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ORIGINAL CONTRIBUTION

Effect of Vitamin A status during pregnancy on maternal anemia and newborn birth weight: results from a cohort study in the Western Brazilian Amazon

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Abstract

Purpose Inadequate Vitamin A (VA) status during pregnancy has been associated with maternal anemia and suboptimal newborn birth weight (BW). We assessed the effect of gestational serum retinol and β-carotene (µmol/L), in different moments during pregnancy, on maternal hemoglobin (Hb, g/L) and anemia (Hb < 110.0 g/L) at delivery, and newborn BW (kg).

Methods In a prospective cohort study in Cruzeiro do Sul, Western Brazilian Amazon, biomarkers of the VA status were assessed in the second and third trimesters in pregnancy. Serum retinol and β-carotene were analyzed considering their effects in each and in both assessments (combined VA status), and the difference of serum values between assessments. Multiple linear and Poisson regression models were used with a hierarchical selection of covariates.

Results A total of 488 mother–newborn pairs were surveyed. Combined VA deficiency status increased the risk for maternal anemia (adjusted prevalence ratio: 1.39; 95% CI 1.05–1.84), and was negatively associated with maternal Hb (β − 3.30 g/L; 95% CI − 6.4, − 0.20) and newborn BW (β − 0.10 kg; 95% CI − 0.20, − 0.00), adjusted for socioeconomic, environmental, obstetric, and antenatal characteristics, and nutritional indicators. However, the association for newborn BW was no longer significant after further adjustment for plasma ferritin. There were no significant associations between serum β-carotene and the outcomes studied.

Conclusion Poor serum retinol status throughout pregnancy was associated with maternal anemia at delivery in Amazonian women. The current World Health Organization protocols for supplementation during antenatal care should consider VA status for planning recommendations in different scenarios.

Keywords Vitamin A · Pregnancy · Hemoglobin · Anemia · Birth weight · Amazon

Introduction

Vitamin A (VA) status during pregnancy, a unique period of the life cycle when cell differentiation occurs rapidly, is essential for fetal growth and maternal metabolism [1–3]. Retinol may act in early embryo development, differentiation, and organ maturation of a countless number of cells and tissues as pregnancy progresses [4, 5]; β-carotene has an antioxidant role in humans, being associated with the reduction of oxidative stress and hence with the lower risk of restricted fetal growth [6]. Nonetheless, vitamin A deficiency (serum retinol < 0.7 µmol/L, VAD) is still one of the most prevalent nutritional deficiencies worldwide, affecting mostly pregnant and lactating women, and pre-school children [3]. According to the latest WHO estimates for the period of 1995–2005, the prevalence of VAD in pregnancy in low- and middle-income

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countries (LMIC) was 15.3%, with more than 19 million women affected [3].

Several studies investigated VA supplementation during pregnancy and maternal and newborn outcomes, such as maternal anemia and birth weight (BW) [7–9]. Three meta-analysis found positive effects for oral VA supplementation during pregnancy on maternal anemia using safe doses for pregnant women in LMIC (< 10,000 IU/d) [10–12]. Thorne-Lyman and Fawzi [10] showed a reduction in the risk of anemia of 19% (95% CI 0.69, 0.94). McCauley et al. [11] and Cunha et al. [12] found similar results, with relative risks of 0.64 (95% CI 0.43, 0.94) and 0.78 (95% CI 0.63, 0.96), respectively. However, the quality of the evidence was considered moderate and the heterogeneity was significant among the studies [10–12].

The evidence for possible associations between serum retinol or β-carotene in pregnancy and newborn BW is still unclear. In high-income countries (e.g., Canada and United Kingdom), where gestational serum retinol was found to be higher when compared with LMIC, serum retinol concentrations during pregnancy were inversely associated with BW, whereas a positive effect of serum β-carotene was found [6, 9, 13]. In Southern Ethiopia, a cohort study found that VAD was not associated with low BW (LBW) (RR 1.27; 95% CI 0.86, 1.87) [14]. Two meta-analysis of randomized trials in LMIC found contradictory effects for oral gestational VA supplementation on LBW [10, 11].

Anemia is the most prevalent nutritional deficiency worldwide, affecting about 41.8% of all pregnancies [8]. Observational and meta-analysis studies to date have shown benefits of higher serum retinol concentration during pregnancy on maternal anemia, and unclear effects for newborn BW. Thus, as maternal VA status remains a relevant public health concern in developing countries, further assessments of possible effects of serum retinol and β-carotene during pregnancy are important for defining future strategies for antenatal care and advancing the current scientific knowledge [15].

In the present study, we investigated the relationship between gestational biomarkers of VA status (serum retinol and β-carotene) with maternal anemia and newborn BW in a prospective cohort study in the Western Brazilian Amazon. We hypothesized that optimal status of these VA biomarkers during pregnancy could modify the risk for maternal anemia at delivery and positively affect newborn BW. To the best of our knowledge, no previous studies have addressed the potential relationship between VA status during pregnancy and these outcomes in an Amazonian population.

Subjects and methods

Study design and setting

Prospective cohort study in Cruzeiro do Sul, Acre State, Western Brazilian Amazon, named MINA-Brazil (Maternal and Child Health and Nutrition in Acre, Brazil). Cruzeiro do Sul is the second largest city in Acre State, with an estimated population of 82,000 inhabitants in 2017 [16]. Its distance from Acre's capital city, Rio Branco, is nearly 640 km. The 2010 municipal-level Human Development Index for Cruzeiro do Sul was 0.664 (medium). Based on the 2010 Demographic Census, only 12.7% of the households had access to proper sanitation in Cruzeiro do Sul [16, 17]. Further, the municipality is located in the main malaria endemic hotspot in Brazil, the Juruá River Valley [18, 19].

