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Maternal Anemia and Iron Deficiency Anemia: Similarities and Singularities

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Abstract

Maternal anemia is a major global public health problem, and although widely discussed, there are few studies investigating the condition in pregnant women. In this article, issues related to the diagnosis, biological mechanism and prevalence of maternal anemia. In addition, iron deficiency anemia will be considered a proxy for maternal anemia. In previous studies, the concepts of maternal anemia have been controversial. It is also noted that isolated actions are not sufficient to combat this disease, and policies to address the primary causes of the associated nutritional deficiencies are necessary.

Keywords: Anemia; Iron deficiency; Iron deficiency anemia; Pregnancy outcome; Differential diagnosis

Introduction

Anemia is a relevant problem worldwide, typical of large urban centers and affecting countries of various economic levels from North America to Sub-Saharan Africa [1]. On a biological level, this deficiency is characterized by a reduction in hemoglobin levels due to a lack of essential nutrients, such as B vitamins, zinc, protein and iron [1,2]. Both the definition and the classification of anemia were determined by consensus by multiple international institutions approximately two decades ago at the New York Summit Meeting [2]. As a result of this discussion, anemia has become a priority for many countries, with the main goal being its reduction across different population groups [3]. There are many studies with different methodological strategies focusing on anemia [4-12]. Such studies include distinct population subgroups and different sample sizes, producing conflicting results [12]. Furthermore, the majority of studies use hemoglobin level as the only diagnostic criterion, ignoring the various types of anemia [12].

The World Health Organization (WHO) considers iron deficiency anemia to be the main cause of maternal anemia [1]. While some studies consider hemoglobin level the only diagnostic criterion for iron deficiency anemia, other studies show that the frequency of iron deficiency is lower when diagnosed using both hemoglobin and ferritin levels [5-7,13-16]. Therefore, there is no consensus that maternal anemia has a frequency similar to that of iron deficiency anemia Thus, we aimed to review the main aspects of health-disease-care process of maternal anemia, focusing on the comparison of maternal and iron deficiency anemia. Biological mechanisms, diagnostic criteria and prevalence were discussed [5-7,13-17].

Materials and Methods

Eligibility criteria

Cross sectional and baseline of cohort studies assessing the maternal anemia or iron deficiency anemia were considered for inclusion. Publication date or languages were not exclusion criteria.

Information sources

We searched for eligible articles on December 17th, 2017, on the following electronic databases: Medline via PubMed, EMBASE, Scopus, Web of Science, SciELO and Lilacs. We also gray literature and hand searched reference lists from selected articles.

Search strategies

Mesh and similar terms were combined using Boolean operators (AND, OR), and the search strategy below was primarily used for PubMed and afterwards adapted for the remaining databases: (anemia OR anaemia OR anemia, iron deficiency) AND (Pregnancy OR Pregnant Women OR Gravidity OR Maternal exposure OR Mother OR Gestation) AND (Prevalence OR Frequency) AND (Cross Sectional Studies OR Cross Sectional Study Cohort studies OR Longitudinal Studies OR Follow-Up Studies OR Prospective studies OR Cohort OR Longitudinal OR Prospective OR Retrospective OR Incidence study OR Follow up).

Studies selection

After duplicate removal, titles and abstracts were screened for eligible articles independently by two reviewers (ACMGF and SSC). Two reviewers selected articles by reading titles and abstracts. During the process of selecting the articles the researchers were not aware of the decisions made by their colleague. After that, full text articles were assessed for eligibility. Discordant events were resolved by consensus.

Data extraction

Data extraction was performed independently by two researchars (ACMGF and RBS) and discordant events resolved by consensus. We used a standardized electronic spreadsheet to extract the following information: author's name, year of publication, year of data collection and geographic region, study design, sample size, anemia diagnosis criteria, frequency of maternal anemia and iron deficiency anemia. Authors were contacted for additional information considered important for this review.

Data synthesis

Information regarding maternal anemia and iron deficiency anemia was described and summarized in figures.

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Results and Discussion

In the search of the databases, 2243 records were identified. After removing the duplicates and reading titles and abstracts, 192 articles were selected for full reading. Only 36 texts met the eligibility criteria of this review (Figure 1).

