

## Folic acid supplementation among pregnant women in southern Brazil: prevalence and factors associated

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**Abstract** Objective: To identify the prevalence and factors associated with the use of folic acid supplementation in pregnancy. Methods: A cross-sectional population based study, in Rio Grande, RS. In 2013, all pregnant women and had children with birth weight less than 500 grams or at least 20 weeks of gestation were included in the study. They investigated demographic characteristics, socioeconomic, reproductive life and assistance to prenatal care. We conducted multivariate analysis with Poisson regression, considering a hierarchical model and  $p < 0.05$  for the association. Results: 2,685 mothers were interviewed. Prevalence of folic acid use during pregnancy was 54.2%. Factors associated with the use of folic acid were: women with white skin color, living with a partner, higher schooling and family income, being primiparous, they planned their pregnancies, have six or more prenatal consultations and have started prenatal care in the first trimester of pregnancy. Conclusions: The low prevalence of folic acid use in this study is worrisome, especially among mothers color black skin, less educated and poorer, then with the greatest potential to have complications during pregnancy. To implement more effective campaigns, targeting, especially for women with lower socioeconomic status is necessary.

**Key words** Folic acid, Pregnancy, Prenatal, Supplementation

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## Introduction

Folic acid is a B-complex vitamin that is essential to a healthy pregnancy<sup>1</sup>. The folic acid chemical structure consists of a pteridine ring, a p-aminobenzoic acid, and a molecule of L-glutamic acid<sup>2,3</sup>. Dietary folates are mostly (90%) in the form of reduced polyglutamates bound to proteins<sup>3</sup>. Folic acid plays an important role in the synthesis of purines and thymidylate, and is thus essential for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Folic acid is key for erythropoiesis, regulation of normal development of nerve cells, prevention of neural tube defects (NTDs), and promotion of normal human growth and development<sup>3,4-6</sup>.

Folic acid plays an important role in new blood cell generation and maintenance, and red and white cell formation and maturation in the bone marrow<sup>7,8</sup>. Folic acid deficiency is associated with increased fetal NTDs and maternal megaloblastic anemia<sup>7-11</sup>. A good body of evidence shows that folic acid supplementation in early pregnancy reduces by 75% the prevalence of NTDs<sup>8,10,12</sup>.

Drawing on this evidence, the World Health Organization (WHO) and the Brazilian Ministry of Health of Brazil guidelines advocate a daily intake of 400 µg (0.4 mg) of folic acid during at least 30 days before conception through the first trimester of pregnancy for prevention of NTDs<sup>6,13</sup> and throughout pregnancy for prevention of anemia<sup>6,13</sup>. The Brazilian Ministry of Health recommendation for women with a history of NTDs is a daily intake of 5 mg of folic acid to prevent recurrence of birth defects<sup>5</sup>.

The use of supplemental folic acid during pregnancy varies according to population characteristics and stage of use. Studies that have investigated the use of folic acid during pregnancy found prevalences ranging from 72.0% in the Netherlands<sup>14</sup> and 89.2% in the United States (US)<sup>15</sup>. Other studies have assessed folic acid supplementation before conception through the first month of pregnancy. One study in France found a prevalence of 26.5%<sup>16</sup>; a population-based study in Australia found 36.0% in Victoria and 46.0% in New South Wales<sup>17</sup>; a prevalence of 67.7% was reported in a study in China<sup>18</sup>; and 30.0% in Spain<sup>19</sup>. In Brazil, a population-based study conducted with postpartum women in the southern city of Pelotas found a prevalence 32.0% of folic acid supplementation during pregnancy<sup>20</sup>. The prevalence of use of supplemental folic acid during pregnancy was 31.0% in the city of Dia-

mantina, southeastern Brazil<sup>21</sup>; and a study with labor women at Fernandes Figueira Institute (Fiocruz) in Rio de Janeiro reported that 22.4% used supplemental folic acid<sup>22</sup>.

As for factors associated with folic acid supplementation during pregnancy, some studies have suggested that younger women, less educated, of low income, multiparous, reporting attending less than seven prenatal care visits, and having an unplanned pregnancy are less likely to use supplemental folic acid<sup>1,14-21</sup>.

A small number of studies have been conducted on the prevalence and factors associated with folic acid supplementation during pregnancy, especially in nationally representative samples. While supplemental folic acid is currently recommended during pregnancy worldwide, the prevalence of use is much lower than expected and is apparently higher among well-off women.

This study aimed to assess the prevalence of folic acid supplementation during pregnancy and factors associated among all women who gave birth in the municipality of Rio Grande in 2013.