Pregnant women up to 20 gestational weeks as measured by the last menstrual period (LMP), living in the urban area of the municipality, attending Primary Health Care Units for antenatal care ($n = 13$), and intended to give birth at the only maternity hospital in Cruzeiro do Sul were considered eligible to participate in this study. The recruitment of pregnant women took place from February 2015 to January 2016 on a weekly basis. Only singleton deliveries were included in this present analysis.

All potential participants had their contact information recorded in a standardized form by the research team. Phone calls were performed to explain the research protocol to the woman or caregiver (in the case of teenage pregnancy), and to invite for participation in the MINA-Brazil study. Upon acceptance, a home-visit was scheduled to obtain written consent and to collect initial socioeconomic and health data. Following the interview, a first assessment was scheduled between 16 and 20 weeks of pregnancy, to collect clinical data, blood samples, and additional health and behavioral information, as well as to perform ultrasound examinations for confirmation of gestational age (GA). The ultrasound examination was performed by trained physicians using a portable SonoSite TITAN® (SonoSite, Inc., Bothell, WA, USA). All images were reviewed by an expert obstetrician in São Paulo who was not involved with the field work. The first assessment took place between March 2015 and March 2016 and was scheduled based on the LMP. A second assessment was held from May 2015 to May 2016, at about 28 weeks of pregnancy, based on the best estimate of GA, as described elsewhere [18].

Lastly, data on labour and newborn health were collected at the only maternity ward in Cruzeiro do Sul, where 96% of birth assistance occurs [18].

Data collection and laboratory procedures

During the socioeconomic and health interview, data were collected and categorized as the following levels of determination: (a) socio-demographic: maternal age (≥ 20 or < 20 years), maternal education (> 9 or ≤ 9 years), skin color (white or non-white), head of the family (pregnant woman or other), living with a partner (yes or no), beneficiary of the *Bolsa Família* conditional cash transfer program (yes or no), maternal occupation (unpaid job or paid job), ownership of varied assets; (b) environmental: water supply (general water distribution or water well/natural source—such as river or rain), sanitation facility (septic tank or open air/river), number of people living in the household (1–2, 3, 4, or ≥ 5), type of household (masonry or wood/mix [masonry + wood]), number of rooms in the household (< 3, 4, 5, or ≥ 6); (c) clinical and obstetric history: menarche age (< 14 or ≥ 14 years), previous fetal losses (e.g., abortion and/or stillbirth—none, 1, or ≥ 2), number of live births (none, 1–2, or ≥ 3).

A wealth index was constructed as a proxy of the socioeconomic status of the participant's family based on the ownership of assets by the household. We applied principal component analysis [20] and used the first component (which explained 18.9% of the variation between the households) to generate the index. The quintile distribution of the index was included in the analysis.

During both assessments we registered maternal anthropometry (pre-pregnancy weight and height), smoking during pregnancy, biochemical measurements (serum retinol, µmol/L; β-carotene, µmol/L; ferritin, µg/L; C-reactive protein—CRP, mg/L; and hemoglobin concentrations—Hb, g/L), and conducted the ultrasound exam. Maternal height was measured to the nearest 0.1 cm, and the pre-pregnancy BMI (kg/m^2) was calculated following WHO recommendations [21, 22]. As the reporting of smoking was very low in each assessment (< 4%), we considered a dummy variable to indicate smoking either in one or both assessments. Gestational malaria episodes were retrospectively obtained from the Malaria Epidemiological Surveillance and Information System (SIVEP) database from the Ministry of Health of Brazil (http://200.214.130.44/sivep_malaria/).

At delivery, the following information was collected: occurrence of gestational urinary tract infection (yes or no), gestational supplementation (none, iron-folic acid, or multiple micronutrients with VA), number of antenatal care appointments (< 6, 6–8, or ≥ 9), type of delivery (vaginal or cesarean section), preterm birth (deliveries < 37 gestational weeks, yes or no), pre-birth maternal weight, newborn sex and BW. The total gestational weight gain was calculated by subtracting the pre-birth gestational weight from the pre-pregnancy weight, then further categorized by the adequacy of the gestational weight gain according to the pre-pregnancy BMI as insufficient, adequate, or excessive, considering the Institute of Medicine protocol [23]. The newborn BW was measured to the nearest 0.005 kg using a Toledo® *Júnior* portable scale (São Bernardo do Campo, Brazil) with a capacity of 15 kg and registered from hospital records. All maternity staff involved in newborn care received training on BW measurement. Calculations for newborn BW z-score were performed with Intergrowth 21st Project application (https://intergrowth21.tghn.org/intergrowth-21st-applications). All data collection were performed by trained researchers using a personal digital assistant and tablets programmed with CSPro software (https://www.census.gov/programs-surveys/international-programs.html) for data-entry.

For pregnant women, around 10 mL of fasting (8 h) venous blood samples were collected in the morning of each scheduled assessment. The serum samples were collected in a dry test tube, protected from light and centrifuged within 2 h of collection. Serum was frozen at − 20 °C before it was sent on dry ice to the Laboratory of Human Nutrition, School of Public Health, University of São Paulo, and maintained at − 70 °C until it was analyzed (within 6 month of the blood being drawn). Serum concentrations of retinol, and β-carotene were measured using HPLC methods (HP-1100 HPLC system, Hewlett Packard, Palo Alto, California, USA) [24], with intra- and inter-assay CVs < 7%. Gestational Hb was determined at the time of blood collection by a portable hemoglobinometer from Hemocue® (Hb301; Angelholm, Sweden). Gestational anemia was defined as Hb < 110.0 g/L in each assessment [8]; subsequently, one categorical variable was created indicating no anemia in both assessments, anemia at least in one assessment, or anemia in both assessments. Plasma ferritin concentrations were measured by enzyme immunoassays (Ramco, Houston, TX) and the cutoff adopted for iron deficiency was < 15 µg/L [25]. CRP was measured by an IMMAGE Immunochemistry System (Beckman Coulter, Brea, CA, USA), and concentrations ≥ 5 mg/L were adopted as acute inflammation [26]. Plasma ferritin and CRP concentrations were only available for the second assessment. At delivery, venous blood samples were collected, and maternal Hb was determined by an automated cell counter (Labtest SDH-20, Lagoa Santa, Brazil).