Biological mechanisms and diagnostic criteria for anemia in pregnant women

Basal hemoglobin, which is produced in the bone marrow through erythropoiesis, is a protein formed by four amino acid chains that has one heme peptide in each of the four globins [17,18]. The heme group comprises porphyrin and a central iron ion responsible for oxygen transport and energy production inside the cell. Hemoglobin is responsible for red blood cell formation, while hematocrit is the percentage of red blood cell volume [17,18]. From a physiological perspective, pregnant women are most vulnerable to anemia due to their increased nutrient needs, pregnancy-related changes and fetal growth [19,20]. Anemia is closely related to blood loss and/or decreased hemoglobin, which can occur due to a lack of erythrocyte production or to the hemodilution inherent in pregnancy [19,20].

Hemodilution results from an increase of 50% in plasmatic volume beginning in the sixth gestational week and continuing to the end of pregnancy to compensate for increased cardiac output and to meet fetal demands [18,21]. Hemodilution decreases red blood cells/hemoglobin in the blood; however, it does not impact the body's total oxygen transport capacity [22]. Notably, the reduction in the number of circulating red blood cells decreases the lifespan of these cells from 18% to 33% [23-28]. Thus, red blood cell depletion may lead to a reduction in iron in the blood [29]. A persistent decrease in iron ions can promote iron deficiency anemia because unavailability of this metal prevents the formation of new hemoglobin [17,18]. In the event of a decrease in iron levels, the human body has additional sources of this nutrient in the liver. Kupffer cells are responsible for identifying erythrocytes in decay and for stimulating macrophages to remove these senescent cells through phagocytosis [17]. This process will increase iron availability in the intracellular medium that can be exported through ferroportin (FPT) to other cells or stored in the macrophages themselves [17].

There are two sources of dietary iron: 1) animal foods provide heme or ferrous (Fe^{+2}) iron and 2) vegetable foods provide non-heme or ferric (Fe^{+3}) iron [17,24]. Ferrous iron is absorbed into the interior of the cell through heme carrier protein (HCP) [17,24]. Ferric iron is synthesized

in enteric cells, duodenal cytochrome b (Dcytb), where it becomes ferrous and is conducted to the intracellular medium through divalent metal transporter protein (DMT-1) [17,24]. Ferroportin transports ferrous iron, which is synthesized in ferritin, to the extracellular medium (17, 24). Ferritin conduction occurs after this step through the carrier protein transferrin to the place where hemoglobin is produced [17]. The WHO criteria for maternal anemia area hemoglobin of less than 11.0 g/dL or a hematocrit of 33% or less, regardless of the gestational trimester or type of anemia, which differs from those of previous investigations [1,4,25-28]. Studies indicate that the cut-off for the diagnosis of maternal anemia in the second trimester should be in the range of 10 to 10.5 g/dL or two or less standard deviations from the mean of hemoglobin and/or hematocrit [25,26]. Iron deficiency anemia is characterized by ferritin levels of less than 15 fL and is related to low levels of hemoglobin (<11 g/dL) [4,29]. When iron deficiency anemia occurs, serum ferritin is decreased and/or transferrin is increased [4,29]. Other types of anemia can be diagnosed during pregnancy, even if blood iron levels are normal, such as anemia of chronic disease, also known as anemia of inflammation [30].

Prevalence of maternal and iron deficiency anemia

Maternal Anemia reaches across social strata and is considered the most prevalent nutritional deficiency in the world [1] (Figure 2). The WHO classification of the prevalence of maternal anemia is as follows: 1) normal – 0 to 4.9%; 2) mild – 5 to 19.9%; 3) moderate – 20 to 39.9%; and 4) severe ≥ 40% (Figure 3). Notably, there is considerable variability in the prevalence of maternal anemia worldwide, especially when comparing developed countries with economically disadvantaged countries [1]. In 2011, the global frequency of iron deficiency anemia in pregnant women was 19.2% (95% CI: 17.1-21.5%) [5]. The worldwide frequency of the condition was as follows: the Americas and the Caribbean – 15.2% (95% CI: 11.7%; 18.6%); Europe – 16.2% (95% CI: 12.6%; 19.7%); Oceania – 17.2% (95% CI: 9.7%; 25.6%); Asia – 19.8% (95% CI: 15.8%; 23.5%); and Africa – 20.3% (95% CI: 18.3%; 23.4%) [15].

