and can prevent adverse outcomes.

The findings also highlight the importance of health education and reproductive planning strategies during prenatal care aimed at increasing adherence to supplementation, reducing the risks of maternal and neonatal morbidity and mortality, and avoiding unnecessary costs to the health system.

Finally, the need for further studies investigating other variables related to folic acid deficiency is highlighted, contributing to the improvement of maternal and child health policies and practices.

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