Outcomes and exposures of interest, and data analysis

Maternal outcomes were Hb and anemia (Hb < 1100 g/L) at delivery [25], and the newborn outcomes were the BW (kg) and the BW z-score, according to Intergrowth 21st Project [27].

As the main exposures, we considered the serum retinol and β-carotene measured in the two assessments. We used three continuous variables for VA biomarkers status: (a) the

concentrations in the first assessment, (b) the concentrations in the second assessment, and (c) the difference in concentrations between the assessments, to capture if retinol and β-carotene concentrations improved (positive values), did not change (null values) or decreased (negative values).

We followed WHO recommendations [3] for classification of serum retinol concentrations in each assessment (VAD, < 0.7 µmol/L; VA insufficiency, 0.7 −< 1.05 µmol/L; VA sufficiency, ≥ 1.05 µmol/L). We further explored the VA status creating two variables deeming the occurrence of VAD and VA insufficiency using data from the two follow-up assessments, regardless if they occurred in any assessment or both: combined vitamin A status—deficiency (yes or no during pregnancy) and combined vitamin A status—insufficiency (yes or no during pregnancy). We also explored the variation of serum retinol and β-carotene concentrations between assessments as the difference between assessments (remained/improved or lowered), and as tertiles of the difference distribution.

The sample size calculation was based on detecting changes in the maternal Hb and newborn BW in at least 10% of variation. For a power of 95% with a two-tailed level of significance of 5%, at least 120 participants were needed. As anemia at delivery was a common event in this population, any assumption of sample size based on the method described would include a sufficient sample size to this outcome.

To visualize the relationship between exposures and continuous outcomes we used scatter-plots; for categorical outcomes we used one-way ANOVA and χ^2 tests. The Shapiro–Wilk test, scatter-plots, and comparisons between mean and median values were used to assess the normality of continuous variables. We performed *t* test, test for proportions, Kruskal–Wallis test and Wilcoxon signed-rank test for comparisons of gestational characteristics between assessments and maternal age stratified by adolescent and adult pregnant women. Also, we explored whether the supplementation during pregnancy could impact on maternal anemia, iron deficiency, and serum retinol in the assessments.

Different multiple regression models were tested considering the influence of relevant covariates in each outcome. For maternal Hb (linear regression) and anemia at delivery (Poisson regression) [28], we ran model 1 (covariates were selected following hierarchical levels of determination) and model 2 (further adjustment for gestational anemia). For newborn BW and BW *z*-score (linear regression), as the GA at delivery and gestational iron deficiency can affect the newborn BW [8, 27, 29], two different models were tested: model 1 (controlled for newborn sex and gestational age at delivery, and adjusted for covariates) and model 2 (further adjustment for plasma ferritin concentrations). Control for GA at delivery was not performed to BW *z*-score [27]. First, we ran unadjusted models, which were then adjusted for covariates with a hierarchical selection of variables. Based on a theoretical model of potential determinants of maternal anemia [25] and newborn BW [2], we considered the following hierarchical levels of determination: (a) socio-demographic; (b) environmental; (c) clinical and obstetric history; and (d) antenatal care and nutritional indicators (pre-pregnancy BMI, smoking during pregnancy, gestational urinary tract infection, number of antenatal care appointments, gestational supplementation, adequacy of total gestational weight gain, gestational biochemical indicators [anemia and ferritin], GA at delivery, type of delivery, preterm birth, gestational malaria). The crude analysis for each covariate was performed retaining those associated with the outcome at $P \leq 0.20$. Afterwards, at each level of determination, covariates associated with the outcomes at $P < 0.10$ remained in the subsequent analysis until the most proximal level. We also deemed the inclusion of covariates relevant in the literature in the multiple models. Additionally, stratified analyses for the effect of the exposures on the outcomes by maternal age were performed.

The effect of each biomarker of VA status on each outcome was considered significant when $P < 0.05$. Missing data were included in the multiple models by creating missing-value categories. The fit of the model was ascertained by an examination of residuals, which did not show any potential harmful effect. Collinearity was examined by the correlation matrix. All analyses were done in Stata 14 (StataCorp, College Station, Texas, USA).

Results

A total of 860 pregnant women were recruited for the MINA-Brazil study; 699 were eligible (81.3%), and 587 participants (68.2%) were enrolled in the study. Among the enrolled, 528 participants (75.5% of the eligible participants) completed the first assessment. Further, 467 participants (66.8% of the eligible participants) completed the second follow-up assessment. We had available data on VA biomarkers for 509 participants in the first assessment, and for 459 in the second assessment. The final sample surveyed in the assessments, according the outcomes was: maternal outcomes − 467 in the first assessment, 425 in the second assessment, and 411 in the combined assessment analysis; newborn outcomes − 488 in the first assessment, 447 in the second assessment, and 431 in the combined assessments analysis (Fig. 1). During follow-up of enrolled participants there was loss of 20.4% of participants. We did not observe significant differences between the participants surveyed and those lost to follow-up, respectively, to maternal age (24.7 ± 6.4 years vs. 24.4 ± 6.5 years), years of former schooling (10.4 ± 2.8 years vs. 9.8 ± 3.4 years), gestational age at delivery (38.9 ± 1.6 weeks vs. 38.7 ± 1.5 weeks), newborn BW (3.2 ± 0.5 kg

