Prevalence Of Vitamin B Complex Deficiencies In Women In Reproductive Age, Pregnant Or Lactating Woman In Brazil: A Systematic Review And Meta-Analysis Protocol

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Protocol

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Abstract

Background: Complex B vitamin deficiency are involved with several outcomes in fertility and pregnancy. In Brazil, the national prevalence rates of these micronutrients deficiencies in women at reproductive age was not known. Therefore, this study aims to systematically identify, select, evaluate, analyze and report the prevalence rates of complex B vitamins deficiencies in women at reproductive age in Brazil, and identify variables that may modify the outcome rates.

Methods: A systematic review will be conducted guided by the following question: “What is the prevalence of vitamin B complex deficiencies in women at reproductive age in Brazil?”. The studies will be identified and selected from a literature search using electronic databases, consultation to researchers/specialists, as well as reference lists of eligible studies and reviews on the topic. Major eligibility criteria include observational cross-sectional and cohort studies performed in women with 10-49 years old from Brazil; pregnant and lactating mothers; and which that investigated the deficiency of complex B vitamins by laboratorial test. Two reviewers independently will perform the screening and selection of studies, to subsequently perform data extraction and risk assessment of bias. For data report, a narrative approach will be used to summarize the characteristics of the included studies and the individual prevalence found for each micronutrient tested, and if the studies are sufficiently homogeneous, a quantitative synthesis (meta-analysis) will be performed.

Discussion: Identify the national and regional prevalence rates of complex B vitamins deficiencies allow the policy makers discuss, plan and implement public policy to prevent and/or reduces the rates, if they are larger, or at least highlight discussions about a program of screening the vitamins deficiencies in this specific population for to know the epidemiologic scenario among the years, serving as an indirect indicator of the socioeconomic and dietary patterns of this population. Also, specifically for folates, this study allows to compare the prevalence rates of deficiency of this vitamin before and after the mandatory fortification of wheat and corn flours implemented since 2004. Nevertheless, the evidence gathered may highlight the need for population-based studies to investigate the deficiency of these vitamins.

Systematic review registration: PROSPERO registration number: CRD42020188474

Background

Almost two billion people have some kind of micronutrient deficiencies, affecting mainly women of reproductive age, pregnant women and children in low- and middle-income countries, for example Brazil (1,2). Among the possible causes are poor diet quality, characterized by high consumption of ultra-processed foods, rich in saturated fat, sugar and sodium (3) and, the presence of infections and/or chronic diseases that can compromise food intake and nutrient absorption (4).

At the same time, the continuous use of oral contraceptives can also trigger the deficiency of micronutrients such as folic acid, vitamins B2, B6, B12, vitamin C and E and the minerals magnesium, selenium and zinc (5,6). In turn, the periods of pregnancy and lactation are characterized by high

nutritional demand, specifically the B vitamins (7,8), making it more challenging to maintain nutritional adequacy (9). Low concentrations of these vitamins have been associated with pregnancy complication such as neural tube defects (NTDs) (10,11) and spontaneous abortion (11).

B complex are involved in the one-carbon metabolic pathway responsible for homocysteine (Hcy) metabolism and formation of S-adenosylmethionine (SAM), which serves as the main methyl donor for methylation, collaborating in an epigenetic mechanism to regulate gene expression and is essential for normal embryonic development (12,13).

However, dietary deficiency of vitamins B6, B12 and folate or genetic alterations in the folate activation pathway can lead to Hcy accumulation (14). In high concentrations, Hcy is pro-inflammatory, leads to oxidative stress (13,14) and has been identified as an independent risk factor for atherosclerotic vascular disease (15,16), and associated with infertility (17), and adverse pregnancy outcomes (10), as pre-eclampsia(18,19), and preterm birth (20).

In order to decrease the prevalence of micronutrient deficiencies that mainly affect the maternal-infant group, public health policies have been implemented for decades, such as fortification of wheat and maize flours (21), and the universal folic acid supplementation for women of childbearing age who wish to become pregnant and for all pregnant women until the end of pregnancy recommended by WHO (22) and the Brazilian Ministry of Health (23).

Despite all efforts so far implemented, monitoring the effectiveness of micronutrient supplementation or fortification interventions, as well as the evolution of cases of deficiency, is still a challenge in the country, due to the scarcity of screening studies of epidemiological and population-based nutrient deficiency rates. It is added that the heterogeneity that characterizes the Brazilian population, either in relation to the socioeconomic and cultural conditions reinforces the importance of identifying the real number of cases of micronutrient deficiencies that affect women of fertile age, pregnant and lactating women in the country.