These results were obtained based on the supplementation dosage of ferrous sulfate taken by pregnant women [15]. Some investigations performed on the American continent show the profile of maternal anemia. In Alaska, United States of America, between 1993 and 2006, it was reported that the prevalence of maternal anemia was 18% [31]. It is estimated that in Mexico in 2012, 21% of pregnant women were diagnosed with anemia and that only half of cases were caused by iron
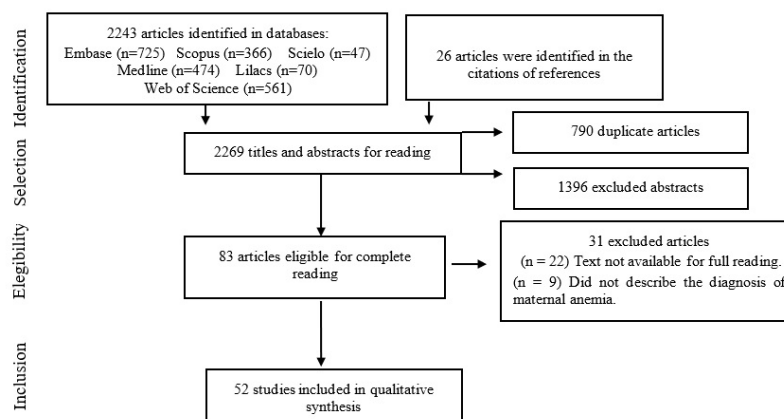

Figure 1: Flowchart of the search, selection and inclusion of the studies.
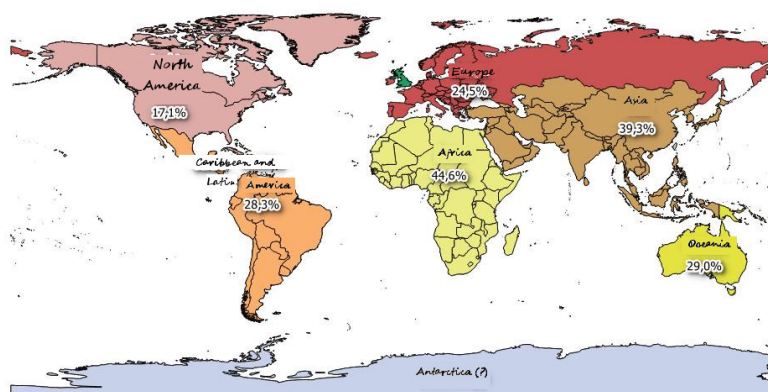
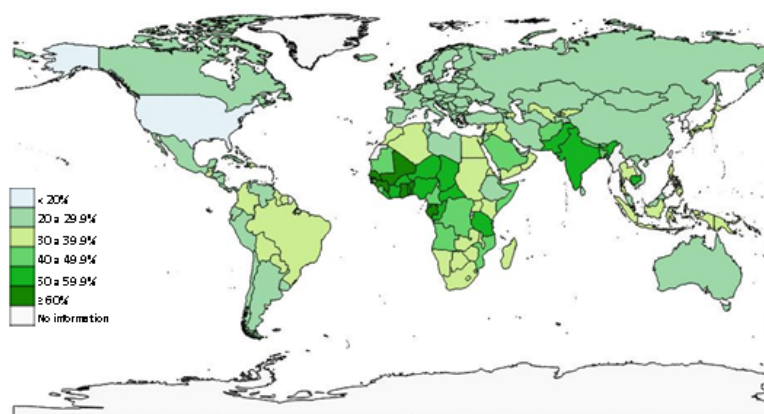**Figure 2:** Prevalence of maternal anemia worldwide [1].