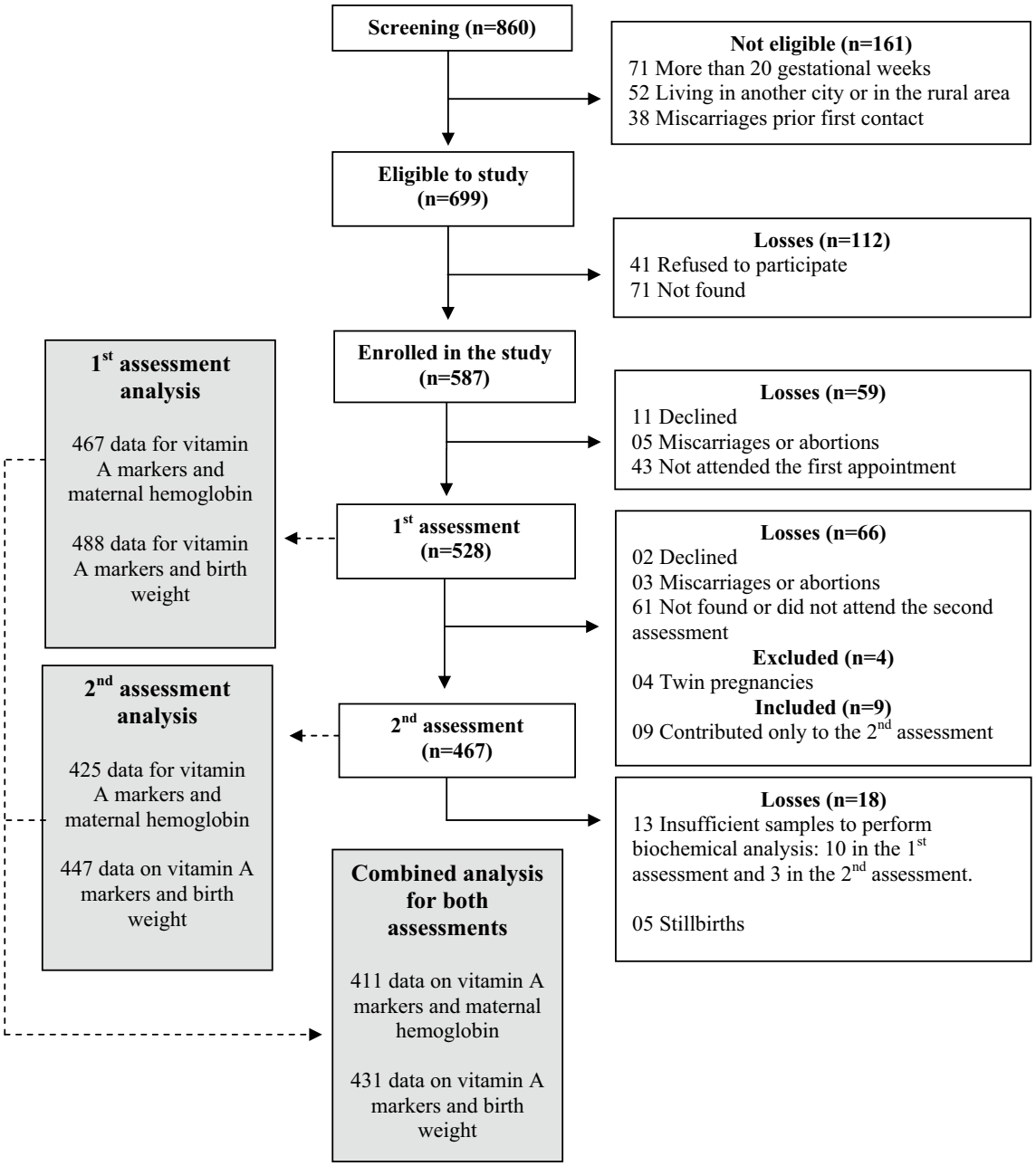

Fig. 1 Flow-diagram of cohort recruitment and outcome assessments

vs. 3.2 ± 0.5 kg), and maternal Hb (108.8 ± 18.7 g/L vs. 112.8 ± 13.3 g/L) ($P > 0.06$).

The characteristics of the participants regarding socio-demographic, environmental, clinical and obstetric history, antenatal care, and biochemical indicators are presented in Tables 1 and 2. We observed that 27.4% of participants were teenagers, and less than 70% had either proper access to water supply or to sanitation facilities (Table 1). The average pre-pregnancy BMI was 23.4 ± 4.3 kg/m^2 ($n = 527$); 60.3% of participants used only iron-folic acid supplements, while 34.7% used multiple micronutrients with VA ($n = 527$). Overall, 74.6% of women did not present with anemia in any assessment, and 18.2% presented anemia in one of the two assessments ($n = 452$). Frequencies of iron deficiency and acute inflammation were 42.4% and 0.2% ($n = 464$), respectively. The median of the difference of serum VA markers between the two assessments was 0.20 µmol/L (− 0.80 to 1.10) for retinol and 0.04 µmol/L (− 0.26 to 0.38) for β-carotene ($n = 443$). Roughly, 17% and 43% ($n = 443$) of participants experienced VAD and VA insufficiency in at least one or both assessments, respectively (data not shown in Tables). The

Table 1 Socio-demographic, environmental, and clinic and obstetric characteristics of pregnant women from the MINA-Brazil cohort study