OBJECTIVE

This review will systematically examine, identify, select, evaluate and analyze all studies that report the prevalence rates of vitamin B complex deficiencies in Brazilian women at fertile age, pregnant, or in lactation, and identify possible variables that may modify the outcome rates.

Methods And Design

The review protocol follows the recommendations of the Briggs Institute Manual of Evidence Synthesis(24). In addition, to ensure transparency and non-duplicity of the publication, as well as to minimize the presence of biases during its execution, this protocol was publicly registered in Prospero database (registration number CRD42020188474).The present study protocol is being reported in

accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement(25).

Review question

What is the prevalence of complex B vitamins deficiency in women at reproductive age in Brazil?

Eligibility criteria

Studies will be selected according to the following criteria:

Population/participants

Women of reproductive age (10 to 49 years of age), including pregnant and lactating mothers. Initially, any study conducted in Brazil aimed identify the deficiency of complex B vitamin will be selected, and their study`s participants will be analyzed. If they includes women at 10 to 49 years, but not only, the authors of study will be contacted to provide the proportion of women in this age group with the outcome. The study will be only eligible if the authors return with the requested information.

Outcome(s)/clinical situation of interest

The outcome of this review is the body deficiency of the Complex B vitamins. The diagnostic of vitamin deficiency should be done by biochemical assessment following the recommended laboratory methods/techniques. The cut-off values for deficiency could vary according to the method/technique used and subsets of the population. Studies in which the deficiency was identified by clinical signals and symptoms will not eligible.

Study design

This systematic review will include cross-sectional studies or cohort. In case of cohort with multiple investigations of our interesting outcome, in global analysis, we will use the rate of the most recent analysis in which it was investigated, but for temporal analysis, all rates investigated in distinct moments of the follow-up will be included. Only fully published studies in the form of a scientific article or academic thesis, dissertation or monograph will be eligible. No published studies or studies without full text access, besides conference proceedings, editorials, case reports, case-control, letters and trials will be not eligible.

Epidemiologic indicator

Studies that provided the prevalence rates of the outcome will be eligible. Original studies that did not present the prevalence rates but described the proportion of eligible women with deficiency of any vitamin from complex B will be eligible if the prevalence may be calculated.

Setting/location

Only studies carried out in Brazil will be eligible. Studies in any setting (primary care, hospital, outpatient, clinic patients) representing the general population or subgroups that reflects populational conditions will be eligible. It will be ineligible: studies carried out only with patients with diseases or any pathological condition (except obesity associated to their comorbidities); situations that affect the digestion, absorption, metabolization rates and daily requirements of the vitamins such as post-bariatric surgery, athletes and vegetarians; and studies on which the vitamins deficiencies are assessed in woman with genetic polymorphisms/variants that affect the body status of the vitamins B complex. However, studies that determine the prevalence of the polymorphism related to and the deficiency rates of the vitamin B, not conditioning one to another, will be eligible.

Information sources and search strategy

The primary source of literature will be a systematic and structured search of the following electronic databases: MEDLINE (PubMed), Embase, Web of Science (main collection), Scopus, SciELO Citation Index (by Web of science), *Literatura Latino Americana e do Caribe em Ciências da Saúde* - LILACS (by Biblioteca Virtual em Saúde - BIREME) and a Brazilian database of academic thesis and dissertations (Biblioteca Digital Brasileira de teses e dissertações - BDTD). The secondary source of potentially relevant studies will be a consultation to Brazilian researchers in the areas of Health, Medicine, Nutrition, and Public Health allocated in public Universities of the country, by e-mail. The literature searches were designed using search terms underpinning by the inclusion criteria and ensured by MeSH Terms and Emtree terms. The search strategies were created by combining search terms with Boolean operators and using search facilitators (quotation marks, truncation symbol, proximity operators) and were adapted by each database. Before official electronic search, the search strategies were piloted to ensure sufficient specificity and sensitivity. After this step, to improves the specificity we included in the search strategies general terms of exclusion criteria. The search strategies that will be used in the official literature search are presented in supplementary file 1. Additionally, we will perform hand-searching of the reference lists of included studies, relevant reviews, or other relevant documents. No limits of publication date and languages will be defined.

Study selection

The results from the literature search will be transferred to Ryyan QCRI, the Systematic Reviews web app (26) for the management of the references. In the app, the repeated references will be identified by one reviewer and only one of its multiple records will remain for the next step. In the phase of study selection, two reviewers will be analyzing the titles, abstracts and full texts for eligibility. They will be blinded and at the conclusion of the process, the judgement of each will be confronted. In case of discrepant judgment about the study eligibility, this study will be analyzed by the reviewers, and a consensus will be reached by discussion. Initially, the titles will be read and if it appears eligible, the abstracts and full texts will be read to confirm eligibility.