## Methods

The present study was based on data from a large study (The Perinatal Study) that has been conducted in the municipality of Rio Grande, southern Brazil, every three years since 2007. This is a population-based cross-sectional study.

Rio Grande is located in southern Brazil, has a territorial area of 2,700 km<sup>2</sup> and approximately 207,000 inhabitants, 96% of them living in urban areas according to the Brazilian Institute of Geography and Statistics (IBGE)<sup>23</sup>. Its Human Development Index (HDI) is 0.744<sup>24</sup>. The city has two hospitals providing maternity services (Santa Casa de Misericórdia of Rio Grande [SC-MRG] and Dr. Miguel Riet Correa Jr. University Hospital affiliated with Universidade Federal do Rio Grande [HU/FURG]).

The inclusion criteria included women living in urban or rural areas of the city who gave birth to children weighing 500 grams or more at birth and gestational age of at least 20 weeks of gestation. Data was collected between January 1 and December 31, 2013 at the two participating maternity hospitals.

The sample size was calculated retrospectively based on data from this same study. Based on the available sample size (n) of 2,685 postpartum women, a 54.2% outcome prevalence, a desired

95% confidence level and 3% loss rate, the study margin of error was 1.9 percentage points. To identify factors associated with folic acid supplementation, for an alpha error of 0.05, beta error of 0.20, a non-exposed/exposed ratio of 14/86, disease prevalence in the non-exposed group of 14%, and odds ratio (OR) of 1.5, the sample size estimated was of at least 2,520 postpartum women (the variable “number of prenatal care visits” required the largest sample size). It was already increased by 15% to control for potential confounders and 3% for losses. These calculations were performed using Epi Info 7.0.

The study outcome was “use of folic acid supplementation during the current pregnancy” starting at any time during pregnancy (stage of use). Independent variables included demographic characteristics—maternal age; marital status; and self-referred skin color; socioeconomic characteristics—maternal schooling (full years); household income (total income of all household members in the month prior to the study interview in quartiles); reproductive life—parity; planned pregnancy; prenatal care—number of visits; trimester of prenatal care initiation; care setting (public or private). All variables were collected through interviews with postpartum women, preferably within 24 hours after delivery, using a pre-coded standardized questionnaire.

Four female interviewers carried out all interviews. They underwent theoretical training that consisted of a discussion of the study questionnaire and instruction guide. They then participated in a pilot study held in the first half of December 2012 at the same maternity hospitals. Two interviewers were employed full-time and two worked on weekends and holidays. They rotated every month so that all interviewers worked in both maternity hospitals.

The interviewer paid daily visits to the two maternity hospitals in the city and examined hospital admission records to identify pregnant women living in Rio Grande who were admitted to the hospital. She then approached the postpartum women in the maternity ward and invited them to participate in the study. Those who agreed to participate in the study were asked to sign two copies of an informed consent form. One copy was given to the participant mother be kept by her. The questionnaire was administered and all questionnaires were reviewed and coded for data entry by the end of a working day.

Data was double entered in reverse order by different assistants using Epidata 3.1<sup>25</sup>. All data were automatically checked for consistency. In

case of inconsistencies, the reviewers checked the questionnaires and contacted the women by telephone as needed to clarify any issues. After error correction, data was transferred to Stata version 12 for analysis.

First, the population was described by calculating the prevalence of each independent variable. Then the outcome prevalence was estimated according to the variables studied. In the multivariate analysis, a three-level hierarchical model was built and variables were adjusted for same-level or next-level variables<sup>26</sup> and remained in the model if  $p < 0.20$ <sup>27</sup>. At level 1, sociodemographic variables (maternal age, marital status, skin color, maternal schooling, and household income) were included. At level 2, level 1 variables plus reproductive life variables (parity and planned pregnancy) were included. In addition, at level 3, all variables of previous levels plus prenatal care variables (number of prenatal care visits, trimester of prenatal care initiation, and care setting). We performed crude and adjusted analyses by Poisson regression with robust variance<sup>28</sup> for estimating prevalence rates and related 95% confidence intervals of 95% (95% CI). Those variables with  $p < 0.05$  in the Wald test of heterogeneity or linear trend for ordinal exposure variables were considered associated with the outcome. The measure of effect was the prevalence rate (PR).

For quality control, 7% of the sample was repeatedly interviewed using part of the questions. We calculated the kappa coefficient of agreement for 24 questions and most of them showed an agreement above 0.70.

The study protocol was reviewed and approved by the Health Research Ethics Committee (CEPAS) at Universidade Federal do Rio Grande (FURG). All participants signed an informed consent form. Confidentiality of data was ensured, participation was voluntary, and participants could withdraw from the research study at any time for no reason.