Variables	*n*	Values
Maternal age, y[a]	583	24.69 ± 6.39
Maternal skin color[b]	583	
White		14.2
Non-white		85.8
Maternal education[b]	583	
≤ 9 years		32.4
> 9 years		67.6
Head of woman's family[b]	583	
Pregnant woman		13.7
Others		86.3
Living with a partner, yes[b]	583	77.4
Maternal occupation[b]	583	
Not paid job		56.8
Paid job		43.2
Bolsa Família cash transfer program, yes[b]	583	39.5
Water supply[b]	583	
General water distribution		63.0
Water well/ natural source		37.1
Sanitation facility[b]	579	
Septic tank		67.4
Open air/ river		32.7
Number of people living in the household[a]	583	4.11 ± 2.11
Type of household[b]	583	
Masonry		25.4
Wood/mix (masonry + wood)		74.6
Number of rooms in the household	583	4.54 ± 1.78
Menarche age, y[a]	583	13.54 ± 5.22
Previous fetal losses[b,c]	324	
None		72.8
1		21.6
2 or more		5.6
Number of live births[b]	583	
None		48.5
1–2		38.7
3 or more		12.7
Maternal height, cm[a]	528	157.12 ± 5.89

Totals differ due to missing values

[a]Mean ± SD

[b]Percentage

[c]Only for those who had been pregnant previously

Online Resource Table 1 presents the differences on VA markers and on the outcomes deemed in this study by maternal age groups. Median serum retinol did not change among adolescent pregnant women between assessments. The occurrence of VAD at the first assessment and combined, maternal hemoglobin and anemia, and newborn BW and LBW were significantly lower among adult participants than in their younger counterparts. Supplementation during pregnancy was not associated with maternal anemia ($P = 0.08$), iron deficiency ($P = 0.78$), as well as with median serum retinol in both assessments (1st assessment—$P = 0.83$; 2nd assessment—$P = 0.41$).

In the crude analyses, VAD in the first assessment, as well as the combined VAD and the combined VA insufficiency, were negatively associated with Hb at delivery. VAD in the first assessment, combined VAD, and combined VA insufficiency increased the risk for maternal anemia at delivery; VAD in the second assessment was not associated with maternal anemia. Variations of serum retinol and β-carotene concentrations measured as the difference between assessments or tertiles of the differences were not associated with the maternal and newborn outcomes. Neither of these exposures was associated with newborn BW outcomes (Online Resource 2).

For maternal anemia at delivery, VAD in the first assessment, combined VAD, and combined VA insufficiency were associated with the risk for anemia in model 1. After further adjustment for gestational anemia (model 2), only combined VAD remained associated with a higher risk of maternal anemia at delivery (adjusted prevalence ratio—aPR: 1.39; 95% CI 1.05–1.84) (Table 3).

Continuous exposures (serum retinol and β-carotene) were not significantly associated with maternal Hb at delivery. In contrast, combined VAD was negatively associated with maternal Hb at delivery in both models. Combined VA insufficiency in model 1 was negatively associated with maternal Hb at delivery, yet in model 2 this association was no longer significant (Online Resource 3).

There was a negative association between combined VAD and newborn BW. After further adjustment for plasma ferritin (model 2), the association was smoothed, and no longer significant (Table 4). There was no association in the adjusted models for newborn BW *z*-score (Online Resource 4).

When stratified analysis by maternal age was performed, the VA status during pregnancy was not associated with the increased risk of anemia at delivery among adolescent pregnant women (Online Resource 5). Conversely, combined VA deficiency and insufficiency were negatively associated with maternal hemoglobin at delivery for both adolescents and adult participants (Online Resource 6). In the same direction as maternal anemia, VA status during pregnancy only affected the newborn BW and the BW z-scores in adult pregnant women (Online Resource 7). Combined VA deficiency was negatively associated with the BW z-score in 0.3 SD only among adults (Online Resource 8).

Table 2 Antenatal care characteristics and nutritional indicators of pregnant women and their newborns from the MINA-Brazil cohort study

Characteristics	First gestational assessment		Second gestational assessment		*P* value	At delivery	
	n		*n*			*n*	
Smoking during pregnancy, yes[a]	519	3.8	462	3.4	0.723	–	–
Gestational urinary tract infection, yes[a]	–	–	–	–	–	523	64.8
Number of antenatal care appointments[b]	–	–	–	–	–	523	7.7 ± 2.3
Adequacy of gestational weight gain[a,c]	–	–	–	–	–	462	
Insufficient	–	–	–	–	–		29.9
Adequate	–	–	–	–	–		29.4
Excessive	–	–	–	–	–		40.7
Gestational age, weeks[b]	517	20.03 ± 2.91	462	27.75 ± 1.61	< 0.001	539	39.30 ± 1.88
Type of delivery, cesarean section[a]	–	–	–	–	–	541	45.4
Preterm birth (< 37 weeks)[a]	–	–	–	–	–	539	8.4
Gestational malaria, yes[a]	–	–	–	–	–	553	6.3
Retinol, µmol/L[d]	509	1.77 (1.00–2.60)	459	1.90 (1.20–2.70)	0.294	–	–
β-carotene, µmol/L[d]	509	0.45 (0.25–0.78)	459	0.52 (0.27–0.87)	0.932	–	–
Vitamin A deficiency (< 0.7 µmol/L)[a]	509	10.8	459	6.5	< 0.001	–	–
Vitamin A insufficiency (< 1.05 µmol/L)[a]	509	27.1	459	20.4	< 0.001	–	–
Hemoglobin, g/L[b]	506	121.40 ± 1.26	461	118.55 ± 0.96	< 0.001	521	112.45 ± 1.39
Maternal anemia (hemoglobin < 110.0 g/L)[a]	506	15.4	469	17.3	0.203	521	39.3
Ferritin, µg/L[d]	–	–	464	17 (10.50–27.00)	–	–	–
C-reactive protein, mg/L[d]	–	–	464	0.36 (0.19–0.63)	–	–	–
Newborn birth weight, kg[b]	–	–	–	–	–	539	3.24 ± 0.53
Low birth weight (< 2.5 kg)[a]	–	–	–	–	–	539	8.1
Newborn birth weight, z-score[b,e]	–	–	–	–	–	539	0.05 ± 0.98