Data extraction

Data extraction of the eligible studies will be performed by two reviewers, independently, registering the data in a customized Microsoft Office Excel® sheet, that will be pilot tested prior to initiating the data extraction process. The extracted data by the two reviewers will be confronted and any disagreement resolved by new consultation of the study. In this process, the original authors may be consulted for any additional information not (fully) presented in the publication by e-mail or by Research Gate. The information that will be extracted from the studies are: study identification; year of publication; type of publication; local (city and State) and period in which the study was conducted; study design; population group (pregnant, lactating woman or women not pregnant or lactating) and their characteristics (age range or mean/median, setting of recruitment, proportion of obese or malnourished participants, proportion of chronic diseases; use of medicines and vitamins supplements; and other clinical and demografic characteristics; for pregnant, trimester of the analysis); sampling process; number of participants recruited and analyzed; sample size calculation; vitamins B deficiencies investigated and their diagnostic method; the prevalence data and their 95%ICor the number of cases for prevalence calculation.

Data synthesis

Initially we will perform a narrative description of the summary of results. For the selection process, the results will be presented in accordance with the PRISMA flow diagram. The information extracted about each study (characteristics) and the prevalence rates (and 95% IC) of complex B vitamins deficiencies will be presented in a summary table. The results will be presented separately for pregnant, lactating woman and women not pregnant or no lactating and for each vitamin B assessed.

Meta-analysis will be done using random model and using STATA 16.0 software and the Metaprop and Metapreg packages. Random effects model will be applied to estimate the pooled prevalence, since we will expect heterogeneity among the studies a priori. The proportion (prevalence) of cases will be transformed to logit before combine the data in the metanalytic approach. Statistics for heterogeneity (test Q de Cocran and I^2), publication bias (Begg$stest, Eg \geq r$s test and Trim & Fill method) if there are ten or more studies in a global meta-analysis, and sensitivity analysis will be also done. For meta-analysis, we entry in the software the prevalence rates and their 95%IC.

For each subpopulation (pregnant, lactating woman and women not pregnant or no lactating) and each vitamin B, if there are two or more studies that fulfilled each subgroup criteria, we intend to stratify the analyzes by:

- Time/Year (temporal analysis), showing the prevalence rates in a timeline graph, and specific for folate, we will stratify in before 2002 and after 2002, because this year it became mandatory to enrich wheat and corn flours with folic acid in the country.

- Age group: 15 to 19 y; 20 to 35 y; >35 y.

- State and Geographic Region of the Brazil: 24 States + Federal District; 5 macro-regions of the country (north, south, southeast; midwest; and northeast).

- For pregnant: trimester of gestation (1st, 2nd or 3th).

- Lactation period: 1st semester; 2nd semester; 2nd year.

- Other that may reduce the possible heterogeneity among the studies and/or modify the prevalence rates. Individual meta-analysis will be done by each subgroup above described, including only studies that attend this subgroup criteria. Meta-regression may be applied to investigate these factors/variables associate with the modification of the prevalence rates.

Risk of bias

The risk of bias will be assessed following the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (available in https://jbi.global/sites/default/files/2020-08/Checklist_for_Prevalence_Studies.pdf). This tool encompasses nine items about the sampling process, sample size, description of the study subjects, identification / diagnosis of the clinical condition, statistical analysis and response rate. Adequation for each domain / items will be classified as adequate (YES), inappropriate (NO), absence of clear information to judgment (UNCLEAR) or not applicable (N / A). This procedure will be done by two reviewers, independently, and the judgments will be confronted. Eventual disagreements in the risk of bias assessment process will be solved by discussion until consensus. The results of this step will be presented in a table, describing the judgment for each domain assessed and their reason (s).

Discussion

There are few studies that analyzed the deficiency of vitamins of complex B, especially in low and middle countries. Since the B vitamins have an influence on women's health and knowing that there are no national surveys with synthesized data on the prevalence of these vitamins among women of childbearing age, pregnant women and lactating women, it is extremely relevant to know the current panorama regarding deficiencies of these vitamins in the female population. Which may support the development of strategic actions related to the prevention, treatment and reduction of the lack of B vitamins. In addition, it can also assist in the development or strengthening of public policies aimed at this group in particular, such as the fortification of flours with folic acid, to guide on possible studies needed in the future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study will be included in the published systematic review article and will also be available upon request. The Prisma-P checklist is available in Additional file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors conceptualised the study and prepared the draft protocol under the guidance and supervision of MM. All authors contributed to the development of the background and planned output of the research as well as the design of the study. All authors read and approved the final manuscript.

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