## Results

A sample of 2,685 postpartum women were interviewed, accounting for 97.0% of all women who gave birth in the municipality of Rio Grande in 2013.

Table 1 shows that a third of the postpartum women studied were 30 years of age or older; 66.2% self-referred as being white-skinned; 85.8% were living with a partner; and 44.8% had

9–11 years of schooling. Regarding their reproductive life, 47.4% were primiparous and 37.5% planned the current pregnancy. As for prenatal care, 85.8% attended six or more visits, 78.6% initiated prenatal care in the first trimester of pregnancy and just over half of them (51.6%) were provided care at a public setting. The prevalence of use of folic acid supplementation during pregnancy was 54.2% (95% CI 52.4–56.1).

Table 2 shows that the prevalence of folic acid supplementation ranged from 9.9% among those who attended one to three prenatal visits to 74.5% among those who had 12 or more years of schooling. All variables in the crude analysis remained significantly associated with the outcome after adjustment in the hierarchical model, except maternal age that was no longer associated after adjusted for other demographic and socioeconomic variables.

The adjusted prevalence rate for use of folic acid supplementation during pregnancy was higher among postpartum women self-referred as white-skinned (PR 1.20 95% CI 1.04–1.38) compared to those self-referred as black-skinned; those living with a partner (PR 1.30; 95% CI 1.14–1.49) compared to those without a partner; those who had 12 years or more of schooling (PR 2.17; 95% CI 1.69–2.81) compared to those who had 0 to 4 years of schooling; belonging to the upper income quartile (PR 1.25; 95% CI 1.11–1.40) compared to those belonging to the lower quartile; who were primiparous (PR 1.27; 95% CI 1.18–1.36) compared to those who were multiparous; those reporting planned pregnancy (PR 1.33; 95% CI 1.24–1.42) compared to those reporting unplanned pregnancy; those attending six or more prenatal care visits (PR 1.69; 95% CI 1.18–2.42) compared to those attending three visits or less; and those who initiated prenatal care in the first trimester of pregnancy (PR 1.50; 95% CI 1.31–1.72) compared to those who initiated it later (Table 2).

## Discussion

While WHO<sup>6</sup> and the Brazilian Ministry of Health<sup>5,13</sup> 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, our study found a low prevalence of folic acid supplementation (54.2%) in the municipality of Rio Grande. The response rate in our study was 97.0%, accounting for all births in 2013. With re-

**Table 1.** Main characteristics of postpartum women who gave birth in the municipality of Rio Grande, Brazil, 2013.

Variable	N	Percentage
Maternal age (years)		
13–19	464	17.3%
20–24	707	26.3%
25–29	648	24.1%
≥ 30	866	32.3%
Self-referred skin color		
Black	312	11.6%
Brown/mixed	597	22.2%
White	1,776	66.2%
Living with a partner	2,303	85.8%
Maternal schooling (years)		
0–4	162	6.0%
5–8	902	33.6%
9–11	1,201	44.8%
≥ 12	420	15.6%
Household income in quartiles		
First (lower)	680	25.3%
Second	693	25.8%
Third	641	23.9%
Fourth (upper)	671	25.0%
Number of children		
None	1,273	47.4%
One	795	29.6%
Two or more	619	23.0%
Planned pregnancy	1,008	37.5%
Number of prenatal visits		
1–3	111	4.2%
4–5	261	10.0%
6 or more	2,244	85.8%
Trimester of prenatal care initiation		
First	2,056	78.6%
Second	511	19.5%
Third	48	1.8%
Care setting		
Public	1,351	51.6%
Private	1,265	48.4%
Folic acid supplementation during pregnancy	1,458	54.2%
Total	2,685	100%

gard to factors associated with use of folic acid supplementation, after the adjusted analysis, the highest prevalences were among women self-referred as white-skinned; who were living with a partner; were more educated and better off; primiparous; who had planned their pregnancy;

**Table 2.** Prevalence of folic acid supplementation during pregnancy by category and crude and adjusted analyses. Rio Grande, Brazil, 2013 (n = 2,685).