Totals differ due to missing values

[a]Percentage

[b]Mean ± SD

[c]According to the Institute of Medicine, 2013 [21]

[d]Median ($IQR_{25–75}$)

[e]According to the Intergrowth 21st Project [25]

[f]Difference in biochemical indicators between assessments (Second assessment − first assessment)

[g]Deficiency or insufficiency during pregnancy combined: in at least one or both assessments

Discussion

In this prospective cohort study in the Western Brazilian Amazon, we showed that serum retinol during pregnancy was associated with maternal anemia and Hb, as well as newborn BW. The occurrence of VAD during pregnancy was associated with maternal anemia at delivery, with an adjusted prevalence ratio of 39%. In a condition without gestational anemia, VAD and/or VA insufficiency in different moments during pregnancy were also associated with maternal anemia at delivery. A deleterious effect of combined VAD was also seen for maternal Hb at delivery. We saw a negative effect for BW of babies born to women who presented combined VAD, yet after further adjustment for iron deficiency status the effect was smoothed. Finally, stratified analysis by maternal age showed that VA status during pregnancy was associated with maternal hemoglobin at delivery only among adolescent pregnant women, while for adult participants significant association was found between combined VAD and decreased values of the BW z-score. It must be highlighted that these results were observed after controlling for a set of confounders [2, 25].

Our hypothesis was only confirmed for retinol concentrations in pregnancy, as we did not observe any effect for *β*-carotene in this population. It is likely that we have not seen any effect for serum *β*-carotene because it is a less active and effective source of VA when compared with serum retinol [5].

Previous meta-analyses of randomized controlled trials have shown positive effects for VA supplementation during pregnancy in reducing the risk of maternal anemia [10–12]. Such evidences reinforce our results that poor VA status

Table 3 Effect of gestational vitamin A status on the risk of maternal anemia at delivery in the MINA-Brazil cohort study

	Maternal anemia at delivery ($n=467$)[a]					
	Crude		Model 1[d]		Model 2[e]	
	PR[f] (95% CI)	*P*	aPR[g] (95% CI)	*P*	aPR[g] (95% CI)	*P*
Vitamin A status at first assessment[b]		0.011[h]		0.033[h]		0.289[h]
≥ 1.05 µmol/L	Reference		Reference		Reference	
0.7–1.05 µmol/L	1.06 (0.76; 1.47)		1.03 (0.74; 1.42)		0.86 (0.62; 1.19)	
< 0.7 µmol/L	1.53 (1.15; 2.05)		1.50 (1.08; 2.09)		1.36 (0.96; 1.93)	
Vitamin A status at second assessment[b]		0.099[h]		0.079[h]		0.081[h]
≥ 1.05 µmol/L	Reference		Reference		Reference	
0.7–1.05 µmol/L	1.09 (0.78; 1.54)		1.09 (0.78; 1.52)		1.09 (0.78; 1.52)	
< 0.7 µmol/L	1.42 (0.96; 2.10)		1.45 (0.99; 2.19)		1.43 (0.99; 2.06)	
Vitamin A status combined—deficiency[c]		0.003		0.007**		0.019*
No deficiency during pregnancy	Reference		Reference		Reference	
Deficient during pregnancy	1.49 (1.14; 1.96)		1.48 (1.11; 1.97)		1.39 (1.05; 1.84)	
Vitamin A status combined—insufficiency[c]		0.027		0.019*		0.183
No insufficiency during pregnancy	Reference		Reference		Reference	
Insufficiency during pregnancy	1.32 (1.03; 1.70)		1.34 (1.04; 1.71)		1.18 (0.92; 1.51)	

*$P<0.05$; **$P<0.01$

[a]Hemoglobin < 110.0 g/L

[b]First assessment: between 16 and 20 weeks of pregnancy/second assessment: ~ 28 weeks of pregnancy

[c]For '*deficient during pregnancy*' deficiency (retinol < 0.7 µmol/L) in at least one assessment or both was considered/for '*insufficient during pregnancy*' insufficiency (retinol < 1.05 µmol/L) in at least one assessment or both was considered

[d]Model 1: iron deficiency second assessment (plasma ferritin < 15 µg/L), gestational malaria (no or yes), gestational supplementation (no supplementation, acid folic + iron, multiple micronutrients with vitamin A), number of antenatal care appointments (< 6, 6–8, or ≥ 9), pre-pregnancy body mass index (underweight, normal weight, overweight, or obesity), gestational age at delivery (weeks), number of live births (none, 1–2, or ≥ 3), number of people living in the household (1–2, 3, 4, or ≥ 5), wealth index (quintiles), *Bolsa Família* cash transfer program receipt (no or yes), maternal age (< 20 or ≥ 20 years)

[e]Model 2: Model 1 with further adjustment for gestational anemia (no anemia during pregnancy, anemia at least in one assessment, or anemia in both assessments)

[f]Prevalence ratio

[g]Adjusted prevalence ratio

[h]*P* for trend

during pregnancy is harmful to pregnant women in relation to the occurrence of anemia, as well as decreasing maternal Hb at delivery, as a negative β-coefficient of 3.34 was found for those pregnant women who experienced VAD in at least one or both assessments.