Figure 3: Prevalence of maternal anemia worldwide according to occurrence levels [1].

deficiency [32]. In Cuba and Peru, 2011, the prevalence of maternal anemia was 29.7% and 28%, respectively [33,34]. A study performed in Brazil between 2000 and 2001 [4] showed that 56% of pregnant women enrolled in the study had a diagnosis of maternal anemia and that approximately 11% of those women had iron deficiency anemia [4]. The average frequency of maternal anemia in European countries is 24.5% [1]. In Switzerland, the occurrence of iron deficiency (32.2%) and anemia related to iron deficiency (6.5%) differed [7]. It should be emphasized that other types of anemia were found in 11.8% of pregnant women in this longitudinal investigation [7]. Data from a cohort study of 1,478 pregnant women showed that 15.8% of French women had maternal anemia in 2013 and 2014 [10]. Of these women, approximately 31% had iron deficiency [10]. Asia has the second-highest rate of maternal anemia in the world [1]. In a prospective investigation performed in India, a country considered to have severe maternal anemia, the rate varied between 41% and 55% in the first and third trimesters of gestation, respectively. However, the prevalence of iron deficiency anemia was 3.6% and 5.6%, respectively [16]. In Japan, the frequency of maternal anemia in 2011 increased substantially between the first and second trimesters, (4.5% and 44.1%, respectively) [11].

In Nigeria, a Sub-Saharan country, the percentage of women with maternal anemia in 2014 was approximately 59% at the end of gestation [35]. In Algeria, the occurrence of maternal anemia was approximately 47% in 2010 [36]. No studies reporting the frequency of iron deficiency

and iron deficiency anemia in pregnant women in African countries were found. Research performed in Oceania showed no consensus regarding maternal anemia indicators [37-39]. Betwen 1999 and 2005, the occurrence of maternal anemia in southern Australia was 7.1% [37]. In New Zealand, 2013 data indicate a frequency of maternal anemia of 54.5%; however, only 6.3% and 5.8% of the pregnant women had iron deficiency and iron deficiency anemia, respectively [39]. Another relevant indicator for this hematological disorder concerns the severity of maternal anemia [1].

The data show that the frequencies of mild and moderate maternal anemia are elevated among pregnant women [14,34,36,40-46] and that severity levels vary greatly across countries (Figure 4). From the perspective of minimizing the occurrence of maternal anemia, prophylactic actions, such as ferrous sulfate and folic acid supplementation, have been recommended [28,47]. However, between 1995 and 2011, worldwide epidemiological indicators of maternal anemia decreased by only 3.6% (from 41.8% to 38.2%) [1]. The use of these supplements has not been sufficient to markedly reduce the prevalence of maternal anemia worldwide in recent years [2]. The data we presented indicate discrepancies in the prevalence of maternal anemia in different countries. In the majority of studies, estimates of iron deficiency anemia are always lower than those for maternal anemia [5,13-15]. However, official WHO documents indicate that these events generally occur with similar frequencies [1].
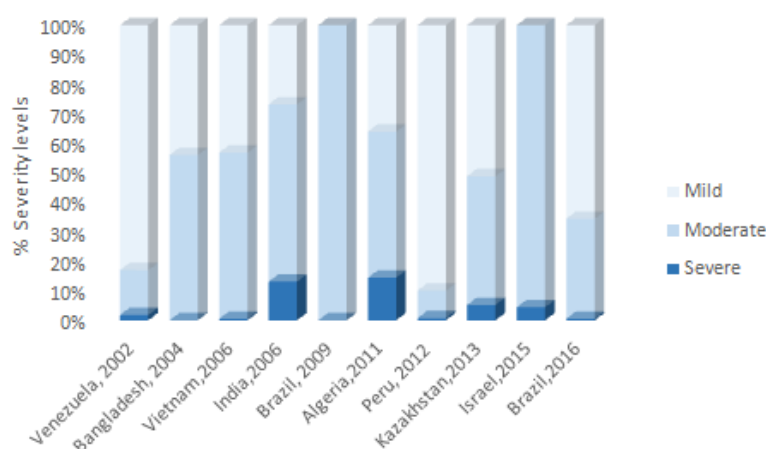
Figure 4: Diagnosis of maternal anemia in different countries by severity, with their respective percentages [14,39,41,44,48-52].