Level	Variable	Folic acid supplementation	Prevalence rate (95% CI)	
			Crude analysis	Adjusted analysis
1	Maternal age (years)		p < 0.001**	p = 0.29**
	13–19	46.3%	1.00	1.00
	20–24	49.7%	1.07 (0.95–1.21)	0.90 (0.78–1.02)
	25–29	58.2%	1.26 (1.12–1.41)	0.97 (0.86–1.10)
	≥ 30	59.4%	1.28 (1.14–1.43)	0.97 (0.86–1.10)
	Self-referred skin color		p < 0.001*	p = 0.03*
	Black	41.7%	1.00	1.00
	Brown/mixed	50.1%	1.20 (1.03–1.40)	1.15 (0.99–1.34)
	White	57.9%	1.39 (1.21–1.59)	1.20 (1.04–1.38)
	Living with a partner		p < 0.001*	p < 0.001*
	No	38.2%	1.00	1.00
	Yes	56.9%	1.49 (1.30–1.70)	1.30 (1.14–1.49)
	Maternal schooling (years)		p < 0.001**	p < 0.001**
	0–4	29.0%	1.00	1.00
	5–8	42.2%	1.45 (1.12–1.86)	1.44 (1.12–1.86)
	9–11	59.8%	2.06 (1.61–2.63)	1.91 (1.49–2.44)
	≥ 12	74.5%	2.57 (2.01–3.29)	2.17 (1.69–2.81)
	Household income in quartiles		p < 0.001**	p = 0.001**
	First (lower)	41.5%	1.00	1.00
Second	50.1%	1.21 (1.07–1.36)	1.08 (0.97–1.22)	
Third	55.1%	1.33 (1.19–1.49)	1.11 (0.98–1.24)	
Fourth (upper)	70.8%	1.71 (1.54–1.89)	1.25 (1.11–1.40)	
2	Primiparous		p < 0.001*	p < 0.001*
	No	46.5%	1.00	1.00
	Yes	62.9%	1.35 (1.26–1.45)	1.27 (1.18–1.36)
	Planned pregnancy		p < 0.001*	p < 0.001*
	No	45.2%	1.00	1.00
	Yes	69.4%	1.54 (1.44–1.64)	1.33 (1.24–1.42)
3	Number of prenatal care visits		p < 0.001**	p < 0.001**
	1–3	9.9%	1.00	1.00
	4–5	15.7%	1.49 (1.00–2.21)	1.25 (0.85–1.85)
	6 or more	50.9%	2.78 (1.95–3.97)	1.69 (1.18–2.42)
	Trimester of prenatal care initiation		p < 0.001*	p < 0.001*
	First	62.7%	2.07 (1.82–2.36)	1.50 (1.31–1.72)
	Second or third	30.2%	1.0	1.0
	Care setting		p < 0.001*	p = 0.004*
	Public	49.4%	1.00	1.00
Private	62.5%	1.26 (1.18–1.35)	0.89 (0.82–0.96)	

Equation 1 (level 1): maternal age, skin color, living with a partner, maternal schooling, and household income; Equation 2 (level 2): equation 1 + primiparous + planned pregnancy; Equation 3 (level 3): equation 2 + number of prenatal visits + trimester of prenatal care initiation + care setting. \*Wald test of heterogeneity. \*\* Linear trend test. PR: prevalence rate.

attended six or more visits; and initiated prenatal care in the first trimester of pregnancy.

Few international population-based studies have investigated the use of folic acid supplementation through the entire pregnancy and most studies have focused on folic acid sup-

plement use during the recommended period to prevent NTDs. The prevalence found in our study (54.2%) is lower than that reported in a population-based study conducted in Rotterdam (Netherlands) (72.0%)<sup>14</sup>, and in the NHANES (US) (89.2%)<sup>15</sup>.

Previous Brazilian studies have reported prevalences lower than that found in our study. A study in the city of Pelotas (southern Brazil) with 1,450 pregnant women found a 32.8% prevalence of folic acid supplementation at any point during pregnancy in 2006<sup>20</sup>. A study in the city of Diamantina (southeastern Brazil) reported a prevalence of 31.3% of folic acid supplementation among 280 pregnant women in 2004–2005<sup>21</sup>. In Rio de Janeiro (southeastern Brazil), a study investigated 285 women with high-risk pregnancies attending a specialized hospital and found 22.4% of folic acid supplementation during pregnancy<sup>22</sup>.

As for level 1 variables, no significant association between maternal age and folic acid supplementation was found. However, the US study<sup>15</sup> and the Pelotas study<sup>20</sup>, reported an association of increasing maternal age and folic acid supplementation. Corroborating the findings of the Pelotas study<sup>20</sup>, white skin color was associated with a higher prevalence of folic acid supplementation compared to black skin color. Women who reported living with a partner were more likely to use folic acid during pregnancy, which is consistent with that reported in the US study<sup>15</sup>. Similarly to that found in the US study<sup>15</sup> and Brazilian studies<sup>20,21</sup>, maternal schooling was strongly associated with folic acid supplementation: more educated women were more likely to use supplemental folic acid. The prevalence of folic acid supplementation among women who had 12 years or more of schooling was twice as high compared to those who had 0–4 years of schooling and it evidences the impact of education on the likelihood of folic acid supplementation. Household income was associated with folic acid use, and its prevalence was higher in the upper than in lower income quartile. This finding is consistent to that reported in the Pelotas study<sup>20</sup> and the US study<sup>15</sup>.