The mechanisms by which VA affects anemia and Hb concentrations remain unclear, although some hypotheses can be outlined: (1) VA plays a role in iron metabolism, mobilizing the mineral from their hepatic stores; (2) the role of VA on erythropoiesis; (3) VA enhances iron absorption in the gut; and (4) VA decreases the inflammatory status, hence also decreasing the risk of anemia [10, 25, 30, 31]. Anemia is a condition affecting mainly pregnant women and children worldwide, and it is associated with poor birth outcomes (including LBW and preterm births), as well as maternal mortality [25]. Roughly, about 50% of anemia cases are caused by iron deficiency [25], and strategies to reduce its burden are recommended, for example iron-folic acid supplementation during antenatal care [8]. However, it seems important to invest in alternatives to boost other strategies that are already in practice. In this sense, our results, in consonance with meta-analyses conducted in LMIC [10–12], strengthen the evidence that decreasing VAD in pregnancy consequently improves maternal Hb as well as reduces the prevalence of anemia and its associated harmful effects during pregnancy and at delivery [25].

Maternal outcomes deemed in our study were not associated with serum β-carotene in pregnancy. Although the β-carotene is a powerful antioxidant [6], there is a lack of evidence in pursuing a potential association between this micronutrient with anemia or Hb during pregnancy.

Meta-analyses and observational studies have failed to show associations between VA biomarkers and interventions during pregnancy on the decrease of risk of LBW in

Table 4 Effect of gestational Vitamin A status on newborn birth weight in the MINA-Brazil cohort study

	Newborn birth weight ($n=488$)[a]			
	Model 1[f]		Model 2[g]	
	β (95% CI)	R^2-adj	β (95% CI)	R^2-adj
Retinol at first assessment[b,c]	0.01 (− 0.02; 0.04)	0.5164	0.00 (− 0.02; 0.04)	0.5212
β-Carotene at first assessment[b,c]	− 0.05 (− 0.11; 0.01)	0.5189	− 0.04 (− 0.11; 0.01)	0.5239
Retinol at second assessment[b,c]	0.02 (− 0.00; 0.05)	0.5206	0.02 (− 0.01; 0.05)	0.5244
β-Carotene at second assessment[b,c]	− 0.03 (− 0.10; 0.03)	0.5192	− 0.03 (− 0.10; 0.02)	0.5243
Δ Retinol[b,d]	0.00 (− 0.01; 0.03)	0.5217	0.00 (− 0.01; 0.03)	0.5231
Δ β-carotene[b,d]	0.00 (− 0.04; 0.06)	0.5212	0.00 (− 0.04; 0.06)	0.5228
Vitamin A status combined—deficiency[e]		0.5259		0.5271
No deficiency during pregnancy	Reference		Reference	
Deficient during pregnancy	− 0.10 (− 0.20; − 0.00)*		− 0.09 (− 0.20; 0.00)	
Vitamin A status combined—insufficiency[e]		0.5211		0.5228
No insufficiency during pregnancy	Reference		Reference	
Insufficient during pregnancy	− 0.00 (− 0.08; 0.06)		− 0.01 (− 0.09; 0.06)	

*$P<0.05$

[a]Birth weight in kg

[b]µmol/L

[c]First assessment: between 16 and 20 weeks of pregnancy/second assessment: ~28 weeks of pregnancy

[d]Difference in biochemical indicators between assessments (Second assessment – first assessment)

[e]For '*deficient during pregnancy*' deficiency in at least one assessment or both was considered/for '*insufficient during pregnancy*' insufficiency in at least one assessment or both was considered

[f]Model 1: controlled for newborn sex and gestational age at delivery; adjusted for total gestational weight gain (insufficient, adequate, or excessive), type of delivery (vaginal or cesarean section), pre-pregnancy body mass index (kg/m^2), preterm birth (no or yes), gestational anemia (no anemia in both assessments, anemia in at least one assessment, or anemia in both assessments), smoking during pregnancy (no or yes), number of prenatal care appointments, gestational malaria (no or yes), number of live births, number of rooms in the household, maternal age (years), and wealth index

[g]Model 2: Model 1 further adjusted for plasma ferritin in the 2nd assessment (µg/L)

low-resource settings, though analyses for BW in continuous form are limited [10, 11, 14]. This might be one reasonable explanation for the discrepancies with our results, as analyses have been focused in the risk of LBW, instead of changes in the BW. Thus, our results suggest that inadequacies in gestational serum retinol might negatively affect BW, yet after adjustment for plasma ferritin the association smoothed. Our hypothesis is that VAD acts as a limiting factor of optimal in-utero growth through pathways that need to be clarified. Conversely, we did not observe associations between any marker of VA status and BW z-scores, though when restricting the analysis to adult pregnant women an association was observed. Therefore, the relation between gestational VA biomarkers and BW is still unclear.

Prior studies in high-income countries have shown disagreement with our findings in relation to BW. Handel et al. [13] in Southampton, UK, found that high retinol levels measured in late pregnancy (~ 34 weeks of gestation) negatively influenced BW, as each unit increment of retinol was responsible for decreasing the BW by 110 g, adjusted for a set of potential confounders. In Portsmouth, UK, Mathews et al. [9] obtained two measurements of serum retinol throughout pregnancy, similarly to our study (first assessment ~ 16 weeks and second assessment ~ 28 weeks of pregnancy), and found that the high serum retinol at the second moment decreased the BW (β − 208.4 g; $P<0.001$), yet they only adjusted the model for maternal height and smoking. They also explored the variation of retinol concentrations during pregnancy, as we did, encountering that large reductions of retinol, as the pregnancy progressed, were responsible for bigger infants ($P=0.002$), though, unfortunately, they did not show any coefficient regression in the paper for this finding. In Montreal, Canada, a case-control study by Cohen et al. [6] encountered that higher retinol values measured between 24 and 26 weeks of pregnancy increased the odds for small-for-gestational-age (adjusted OR: 1.41; 95% CI 1.22, 1.63).