Is iron deficiency anemia a proxy for maternal anemia?

The WHO definition of anemia in pregnant women is a condition caused by cumulative iron deficiency [48]. Therefore, the question is whether maternal anemia is a proxy for iron deficiency anemia [2]. However, there is no consensus regarding this statement [5,7,13,15,16]. Various studies consider iron deficiency an essential condition in the occurrence of maternal anemia, as those studies concluded that most women have iron deficiency during gestation [49]. It is estimated that iron deficiency is 2.5 times more frequent than anemia in pregnant women; therefore, when a pregnant woman has low hemoglobin, it is mistakenly characterized as maternal anemia rather than iron deficiency anemia [49]. The WHO supports the argument that hemoglobin levels and/or hematocrit are good markers of anemia; these markers offer cost-effective ways of screening for the disease and, that in the absence of laboratory tests that allow for differential diagnosis, the women would be diagnosed with iron deficiency anemia [1,48]. The statement is based on the fact countries have financial resources that are too limited to use more than one test to diagnose anemia in pregnant women, this would entail a health cost of approximately 50% more than necessary [4,43]. Studies comparing levels of hemoglobin with ferritin (the gold standard) find that these results are quite close [5,13-15]. Nonetheless, the use of hemoglobin levels as the only test for maternal anemia is not ideal, as it cannot accurately diagnose the type of anemia because of its low sensitivity [4,21]. The use of at least two criteria to clarify the etiology of anemia might improve the specificity of the test and reduce the probability of false positives; that is, the possibility of diagnosing iron deficiency anemia in women who do not have iron deficiency [4,21]. The appropriate use of hematological markers could promote investigations into the type of anemia [48]. For example, the number of red cells might help in the classification of anemia and direct health professionals to request complementary tests, such as ferritin levels [48,49]. Red blood cell values above 4 million and hemoglobin levels below 11g/dL are suggestive of iron deficiency anemia, requiring confirmation by the level of ferritin (<15 fL) for diagnosis [49-51].

The absence of a differential diagnosis or the inability of health professionals to characterize the type of anemia, as well as unawareness of its magnitude, may be an impediment to adequate therapy at the population level. That is, iron supplementation might be erroneously recommended by health professionals who are not certain what type of anemia is to be treated in pregnant women [47,52]. Many authors dis-

agree that maternal anemia might be representative of iron deficiency anemia because some studies show discrepancies in the prevalence of both types of anemia [4,6,7,16,21,43]. Such research shows that the occurrence of iron deficiency anemia is, in most investigations, expressly lower than that of maternal anemia [4,6,7,16,21,43]. There has been an increase in the number of publications regarding diagnostic criteria for iron deficiency anemia in the last decade [4,5,21]. Studies that use serum ferritin and/or transferrin levels to diagnose iron deficiency anemia report results that are more consistent for the population of pregnant women [4,6,7,16,21,52] than studies that used only hemoglobin levels [5,13-15]. The WHO maternal anemia criteria are considered inappropriate by some authors, when there is the intention to estimate iron deficiency anemia [2,4,6,7,21]. This issue is related to the disease pathophysiology, given that the origin of maternal anemia might not be iron deficiency but other uninvestigated causes. The premise that there is a resemblance between maternal anemia and iron deficiency anemia has driven the indiscriminate supplementation of ferrous sulfate during pregnancy. For this reason, the current literature, contrary to the idea that iron deficiency anemia is a proxy for maternal anemia, emphasizes that the use of specific and sensitive diagnostic criteria is very important to minimize adverse effects that could be caused by inadequate supplementation [4,21].

Conclusion

The majority of studies included in this review did not perform anemia differential diagnoses during pregnancy. The absence of anemia differential diagnoses might confound the magnitude of the problem. In other words, the causal mechanisms for both maternal and iron deficiency anemia may differ. as it can be related to other factors rather than iron deficiency, such as under nutrition, infection or other events prior to pregnancy. Preventive actions are of major importance to minimize the occurrence of maternal anemia, as is the accurate diagnosis of the disease, since isolated actions alone are insufficient to impact the nutritional status of the population.

Conflicts Interests

The authors declare that they have no conflicts of interests.

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