As for level 2 variables, primiparity was associated with folic acid supplementation during pregnancy, which contrasts with the US study<sup>15</sup> that found no association between number of children and the outcome. Planned pregnancy was associated with folic acid use, which is consistent with that reported in the Pelotas study<sup>20</sup>.

With regard to level 3 variables, attending six or more prenatal visits was associated with the outcome compared to attending three visits or less. This association was also reported in other Brazilian studies<sup>20,21</sup>. We found no other studies that have assessed the association between tri-

mester of prenatal care initiation and use of supplemental folic acid. However, our study revealed that the earlier prenatal care begins, the greater the likelihood of folic acid supplementation. As to care setting, the crude analysis showed a greater prevalence of folic acid use among those who were provided care in a private setting; however, after adjusting for all levels of the hierarchical model, care in a private setting proved to be protective, i.e., women who received care in a public setting were more likely to use folic acid supplementation than those who received care in a private setting (private insurance coverage or out of the pocket payment). This finding may be explained by the fact that many low-income pregnant women whose husband/partner is employed benefited from their partner's employer-sponsored private health insurance. However, it does not fully explain the 11% protection. Further investigations are needed to better explore it in other studies.

It is worth mentioning that our study assessed folic acid supplementation at any point during pregnancy. The prevalence of folic acid use before conception to prevent NTDs is even lower as reported in many studies. We assessed folic acid use among all women who reported using folic acid at any point during their current pregnancy bearing in mind the WHO<sup>6</sup> and the Brazilian Ministry of Health<sup>13</sup> recommendation of folic acid supplementation from before conception to the end of pregnancy. Of 54.2% of the women reporting folic acid supplementation, only 8.3% used it before conception as well. This proportion is greater than that found in the Pelotas study<sup>20</sup> that only 4.3% of women used supplemental folic acid before conception. These results show very low prevalences of folic acid supplementation in Brazil. Since 2005<sup>5,13</sup> the Brazilian Ministry of Health has recommended the use of supplemental folic acid before pregnancy for the prevention of birth defects and these supplements are available at no cost in health center pharmacies nationwide.

The main strength of this study lies on the use of a representative sample of the population of postpartum women in the city of Rio Grande in 2013. However, because this is a cross-sectional study, while interpreting the results regarding factors associated with folic acid supplementation it should be taken into account that information was collected in a single source approach (postpartum women) and represent only the period of data collection. Another limitation of the study is that recall is prone to errors as information was collected from the mothers after de-

livery. Nevertheless, it does not seem to discredit our results because all interviews were conducted following the same procedure and timeframe similarly to that described in other studies.

It is important to note that our study did not measure the dose of folic acid used by pregnant women. The recommended dose is 400 µg (0.4 mg) a day<sup>6,13</sup> and it must not be exceeded. A review study by Reynolds pointed to evidence of neurological and hematological effects after long-term exposure to folic acid at doses of 0.5 to 1 mg among pregnant women with vitamin B12 deficiency. It calls for reexamining the safety of the recommended dose of folic acid during pregnancy and the addition of vitamin B12<sup>29</sup>.

Folic acid supplementation coverage found in our study was quite lower than recommended during pregnancy especially among the most susceptible population as the lowest prevalences

of folic acid use were seen among black-skinned women, of lower education and income, and with potentially high risk for complications during pregnancy.

The finding that nearly half of the women studied (45.8%) did not use folic acid supplementation in the current pregnancy points to an urgent need for appropriate actions to increase folic acid supplementation before and during pregnancy. Health providers, particularly in primary care settings, should focus their attention on low-income women because they show the lowest prevalence of folic acid supplementation during pregnancy. In addition, public policies to reduce inequalities promoting health education and raising awareness of the benefits of folic acid supplementation before conception and throughout pregnancy to prevent pregnancy complications are necessary.

## Collaborations

AO Linhares was involved in the fieldwork, helped in the data entry, conducted the literature review and data analysis, and prepared the manuscript. JA Cesar designed the original research project, supervised the collection and entry of data, helped in the data analysis, critically reviewed the entire manuscript, and approved its final version.

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