In the same direction for maternal outcomes, we did not find any association of newborn outcomes with serum β-carotene throughout pregnancy. Serum β-carotene seems to have a beneficial effect on BW in high-income countries' (HIC) populations [6, 9, 13]. This might occur because

β-carotene is a powerful antioxidant [6]. Besides, the diet in HIC populations is more likely to be abundant in micronutrients, pregnant women being less likely to experience some deficiencies during this period. As such, as β-carotene does not need to be converted at same rate into retinol in HIC populations, as occurs in low-resource populations with poor nutritional status, it can play its role as antioxidant, significantly reducing deleterious effects on BW in these populations [6, 9, 13].

In this study, although the prevalence of VAD in both assessments was not too high when compared with other settings [32], comparable to values in high-income countries [6, 9, 13], important discrepancies between our study setting and high-income countries must be addressed. Northern Brazil still faces issues in some socioeconomic and environmental characteristics, being a less-advantaged region in the country [33]. Additionally, higher odds for preterm birth are seen in the North region than in the rest of Brazil [34]. This scenario shows the vulnerability of women of childbearing age living in the Amazonian area, as they are more likely to experience episodes of infectious diseases, including malaria and other tropical infections [35, 36]. The relation between infectious disease and nutrition is well established, where a vicious cycle of poor nutritional status and frequent episodes of infections operates in such conditions [35]. Moreover, as VA is the micronutrient with the most synergistic relation with infectious diseases [36] our findings support the positive effect of retinol for this vulnerable population.

Poor micronutrient status during pregnancy is an important risk factor for a range of deleterious outcomes to the mother–baby binomial [15]. Therefore, considering the social vulnerability of the population in Northern Brazil plus the negative effects of VAD and anemia evidenced by our study, strategies addressing nutrition and health assistance during pregnancy should be reviewed. There is some evidence of the benefits of multiple micronutrients (MMN), containing VA and iron-folic acid, delivered in antenatal care for some outcomes included in our study [29, 37]. A recent Cochrane meta-analysis pointed out that MMN supplementation during pregnancy reduced the risk of LBW (RR 0.88; 95% CI 0.85, 0.91) [36]. Smith et al. [29] found that MMN supplementation reduced the risk of LBW (RR 0.81; 95% CI 0.74, 0.89), and for anemic women, reductions in small-for-gestational-age births were observed (RR 0.92; 95% CI 0.87, 0.97). In all studies, comparison was made with iron–folic acid supplementation.

Pregnancy in adolescence involves a broad spectrum of physiological, physical, and emotional aspects than in adulthood [38]. In this sense, it is likely that the investigation of micronutrient deficiencies in this group should consider such specifiers, though specific cut-offs for VAD are not disclosed [3], and little evidence is available in this subject. Moreover, we used internationally standardized methods to measure serum nutritional markers, allowing us to compare our estimates with other previous studies.

Our study has limitations. We had losses to follow-up, potentially due to logistic constraints faced by the research team in attempting to contact the participants for enrollment in the study and to schedule the assessments, which are marked features in this area (i.e., poor internet connection, lack of street labels for many addresses, and intermittent mobile signal). The possibility of unknown confounding factors cannot be excluded as we work with observational data. More precise estimates for adolescent participants in our study might have been impacted by the small sample size. Although associations between supplementation during pregnancy and serum markers of iron and VA status were not observed in our study, we lack information on the onset of the supplementation, which could have given more details to explore the potential effects of this intervention. We did not include information on dietary VA intake which may impact on serum VA markers. However, serum retinol is not a good marker of VA intake, but of liver stores instead [39]; β-carotene has been associated with recent intake of fruits and vegetables, which makes us believe that optimal serum β-carotene might reflect good intake of carotenoid-source foods in this population [40]. Despite these limitations, the strengths must be highlighted, including: (1) the prospective design of the study, with two measurements of potential exposures throughout pregnancy; (2) the biochemical assessments of the main exposures followed standardized laboratory procedures to maintain the quality of the samples; (3) we used WHO's recommended markers for the assessment of body iron depletion in populations (serum ferritin and hemoglobin); (4) confirmation of the GA with ultrasound measurements; (5) inclusion of a wide range of potential confounders in our final adjusted model, which was carefully assessed and measured; and (6) to our knowledge, this is the first prospective cohort study on maternal-newborn health in a challenging Brazilian region.

We found that poor VA nutritional status throughout pregnancy has harmful effects on maternal anemia and Hb at delivery, as well as newborn BW. To the best of our knowledge, this is the first study showing the role of gestational serum retinol and β-carotene in a middle-income country population. This research adds insights to the evidence that the current WHO strategies addressing pregnant women's nutrition through supplementation with only iron–folic acid needs rethinking.

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Authors' contributions PARN participated in the data collection and field overseen. PARN, CVRO, and MBM performed the statistical analysis. MCC, BHL, and MAC conceived the study design and methods. PARN wrote the first draft of the article, with critical appraisal by MCC and MAC. PARN and MAC had primary responsibility for final content. All authors reviewed and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The MINA-Brazil Study was approved by the School of Public Health, University of São Paulo Ethical Review Board (Number 872.613, Nov 13th, 2014), in accordance with the ethical aspects described by the 1964 Declaration of Helsinki. Written informed consent was introduced to the potential participants and approval obtained by their signatures or from the caregivers for teenage pregnancies.

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